Poster Session 1 – Surgery Monday, 4 July 2011 12:15-14:15

P1.305 INFLUENCE OF A SPECIAL SURGICAL SPECIMEN COLLECTION KIT ON THE QUALITY OF MEDIASTINAL LYMPH NODE EXAMINATION DURING RESECTION OF LUNG CANCER.

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Background: Mediastinal lymph node (mLN) status is the key determinant of prognosis and post-operative therapy after curative-intent resection of non-small cell lung cancer (NSCLC). There is some controversy about the optimal LN examination procedure, but systematic nodal dissection is widely advocated. Random examination or lack of examination is associated with inferior survival. However, a 2001 American College of Surgeons survey revealed that 42% of resections had no mLNs examined, identical to our Memphis cohort in which a median of 1 mLN was examined, and 85% of resections had no mLN mapping. In the Memphis cohort, no mLNs were examined in 35% and 52% of patients with 'pN0' and 'pN1' disease, respectively; station 10 was not specifically identified in 59%; only 24% met resection criteria for eligibility for the RADIANT trial, 0.9% met eligibility for the ACOSOG Z0030 trial, and only 8% met the NCCN definition of good quality resection. Suboptimal hilar and mLN examination accounted for most quality failures. We tested the effect of a corrective intervention using a pre-labeled specimen collection kit with separate containers for stations 2-10 to improve examination during curative-intent resection of NSCLC.

Methods: Case-control study to test kit deployment and use in the operating room. We compared our data to a near-contemporary pre-deployment cohort from the same institution, matched for surgeon, pathologist, histology, and extent of resection. Appropriate statistical methods were used for all comparisons.

Results: mLN were examined in all cases in which the kit was used. The median number of mLN examined was 0.5 in the control group, compared to a median of 10 in the case group. Stations 4 and 7 had significantly increased number of LNs examined. The percentage of resections that attained the NCCN definition of good quality resection and the proportion of resections that would have been eligible for the RADIANT trial increased significantly. Attainment of the more stringent ACOSOG definition of good quality resection improved slightly (Table). The duration of surgery and post-operative complication rates were similar between cases and controls. Thirty percent of the cases performed with the kit had one or more positive mLN, compared to 8% of the controls.

	Case			Control			P-value
	Median	Range	Interquartile Range	Median	Range	Interquartile Range	
# mLN examined	10	(5,12)	(9,11)	0.5	(0,6)	(0,5)	0.0078
# mLN positive	0	(0,3)	(0,1)	0	(0,3)	(0,0)	0.99
Station 4	4	(0,8)	(1,4)	0	(0,2)	(0,0)	0.0078
Station 7	1.5	(0,3)	(1,2)	0	(0,1)	(0,0)	0.0313
Station 8	1	(0,5)	(0,2)	0	(0,1)	(0,0)	0.0625
Station 9	1	(0,2)	(0,1)	0	(0,1)	(0,1)	0.0625
Station 10	1	(0,4)	(1,2)	0	(0,6)	(0,1)	0.47
RADIANT trial eligibility	90%			10%			0.0078
NCCN GQR criteria	80%			10%			0.0156
ACOSOG Z0030 criteria	20%			10%			1.0
Median surgery time, minutes (range)	158 (79,231)			151 (80,208)			0.9
Median hospital length of stay, days (range)	6 (0,26)			6.5 (3,27)			0.99
Median intra-op blood transfusion, units (range)	0 (0,2)			0 (0,0)			--
Median estimated blood loss, mL (range)	300 (100,1000)			250 (100,500)			--
Median ICU days (range)	2.5 (0,23)			3 (1,4)			--
Median chest tube days (range)	3 (2,15)			5 (2,15)			--
Median frequency post-op MI (range)	0 (0,0)			0 (0,0)			--
Median frequency post-op pneumonia (range)	0 (0,2)			0 (0,0)			--
Median frequency post-op arrhythmia (range)	0 (0,1)			0 (0,1)			--

Conclusion: The use of a specialized specimen collection kit for mLN examination is feasible, was associated with markedly improved mLN examination and mapping, and detection of more metastatic disease in the mLNs. There was no increase in OR time, post-operative or peri-operative morbidity/mortality, or hospital length of stay.

Keywords: Operative Intervention, Pathologic staging, Systematic mediastinal nodal dissection, Quality improvement

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P1.306 COMPARISON OF SYSTEMATIC MEDIASTINAL LYMPH NODE DISSECTION VERSUS SYSTEMATIC SAMPLING FOR LUNG CANCER STAGING AND COMPLETENESS OF SURGERY

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Background: The best method for performing mediastinal lymphadenectomy after a major pulmonary resection in lung cancer patients is still in dispute. This self-controlled prospective study was designed to investigate the efficacy of systematic sampling (SS), compared to systematic mediastinal lymph node dissection (SMLD), for pathological staging and completeness of surgery.
Methods: Over 11 months, 111 patients were enlisted. All were diagnosed with lung cancer and treated by pulmonary resection. Surgeons systematically sampled mediastinal lymph nodes prior to pulmonary resection, and after pulmonary resection SMLD was performed to each patient using the standard procedure of Mountain [1]. The number of collected lymph nodes from each station was recorded for the different procedures, and the negative predictive values of mediastinal lymph node stations by SS were calculated.
Results: After SMLD, pN status was classified as N0 in 57 cases, N1 in 28, and N2 in 26. SS detected 38.2% of pooled nodes and 37.6% of pooled positive nodes collected from SMLD. Pathological diagnosis after SS was underrated in 9 cases (8.1%), compared to staging after SMLD. However, surgery was incomplete in 24 cases (21.6%) if SMLD was not performed after sampling. Negative predictive value for SS was 86.8% on the right side, and 95.1% on the left. Three categories were generated according to pN status: negative nodes in SS and additional negative nodes from SMLD (S(-)D(-)), negative nodes in SS but additional positive nodes from SMLD (S(-)D(+)), positive nodes in SS (S(+)D(+)). cN2 (p=0.001) and CEA level (p=0.000) were correlated with pN status. There was significant overall survival difference between non-N2 group and N2 group (p=0.003), but not between S(-)D(+) and S(+)D(+) in N2 subgroups (p=0.980).
Conclusion: SMLD may harvest about three times of mediastinal lymph nodes as compared to SS. SS is more likely to affect the completeness of surgery instead of underrating pathological stage.
Keyword: systematic mediastinal lymph node dissection; systematic sampling; self-controlled study

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P1.307 SURGICAL RESULTS OF SUPERIOR SULCUS TUMORS IN OUR INSTITUTE.

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Background: Superior sulcus tumors (SST) often has the anatomical limitations to complete resection. Recently, preoperative chemoradiotherapy showed to improve the rate of complete resection and its prognosis.
Methods: Clinical records of all patients operated on for superior sulcus tumors in Shikoku Cancer Center between 1993 and 2010 were reviewed retrospectively.
Results: Thirty-two patients (mean age 60, 30~79, 31 men and one woman) underwent thoracotomy on this period. All patients underwent lung and chest wall resection. Surgical approaches were as follows; posterolateral thoracotomy(n=28), combined transcervical and transthoracic approach(n= 4). Pathologic stage were IIB, IIIA, and IIIIB were in 20 cases, 5 cases, and 2 cases, respectively. Histology type were Squamous cell carcinoma, adenocarcinoma, large-cell carcinoma were in 14 cases, 11 cases, 7 cases, respectively. Resection was complete in 21 cases(66%). Operative mortality was 0 %. The overall 3-year and 5 year survival rate were 55%, and 43%, respectively. Five year survival was significantly higher after complete resection than

after incomplete resection(60% vs. 20%, p<0.02). The preoperative treatment improved the complete resection rate (surgery alone; 12/19, preoperative treatment; 10/13) . Age, tumor size and histology type did not affect on the survival outcome.
Conclusion: Superior sulcus tumor remains a severe illness, but long term survival can be achieved in the complete resection cases. The preoperative treatment improves complete resection rate, and may improve long term survival subsequently.
Keywords: Superior sulcus tumor, Surgery, Preoperative treatment

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P1.308 SURGICAL TREATMENT OF PULMONARY METASTASIS: OUR EXPERIENCE

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Background: Lung metastases from a primary extrapulmonary malignancy are often a manifestation of widespread dissemination; however, some patients have no other evidence of disease. Extensive experience with pulmonary metastasectomy in a number of different cancers has confirmed that resection can substantially prolong survival and cure some patients . Based upon these observations, aggressive resection of isolated pulmonary metastases has become a widely accepted treatment for appropriately selected patients. The surgical treatment of pulmonary metastases today represents a procedure of tried therapeutic effectiveness, with 5 years survival from the 20 to 40%. We retrospectively reviewed our experience of surgical treatment of pulmonary metastasis.
Methods: From 1995 to the 2010, in 165 patients we performed 205 surgical and curative resections of pulmonary metastases (40 of them were operated two times). The range of the free interval between the presentation of the primary tumor and that of metastases (DFI) was of 28,68 months (range:0-19 years). The age ranging was from 21-80 years (medium 50,1). We removed 319 metastases (medium 1,58; range: 1-7), confirmed by Histologycal examination. The size of the lesions was from 1 to 8 cm, (medium: 2,58 cm). The medium stay in hospital has been of 8,1 days (range 6-24), and were estimated also the post-operative pain and the complication (12,8%). The type of lung resection was wedge resection (53,7%), pneumotomy (38,5%), segmentectomy (4,9%), lobectomy (2,9%). After lung metastasectomy patients were followed up for 12-180 months (median. 65,8months).
Results: The DFI was of 8,74 months (range 0-27 months), while survival after metastases resection was of 24,37 months (range 2-10 years). Until today 53 patients are alive, medium follow-up of 65,8 months (range 12 months-15 years), and only one with disease recurrence. The 1 year survival was 76.2%, 3 years= 44.1%, 5 years= 28.3% and 10 years= 16,2%. We considered several prognostic factors: Histology, DFI, number of metastasis, number of resection, mono/bilaterality, type of resection and diameter of the metastases.
Conclusion: Resection of lung metastases has low mortality and morbidity and in our experience it correlated with prolonged postoperative survival. The surgery of the pulmonary metastases is today a valid treatment for patients at M1 stage, in good general and respiratory conditions and with an effective control of primary tumor.
Keywords: lung resection, pulmonary metastases

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P1.309 A NOVEL PARENCHYMA SAVING TECHNIQUE FOR THE RESECTION OF THE RIGHT TRACHEOBRONCHIAL ANGLE TUMORS

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Background: Resection of tracheobronchial angle tumors is one of the most complicated procedures in thoracic surgery. Tracheal sleeve pneumonectomy was generally the choice of resection in such tumors. Forming a new carina was first described by Barcley and double-barrel method was then described

by Mathey and collegues. Choosing the suitable technique of anastomosis can be challenging in cases with high-calibre mismatch. In this study, we present our experience of carinoplasty technique for such a difficult situation.
Methods: The cases with right tracheobronchial angle tumors operated in 2009 and 2010 are reviewed. A right upper sleeve lobectomy with hemicarinal resection and one-stoma type carinoplasty including the formation of a new carina is applied in all cases.
Results: Seven patients are operated in 18 months period. All patients had a complete resection. One early postoperative (30 days) mortality was seen. One patient had hemopthysis and bronchopleural fistula the operation, had a completion pneumonectomy and died at the tenth postoperative day. Two patients had atelectasis at the contralateral lung that needed bronchoschopy. Five patients are alive and disease free so far.
Conclusion: Resection of the right tracheobronchial angle tumors can be applied safely by saving the uneffected part of the ipsilateral lung by our techniqe . It is also more practical when compared to other previously described techniques .The one-stoma type of carinoplasty technique that we used can be performed to overcome the high-calibre mismatch.
Keywords: bronchoplasty, Lung cancer, Surgery

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P1.310 SQUAMOTOUS TYPE SARCOMATOID CARCINOMA OF THE LUNG WITH RHABDOMYOSARCOMATOUS COMPONENTS, A CASE REPORT.

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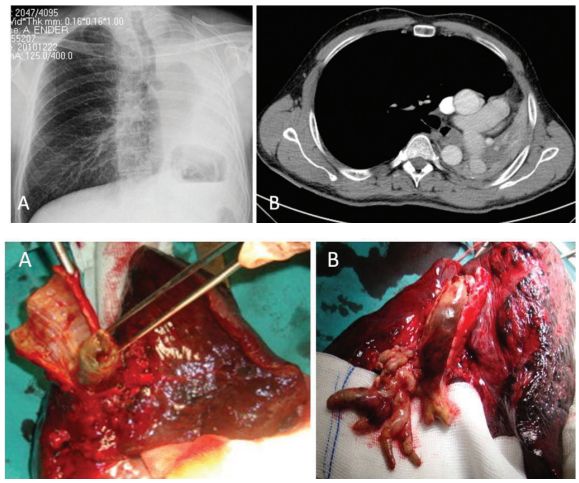
Background: Lung carcinosarcoma is an infrequently biphasic tumors composed of carcinomatous and sarcomatous components. It is divided into endobronchial (squamous type) and peripheral (glandular type) categories. The carcinomatous component is usually a squamous carcinoma, and the sarcomatous component usually resembles a fibrosarcoma or a malignant fibrous histiocytoma. The presence of rhabdomyoblastic differentiation in such neoplasms is exceedingly rare. There are strong associations with smoking and asbestosis.
Methods: In this study, we describe a unique case of sarcomatoid carcinoma in a 43 year old man who has smoked 75 pocket/year and in whom the sarcomatous component of the tumor was a rhabdomyosarcoma and the carcinomatous component was an squamous type.
Results: The patient underwent thoracotomy with left pneumonectomy. Histological examination of the resected specimen showed squamous cell carcinoma and rhabdomyosarcoma components.



Conclusion: The authors know of no previous report of a sarcomatoid carcinoma of the lung in which the carcinomatous component is a squamous.
Keyword: Lung carcinosarcoma, endobronchial type, rhabdomyosarcoma.

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P1.311 CLINICAL OUTCOMES OF THORACOSCOPIC LOBECTOMY

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Background: Many thoracic surgeons are now advocating the use of minimally invasive thoracoscopic surgery to perform lobectomies for early-stage primary NSCLC, with the objective of lessening postoperative morbidity while still providing a good oncologic outcome. This series is reviewed to assess these issues.

Methods: From 2008 to 2009, we performed 51 thoracoscopic lobectomies in 19 women (37,2%) and 32 men (62,8%), with a mean age of 55.3 years. All operated patients had clinical stage I or II of lung cancer. Right upper lobectomy met 14(27,5%), midell – 8(15,7%) and lower – 17(33,3%) from the total number of operated patients. Left completed 8(15,7%) lower and 4(7,8%) upper lobectomy. Of the primary lung cancers, 39 (76,5%) were adenocarcinoma. All patients with primary lung cancer performed hilar and mediastinal lymph node dissection. There are some discussions over approach to VATS. Some authors perform VATS using minithoracotomy in the beginning of an operation, whereas others prefer using exclusively 4-5 ports. In our research we have made minithoracotomy only for removal of a lung at the end of an operation.
Results: Thoracoscopic lobectomy and mediastinal lymph dissection was successfully performed in 47 patients (92,1%); 4(7,9%) patients required conversion to thoracotomy to control bleeding in the setting of dense hilar adenopathy. There were no intraoperative and perioperative deaths. Ð¡omplications included pneumonia - 4 patients and prolonged air leak - 2 patients. Median time to chest tube removal was 3 days, and median length of stay was 6 days.
Conclusion: Thoracoscopic lobectomy is safe and feasible for pulmonary resection. This minimally invasive approach may allow patients to benefit from lobectomy with shorter recovery times and hospital stays compared with conventional open thoracotomy.
Keyword: lung cancer, thoracoscopic lobectomy, clinical outcomes, surgry

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P1.312 CLINICAL EXAMINATION OF LARGE CELL LUNG CANCER

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Background: Lung cancer has been the most course of death in Japan. We choice the patients performed lung resection for the large cell lung cancer patients in our institute. In this study, we try to exam of clinical outcome of large cell lung cancer patients.
Methods: In 2004-2009, we performed lung resection for 422 primary lung cancer patients. In those patients, 16 cases were for large cell lung cancer.
Results: The range of age is 48-78 year old, the average is 67.2 year old. The each pathological stage of those patients were p-IA:1 case (6.3%), IB: 2 cases (12.5%), IIA: 3 cases (18.8%), IIB: 2 cases (12.5%), IIIA: 6 cases (37.5%), IIIB: 2 cases (12.5%). The performed operations were lobectomy for 10 cases (62.5%), bi-lobectomy for 2 cases (12.5%), pneumonectomy for 1 case (6.3%), partial resection for 3 cases (18.8%). Six patients of those 16 patients had any preoperative complication. Two patients had Chronic Obstructive Lung Disease (COLD), 2 patients had pneumoconiosis, 1 patient had Interstitial pneumonia (IP), 1 patient had heart failure. Four patients had postoperative complication. Two patients had prolonged thoracic effusion, 1 patient had pulmonary atelectasis, 1 patient had Acute Respiratory Distress Syndrome (ARDS) and died on 8 postoperative days. All 3 patients who were stage I that were fine without recurrence, but 5 patients of the 13 patients who were stage II or III that were died with primary disease.
Conclusion: The surgical treatment for large cell lung cancer patients is feasible for the case without lymph node metastasis. If lymph node metastasis is positive, patient has a poor prognosis.
Keywords: large cell lung cancer, Surgery

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P1.313 SURVIVAL ANALYSIS OF 171 PATIENTS WITH SURGICALLY RESECTED NON-SAMLL CELL LUNG CANCER

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Background: To summarize the treatment results of recentlly resected non-small cell lung cancer

(NSCLC), to investigate the prognostic factors for surgically treated NSCLC.
Methods: Survival analysis was conducted in 171 cases of resected NSCLC.
Results: Fifty-four cases of squamous cell carcinoma and 117 cases of adenocarcinoma of the lung received surgically resection. Hilar and mediastinal lymph tissues were systematically dissected; 884 groups with 1041 lymph nodes were dissected, averaged 5.2 groups/case, and 6.1 nodes/case; among them, 479 groups with 554 mediastinal lymph nodes were dissected, averaged 2.8 groups/case and 3.2 nodes/case. The rate of mediastinal lymph node metastasis is 20.9% (100/479), and the ratio of mediastinal lymph node metastasis is 21.5% (119/554). There are 47 N2 cases, 14 cases were found without N1 lymph node metastssis; the ratio of skip mediastinal lymph node metastasis is 29.8%. The 5-year survival rate for this group of resected NSCLC is 52.5%. Univariate analysis revealed that gender, age, smoking status, and tumor location, histology are not important prognostic factors, without statistically significant effects on survival (P>0.05); however, pathological stages (pTNM stages), tumor size (T factor), lymph nodes' metastasis (N factor), and postoperative adjuvant chemo-radiation therapy are important prognostic factors affecting the postoperative survival significantly (P<0.05). The 5-year survival rates in stage I, II, III were 68.4%, 50%, and 30.3%, respectively (P=0.000). Patients who received postoperative chemo-radiation therapy (49 cases) had a higher 5-year survival rate of 68.5% when compared with those who received surgery only but without adjuvant chemo-radiation (122 cases) whose 5-year survival was 46.2% (P=0.008). Cox proportion hazard model analysis revealed that pathological stages and postoperative chemo-radiation therapy are independent prognostic factors (P<0.05).
Conclusion: Pathological stages and postoperative chemo-radiation therapy are independent prognostic factors for resected NSCLC. Standardized systematic lymph node dissection should be performed to prevent cancer metastasis left, due to the relatively higher ratio of mediastinal lymph node metastasis and the higher ratio of skip mediastinal lymph node.
Keywords: Survival analysis, Mediastinal lymph node dissection, lung neoplasm, Non-small cell lung cancer

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P1.314 PULMONARY EMBOLISM AFTER PNEUMONECTOMY. WHICH PATIENTS ARE AT RISK?

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Background: Postoperative pulmonary embolism (PE) is a rare event in thoracic surgery (<1%). Few data are available on incidence, risk factors and clinical outcome of PE after pneumonectomy, in which an elevated mortality is expected. The aim of the study was to review a single-center experience in the management of this problem.
Methods: Clinical records of patients who underwent pneumonectomy in the period January 2005 – December 2010 were reviewed searching for cases of PE detected by CT scan, perfusion scan or autopsy. Patients were classed according to the type of pneumonectomy performed: standard pneumonectomy (group A), extended pneumonectomy (pneumonectomy associated with atrial, carinal, caval or chest wall resection and completion pneumonectomy, group B), extrapleural pneumonectomy for mediastinal tumors (group C) and pleuropneumonectomy (group D). PE was considered as outcome variable in univariate analysis testing all covariates as risk factors. Covariates considered clinically relevant or statistically significant were included in the multivariate model.
Results: In the considered period, 179 consecutive pneumonectomies were performed and 6 cases of PE occurred (overall incidence 3.3%). Two of them died early in the postoperative period and one died of cardiac arrest one month after discharge (overall mortality 50%). No case was recorded in group A and group B. Two cases were recorded in group C (9%) and both survived with medical treatment. After pleuro-pneumonectomy, four cases of PE occurred and three of them died. At univariate analysis, extrapleural dissection and diaphragmatic resection resulted as being significant risk factors for PE (p=0.0003 and 0.004 respectively). The role of both factors was confirmed at multivariate analysis.
Conclusion: Pulmonary embolism after pneumonectomy is three times more frequent than after lesser resection, with an overall mortality of 50%. Pneumonectomy requiring extrapleural dissection or complete diaphragm removal is at

higher risk of PE (12.5%) and should probably require a more aggressive anticoagulative prophylactic treatment.
Keywords: pneumonectomy, pulmonary embolism

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P1.315 CLINICAL EXAMINATION OF RECURRENT CASES AFTER LUNG SEGMENTECTOMY FOR PRIMARY LUNG CANCER

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Background: Recently, lung segmentectomy is popular operation for small peripheral primary lung cancer. However, the indication of lung segmentectomy for primary lung cancer is still controversial. So, we attempt to exam the outcome of lung segmentectomy for primary lung cancer patients in our institute.
Methods: In 2004-2010, 463 patients of primary lung cancer had lung resection. In those patients, 95 (20.5%) cases had lung segmentectomy. We choose those patients for study.
Results: Each segmentectomy performed right S1 segmentectomy for three cases, right S1+2 segmentectomy for one case, right S2 segmentectomy for four cases, right S2+3a for two cases, right S2+6 segmentectomy for one case, right S3 segmentectomy for three cases, right S7+8 segmentectomy for two cases, right S8 segmentectomy for one case, right basal segmentectomy for two cases. In the left side, left S1+2 segmentectomy for three cases, left linglar segmentectomy for 14 cases, left S4+5 segmentectomy for one case, left S6 segmentectomy for seven cases, left S8+9 segmentectomy for one case, left basal segmentectomy for two cases, left S9+10 segmentectomy for two cases. In those patients, recurrent cases were seven (7.4%). The local recurrence suspected in three cases of the seven recurrent cases after segmentectomy.
Conclusion: The segmentectomy for primary lung cancer is feasible surgical treatment for peripheral small lung cancer. However, there is a risk of recurrent in several percent in segmental resection for primary lung cancer, so the severe indicated selection for the segmentectomy is still important.
Keywords: segmentectomy, peripheral lung cancer

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P1.316 FACTORS AFFECTING THE PROGNOSIS AFTER RESECTION IN NON-SMALL CELL LUNG CANCER WITH CHEST WALL / PARIETAL PLEURA INVASION

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Background: Factors affecting the prognosis after resection in non-small cell lung cancer with chest wall / parietal pleura invasion
Methods: The primary treatment of non-small cell lung cancer with chest wall / parietal pleura invasion is un-block anatomic resection of chest wall and involved lung paranchima. In the study, it was aimed to evaluate the factors affecting the postoperative survival time in these patients.
Patients undergone to surgical treatment between June-1995 and June-2005, for NSCLC with chest wall / parietal pleura invasion were included. The demographic characteristics, preoperative symptoms, operative procedures, tumor cell type and diameter of tumor, lymph node involvement and stage of disease were assessed.
Results: There were 105 men and 2 women with an average age of 61,3 years. The mean follow-up was 26,5 months, the median survival was 37,0 months and 5 year survival was 42,8%. There were 101 complete and 6 incomplete resections, while 5 year survival was 34,2% and 2 year survival was 0%, respectively (p=0,001). 5 year survival was longer in tumors with a diameter lower than 3 cm, than those higher than 3 cm. Three independent prognostic factor were the diameter of tumor, type of resection and concurrent diseases. Operative mortality was 9,6%. Concurrent diseases and pneumonectomy were independent factors for operative mortality. The recurrence was 60,7%. Independent factors for occurrence of metastasis were neoadjuvant

therapy and type of resection. Factors not affecting the survival were age, extrapleural or chest wall dissection, histology and differentiation of tumor, chest wall or parietal pleura invasion, N stage, stage, neoadjuvant therapy, the presence of adjuvant therapy, method of adjuvant therapy and the width of chest wall resection.
Conclusion: The surgical resection in non-small cell lung carcinoma (NSCLC) with chest wall / parietal pleura invasion (T3) is an effective treatment. The absence of concurrent disease, small diameter of tumor and complete resection are the good prognostic factors.
Keywords: Lung cancer, Surgery, chest wall invasion

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P1.317 CLINICOPATHOLOGIC COMPARISON OF COMPUTED TOMOGRAPHY, POZITRON EMISSION TOMOGRAPHY AND MEDIASTINOSCOPY FOR MEDIASTINAL STAGING

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Background: The aim of this study; to determine the value of mediastinal lymph node metastases, to compare the concordance of clinical and pathological staging results and to evaluate of the cases with surgically treated primary non-small cell lung cancer (NSCLC).
Methods: The study included total 320 NSCLC patients (287 male, 33 female) that were evaluated CT and PET-CT between 2005 and 2011. The patients who underwent proven N2 or N3 diseases with mediastinoscopy and thoracotomy were included the study. Thorax computed tomography (CT) and PET-CT used to evaluate of clinical nodal staging. Involvement of mediastinal lymph nodes was verified to compare the sensitivity and specificity of mediastinoscopy and the related PET results. All the surgically removed tissue was examined histopathological study for pathologic staging.
Results: The most common type was squamous cell carcinoma in male (61.2%) and adenocarcinoma in female (75%). The mean age was 59.56 ± 9.35. Pooled PPV, NPV, sensitivities and specificities for staging the mediastinum were as follows: for CT scanning sensitivity 56%, specificity 75%, positive predictive value (PPV) 54%, negative predictive value (NPV) 77%; for PET-CT scanning: sensitivity 74%, specificity 76%, PPV 59%, NPV 87%. The accuracy of thorax CT was 69%, accuracy of PET-CT was 75% in the mediastinal lymph nodes. NPV of mediastinoscopy was 93%, PPV 100%, sensitivity 94%, specificity 100% and accuracy was 97%.
Conclusion: PET-CT results do not provide acceptable accuracy rates. Mediastinoscopy still remains the gold standart for mediastinal staging of NSCLC.
Keywords: Non-small cell lung cancer, PET-CT, Mediastinoscopy

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P1.318 RESECTION OF LOCALLY ADVANCED (PT4) NON-SMALL CELL LUNG CANCER INVADING CARDIAC STRUCTURES WITH CARDIOPULMONARY BYPASS

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Background: The data related to the treatment of locally advanced non-small cell lung cancer (NSCLC) requiring resection of cardiac structures are rather scarce. It is widely believed that locally advanced (T4) NSCLC is not a matter for surgical resection. The purpose of the study was to evaluate the benefit of surgery with cardiopulmonary bypass in such patients.
Methods: We retrospectively reviewed our prospective database of all 11 patients who underwent en bloc lung and heart resection for NSCLC between January 2003 and December 2010 by using cardiopulmonary bypass (CPB).
Results: The patient's age ranged from 46 to 71 years. IIIB stage was established in all 11 cases, pT4N0M0 in 3 cases, pT4N1M0 in 4, pT4N2M0 in 4 cases. Left atrium was resected in 9 of them. Both right and left atria were resected in 2 cases. In all patients the defect of atrial wall was repaired with bovine pericardial patch. Additionally vena cava superior was resected in 1 case, vena cava inferior-1,

truncus pulmonalis in 3 cases. Carinal resection was performed in 4 cases, resection of the aorta - in 2. Postoperative morbidity and mortality rates were 54,5 % and 36,4 %, respectively. Three of patients live five years or more. Two of them were staged as pT4N2M0.
Conclusion: Our results suggest that long term survival achievable in patients with locally advanced NSCLC invading cardiac structures even in N2 disease. CBP doesn't preclude long term survival in such patients.
Keywords: cardiopulmonary bypass, Locally advanced non-small cell lung cancer

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P1.319 THE VALUE OF METASTASIC LYMPH NODES RATIO(LNR) IN PREDICTING THE PROGNOSIS OF NON-SMALL CELL LUNG CANCER PATIENTS.

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Background: To investigate the relationship between metastatic lymph node ratio and prognosis of non-small cell lung cancer.
Methods: 301 patients with N1 and N2 NSCLC who underwent curative pulmonectomy were analyzed retrospectively. The correlations between LNR and clinical and pathological data were analyzed using χ^2 testing analysis. The influence of LNR on overall survival time(OS) and disease free survival time(DFS) of patients was identified with univariate Kaplan-Meier survival analysis and multivatiate Cox proportional hazard model analysis. The risk groups were classified by LNR associated with N stage.
Results: (1)LNR correlated with age, smoking status, pathological type, clinical stage and N stage($p<0.05$).(2)LNR correlated with positive lymph nodes, resected lymph nodes and the number of positive lymph node station($p<0.0001$) (3)Kaplan-Meier survival analysis identified that the LNR influenced significantly OS($p<0.0001$) and ($p<0.0001$),Cox proportional hazard model showed the high LNR was an independent poor prognostic factor for OS ($p<0.0001$, OR=2.7973, 95%CI 1.8917~4.1362)and DFS($p=0.0005$,OR=2.0857,95%CI 1.3820~3.1478); and in the same N stage, the low-LNR group is better than the high in OS and DFS;(4)Stratification into High-, Medium-, and Low-Risk groups, based on High- (LNR: >18%, N-status:N2) and Intermediate- (LNR: >18%, N-status:N1; LNR: <18%, N-status:N2), Low-Risk Factors (LNR: <18%, N-status:N1) efficiently predicted outcomes. The OS and DFS decreased along with the increase of the risk groups($p<0.0001$).
Conclusion: The LNR is a predictable factor which can help to accurate the prognosis and treatment of NSCLC, and improve TNM system for NSCLC.
Keywords: Carcinoma, Non-Small-Cell Lung Cancer, Lymph nodes, Lymphatic metastasis

Poster Session 1 – Surgery Monday, 4 July 2011 12:15-14:15

P1.320 VIDEO-ASSISTED THORACIC SURGERY REDUCES THE POSTOPERATIVE ACUTE EXACERBATION OF INTERSTITIAL PNEUMONIA COMBINED WITH LUNG CANCER

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Background: Postoperative acute exacerbation (AE) of interstitial pneumonia (IP) is a serious complication in the surgical treatment for primary lung cancer combined with IP. Once exacerbated, the prognosis is extremely poor. Meanwhile, we have constructed a new strategy for surgical resection of primary lung cancer, of which the complete video-assisted thoracic surgery (c-VATS, CV) is the basic surgery, and have decreased postoperative morbidity and mortality rate. We retrospectively reviewed consecutive patients who underwent lung surgery, either the conventional surgery or the new strategy, for lung cancer combined with IP.
Methods: 667 patients underwent the surgical lung resection for primary lung cancer at our hospital between January 2004 and December 2010.
We performed surgeries via conventional open thoracotomy (COT) in 267 cases from January 2004

to March 2007. 400 patients underwent surgical lung resection under the new strategy between April 2007 and December 2010.
We basically performed CV for primary lung cancer. We used 4 access-ports and monitoring vision only when performing either a lobectomy or others via CV. If performing CV was found difficult, we switched to the Hybrid VATS (HV) or the anterolateral thoracotomy (AT). We elongated the incision to 6 or 8 cm when performing HV and used a small rib-opener to allow for partial direct vision. We further elongated the incision to 10 or 12 cm on the anterolateral side of the trunk when performing AT. In the extensive case, we performed the regular thoracotomy (RT) from the outset using a posterolateral or a median sternal incision. We named this strategy CHART.
IP was diagnosed by a pulmonologist and a radiologist at our hospital, based on evaluation of preoperative CT images of patients. IP was classified into three patterns: IPF/UIP pattern, NSIP pattern and combined pulmonary fibrosis and emphysema (CPFE) pattern. We also analyzed other clinical data such as patient's background, hematological examinations, pulmonary function tests and operation-related factors.
Results: In COT group, 61 patients presented with IP (22.8%). 49 of them underwent major lung resection other than partial resection. Among them five patients showed the onset of postoperative AE (10.2%). Four of them were with IPF/UIP, and three died due to AE. On the other hand, four of 14 IPF/UIP patients (28.6%) went on to develop postoperative AE.
In CHART group, 68 patients presented with IP (17.0%). 48 of them underwent major lung resection other than partial resection. 37 patients underwent CV (77.1%). 3 patients underwent HV (6.3%). 5 patients underwent AT (10.4%). 3 patients underwent RT (6.3%).
Interestingly, no patients in this group developed postoperative AE.
In preoperative parameters that include gender, age, BMI, preceding diseases, and pulmonary function, there were not significant differences between COT group and CHART group. In perioperative parameters, infusion volumes, in/out balance and blood loss were significantly less in CHART group. Operation time was not significantly different between them. Postoperative CPK was significantly lower in CHART group.
Conclusion: Our results, though retrospective, suggest that VATS contributes to reduce the onset of postoperative AE of IP.
Keywords: Lung cancer, interstitial pneumonia, acute exacerbation, video-assisted thoracic surgery

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P1.321 NON-SMALL CELL LUNG CANCER INVADING THE SPINE: THE ROLE OF EN-BOC RESECTION

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Background: The aim of the study was to illustrate our surgical en-bloc approach and to evaluate the outcome and survival of non-small cell lung cancer (NSCLC) invading the spine.
Methods: All patients undergoing lung resection with en bloc hemivertebrectomy or total vertebrectomy for NSCLC were retrospectively reviewed from our prospective database of between January 2003 and December 2008 in an individualized multimodality treatment concept. Kaplan-Meier method was applied to estimate survival. Log-rank analyses were used for comparisons of two groups.
Results: Twenty-eight patients with NSCLC invading the spine (aged 58.9±12.9 years) were identified at a single center. Eight of those patients were inoperable at the time of diagnosis. Twenty patients underwent resection with en bloc hemivertebrectomy (n=16) or total vertebrectomy (n=4). Induction chemotherapy was given to 6 patients (30%). Complete resection rate (R0) was achieved in 16 patients (80%). Morbidity and mortality rates were 40% and 0%, respectively. Adjuvant radiation (n=14) or chemoradiation (n=6) were administered with 66Gy. The mean survival was 46.0 months. Five-year-survival for patients who underwent surgery (n=20) was 47%. Inoperability was associated with poorer survival

(14.0 months; p=0.004). Sublobar resections (p=0.002) and incomplete resections (p=0.02) were negative prognostificator. A trend towards prolonged survival were observed in patients with adjuvant chemoradiation (p=0.088), hemivertebrectomy (p=0.062) and age over 70 years (p=0.076), respectively.
Conclusion: En-bloc lung resections with hemivertebrectomy or total vertebrectomy offer promising long-term survival in highly selected patients with NSCLC invading the spine within multimodality treatment concepts. Acceptable morbidity and mortality can be achieved in these extended resections in specialized centers. Patients aged over 70 years should be selected very cautiously for surgery. Sublobar resections should be avoided whenever possible.
Keywords: NSCLC, Vertebrectomy, En-bloc resection, multimodality treatment

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P1.322 SLEEVE RESECTIONS IN CENTRALLY LOCATED NON-SMALL CELL LUNG CANCER AND ADVANCED NODAL DISEASE

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Background: The aim of this investigation was to contrast the short-term and long-term results of sleeve resections in centrally located non-small cell lung cancer (NSCLC) depending on limited nodal disease (N0/N1, LND) and advanced nodal disease (N2/N3, AND).
Methods: All NSCLC-patients undergoing sleeve resections for centrally located NSCLC were reviewed from our prospective database between January 1999 and December 2008. Patients' characteristics, morbidity, mortality, locoregional recurrence, distant recurrence and survival were analyzed corresponding to LND and AND.
Results: One-hundred seventy sleeve resections out of 213 consecutive sleeve resections were performed for ventrally located NSCLC (LND: n=120; AND: n=50). There were no statistically differences between the both groups for age (LND 61.8±12.4 vs. 60.8±9.6 years), gender, co-morbidities, type of sleeve resection (bronchial vs. bronchovascular), number of dissected lymph nodes (LND 40.0±12.4 vs. 36.7±14.0), histology and completeness of resection (LND 96.7% vs. 98.0%), respectively. More patients had induction chemotherapy in AND group (p=0.049). Similar short-term results were monitored with regard to morbidity rate (LND:34.2%, AND:44.0%), secondary pneumonectomy (LND:1.7%, AND:4.0%) and mortality rate (LND:5.0%, AND:6.0%), respectively. Better 5-year-survival rate and mean survival were observed in LND (LND:80.8 months; AND:37.7 months; p=0.014; LND:67%; AND:42%). In the long-term, more distant metastases were identified in AND group (26.0% vs. 14.2%, p=0.079) in comparison of identical locoregional recurrence (LND:1.7%; AND:0%). Mean time to the development of distant metastases was similar (LND:19.1 months; AND:12.4 months; p=0.2) in event of metastazing.
Conclusion: Lymph node involvement is a negative prognostificator with regard to long-term survival. Sleeve resections in AND are not associated with higher morbidity and mortality. Sleeve resections in AND are correlated with promising long-term survival and unexpected high local control of the disease as a result of high complete resection rates. Further investigation for the systemic control of the disease is warranted because of high rates of distant failure.
Keywords: NSCLC, Stage IIIA, Stage IIIb, Sleeve resection

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P1.323 COMPARISON OF THE SURVIVALS OF THE SUBGROUPS OF STAGE IIA ACCORDING TO NEW TNM STAGING

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Background: In this study, the survivals of the subgroups of stage IIA according to new TNM staging are analyzed and evaluated.

Methods: The medical records and the follow-up data of the patients operated for non-small cell lung cancer between January 2005 and December 2009 is analyzed retrospectively. The pateints are staged according to the new TNM staging. The survival data of 78 patients with tumors of T2bN0M0 (n=48), T1aN1M0 (n=9), T1bN1M0 (n=5), T2aN1M0 (n=16) which forms the subgroups of stage IIA according to new TNM staging are compared.
Results: There is no statistically significant survival difference between the subgroups of the stage IIA according to new TNM staging.
Conclusion: The subgroups of the stage IIA of the new TNM staging for non-small cell lung cancer forms an homogenious group by means of survival for operated patients.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P1.324 THE EFFECT OF THE NUMBER OF LYMPH NODES DISSECTED ON SURVIVAL IN OPERATED N0 NON-SMALL CELL LUNG CANCER PATIENTS

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Background: In this study, the effect of the number of lymph nodes dissected on survival in operated N0 non-small cell lung cancer patients is investigated.
Methods: The medical records and the follow-up data of the patients operated for non-small cell lung cancer between January 2005 and December 2009 is analyzed retrospectively. One hundered-forty-one patients without neoadjuvant treatment which were applied lobectomy or pneumonectomy and mediastinal lymph node dissection with pathological stage T1aN0M0 (n=35), stage T1bN0M0 (n=33) and stage T2aN0M0 (n=73) (stage I according to new TNM staging) are included in the study. The significance between the total number of dissected lymp nodes from both N1 and N2 stations and the survival of the patients are evaluated. The patients are also devided into two groups: group A included the patients having less than nine lymph nodes dissected where group B included the patients with nine or more dissected nodes and the survival of the two groups are also compared.
Results: The survival decreases as the total number of lymphy nodes dissected decreases. The survival is lower in the group having less than nine total number of lymph nodes dissected and both of the results are statistically significant ($p<0.05$).
Conclusion: The number of lymph nodes dissected effects the survival even in N0 patients in non-small cell lung cancer. The surgeons must show every effort to dissect as much lymph nodes as they can during lung cancer surgery.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P1.325 DOES NEOADJUVANT THERAPY AFFECT MORTALITY AND MORBIDITY IN PATIENTS WHO UNDERWENT SLEEVE RESECTION FOR LUNG CANCER?

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Background: Sleeve resections enable the preservation of lung parenchyma for patients with benign or malignant tumors. Neoadjuvant therapy have a potential impact on the results of lung resections. The aim of the study was to assess the outcome after neoadjuvant therapy and sleeve resection in patients with non-small cell lung cancer (NSCLC).
Methods: Between 2000 and 2011, 91 patients with NSCLC who underwent sleeve resections were retrospectively investigated. The patients was subdivided into two groups; Group R underwent a sleeve resection without preoperative therapy [n = 76] and Group NR received neoadjuvant therapy before sleeve resection [n = 15]. The two groups were compared with respect to the demographic data

and clinical outcomes.
Results: The type of resections performed were 81 sleeve lobectomies or bilobectomies (in 16 patients with pulmonary artery reconstruction), 4 sleeve lobectomies with carinal resection and 6 sleeve pneumonectomies. The overall surgical mortality (in hospital or 30-days) was 4.3% (n = 4) and more common in R group compared to NR group (5.2% vs 0%, p = 0.369). The incidence of complication was 28.9% (22 of 76) with 9.2% (7 of 76) anastomosis-related complications (bronchopleural fistula = 6; bronchovascular fistula = 1) in the R group. In the NR group the complication rate was 26.7% (4 of 15) without any anastomosis-related problems. Five-year survival in the R group was 53.7% compared with 43.1% in the NR group (p = 0.426).
Conclusion: Neoadjuvant therapy did not increase anastomosis-related complications and mortality in patients with sleeve resection and achieved comparable survival rates
Keywords: Lung cancer, Surgical treatment, Sleeve resections, Neoadjuvant Therapy

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P1.326 AGE-RELATED RISK ASSESSMENT FOR LUNG CANCER SURGERY IN ELDERLY PATIENTS

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Background: The elderly population is heterogeneous, ranging from healthy seniors with no disability and few comorbidities to frail seniors who are disabled and have multiple comorbidities. This makes the assessment and management of this population challenging, especially when deciding on cancer treatment modalities. The purpose of the present study was to identify preoperative risk factors related to age of the patients focusing on comorbidities.
Methods: Retrospective review of the clinical records of all patients operated on thoracic department in 2000-2003. A comparison was carried out between patients with lung cancer 70 years and older (38 patients), and younger lung cancer patients (44patients) who underwent curative open operation. The influence of comorbidity (cardiac, pulmonary, second primary cancer, anemia, diabetes mellitus etc) in postoperative complication were also analyzed. None of the patient received preoperative chemo and/or-radiotherapy. Type of surgery, histology type of tumors was compared in both groups.
Results: No significant difference was observed in the comorbidities between elderly and young patients. The 30-day operative mortality rates were 6.25% in elderly population, postoperative morbidity was - 40.0% - significantly higer in elderly lung cancer population (p0.05).
Conclusion: Elderly patients undergoing curative surgery for lung cancer have a higher risk of developing postoperative complications, but mortality rates is equal to younger population. Age or the presence of comorbidity should not be considered contraindications for lung resection. Additional functional evaluation is indicated in specific subgroup of elderly lung cancer patients.
Keywords: elderly patients, Lung cancer, comorbidities

Poster Session 1 – Surgery Monday, 4 July 2011 12:15-14:15

P1.327 SINGLE CENTRE COMPARISON OF THORACOSCORE AND EUROPEAN SOCIETY OUTCOME SCORE IN THE SURGICAL RESECTION OF NON-SMALL CELL LUNG CANCER

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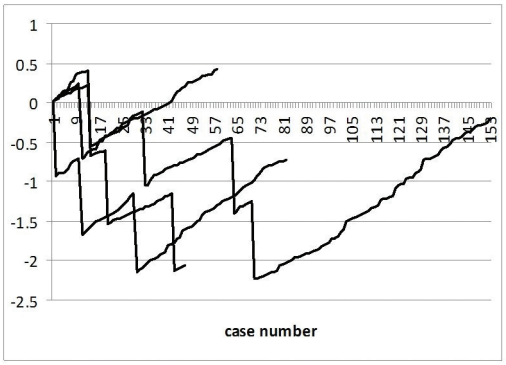
Background: Calculation of risk scores, such as Thoracoscore (TS) and the European Society Outcome Score (ESOS), have been proposed as a useful aid to determine operative outcome in thoracic surgery. The role of risk scores in assessing primary lung cancer surgery quality outcomes related to the surgeon, including later outcomes, is not clear, nor how the TS and ESOS compare.
Methods: Data were collected prospectively on 482 consecutive patients undergoing lung resection for primary non-small-cell lung cancer from Aug 2007 – Mar 2010. ESOS and TS were calculated retrospectively. The correlation between ESOS

and TS was analysed. Differences between four consultant surgeons and survival outcomes were assessed.

Results: Both TS and ESOS were calculated in 340 patients. TS could not be calculated from available data in 120 cases and ESOS in 48: these were excluded from further analysis. There was a significant correlation between TS and ESOS ($r= 0.527$, $p<0.001$), although there were notable outliers. In those cases with scores above the median for both ESOS and TS, this correlation was lost. Median TS was 1.97 (range 0.26 to 12.6), the mean 2.48 (standard deviation 1.93). Median ESOS was 2.18 (0.29-7.36), the mean 2.44 (SD 1.33). The observed in-hospital mortality was 11 patients (3.2%). There were no significant differences in the mean TS and ESOS of patients undergoing surgery by different surgeons. Variable Life Adjusted Display analysis showed that both scores underestimated actual in-hospital mortality (VLAD value -2.7 for ESOS and -2.82 for TS). Surgeon-specific VLAD plots demonstrated the differences in outcome between surgeons.



Conclusion: There was a positive correlation between TS and ESOS, although this was lost at higher values. Both TS and ESOS under-predicted mortality. Further work with co-ordination between centres is required to determine the accuracy of TS and ESOS in predicting mortality and its potential use as a measure of quality of service provision.

Keywords: Thoracoscore, Risk Stratification, lung resection

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P1.328 CLINICAL ANALYSIS OF THE CHARACTERISTICS OF THORACIC LYMPH NODES METASTASIS PATTERNS WITH NON-SMALL CELL LUNG CANCER

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Background: Lymph node metastasis is not only one of the most common and main means of the lung cancer's transfer, but also is one of the important factors which affects the lung cancer' T stage and the prognosis. The aim of this study is to investigate the characteristics and patterns of lymph node metastasis in non-small cell lung cancer and to provide evidence for determining the range of lymph node dissection.

Methods: Combined with systematic lymph node dissection according to the grouping system proposed by Naruke 218 patients with non-small cell lung cancer underwent lobectomy or pneumoectomy in our hospital were retrospectively analyzed, Compare the thoracic lymph nodes Metastasis Patterns of different clinical T stage, pathological type and the different initial locations .

Results: A total of 3509 lymph nodes were dissected from 1308 group s of 218 patients, there were 16.1 group s on the average in each case.623 lymph nodes from 283 groups were confirmed to have metastasis. The metastasis rates of thoracic lymph nodes were 47.5%. There was close correlation between lymph node metastasis and T stage. The metastasis rate of adenocarcinoma was much higher than that of squamous cell carcinoma ($P<0.01$). Mediastinal lymph nodes metastasis was used to uppermediastinum from upper lobe cancer, while both upper and lower mediastinums were the metastasis sites for lower lobe cancers (including middle lobe).

Conclusion: The frequency of lymph node metastasis significantly correlate with size of primary tumor , T stage, initial location and pathological type. It is necessary to perform systemic lymphadenectomy during pulmonary resection.

Keyword: Thoracic Lymph Nodes；Clinical Analysis；NSCLC; Lymphadenectomy

Poster Session 1 – Surgery Monday, 4 July 2011 12:15-14:15

P1.329 UTILITY AND FEASIBILITY OF PURE VATS LOBECTOMY BY USING BIPOLAR SCISSORS THROUGH FLEXIBLE THORACOSCOPE

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Background: To evaluate utility and feasibility of our techniques of VATS lobectomy using bipolar scissors under monitor-view through flexible thoracoscope retrospectively. Especially, we would like to show utility and feasibility of our methods.
Methods: From April 2003, we performed VATS lobectomy via a pure thoracoscope view (Pure VATS) in 120 cases with cStageIA non-small cell lung cancer (NSCLC). The operative field of the view was accessed strictly via a monitor, thus avoiding spreading intercostal space. A flexible thoracoscope, which can contribute more resolved view, was inserted through the seventh or eighth intercostal space. A 2 to 4 cm minithoracotomy was made by cutting only intercostal muscle as same as the skin incision (2 to 4 cm) without the use of a rib spreader. The mini-thoracotomy and three other 0.5 to 1.0 cm ports were added. The operator usually placed on the front of the patients and mini-thoracotomy wound enabled the operator's right hand to hold the bipolar scissors which was useful for cutting, coagulating and dissecting without switching instruments. The operator's left hand was usually holding pick-up through 5mm port. Systematic mediastinal lymph node dissection was performed by means of an enlarged clear view in the same extent as the conventional open thoracotomy. Only difference of the technical maneuver from the conventional open thoracotomy was the direction of operator's eyes to the monitor.
Results: Average operation time, bleeding count and length of hospital stay were 220 minutes, 105 g, and 7.2 days, respectively. Only required painkiller for postthoracotomy pain was suppository diclofenac sodium, which was 11.0 mg on average within one week. Five cases (4.1%) were converted to the conventional thoracotomy. Postoperative complication was seen in 10 cases (8.3%), e.g., prolonged air leakage in three cases. Port recurrence was not seen . One case (0.8%) was died of cerebral infarction within 30 days. As to learning curve of this surgical technique, operation time and bleeding count were gradually reduced within the experience of 20-30 case for each surgeon, and then both indicators reached the plateau. Four young surgeons newly learned and completed this procedure until now.
Conclusion: Pure VATS lobectomy using bipolar scissors through flexible scope is useful, reasonable and feasible for cStageIA NSCLC.
Keyword: lung cancer, VATS lobectomy

Session P2: Poster Session 2

Tuesday, 5 July 2011

Poster Session 2 – Preclinical Models Tuesday, 5 July 2011 12:15-14:00

P2.001 REDUCTION OF THE METASTATIC ACTIVITY OF HYPOXIC LUNG CANCERS AND POTENTIATION OF CHEMOTHERAPY IN VITRO AND IN VIVO USING CYTOKINE.

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Background: Integrins expressed by tumor cells are strongly implicated in various cell functions including those promoting metastasis (invasion, migration, adherence, and survival) and have also been linked to chemoresistance. Our recent study demonstrated that hypoxia significantly increases the expression of several integrins at the cell surface of lung cancer cells. In this study, we describe a new anti-cancer role for cytokine we show that our cytokine markedly inhibits the expression of aVb5, aVb3, and b1 integrins on lung cancer cells both in normoxia and in hypoxia, inhibits metastases and invasion, and chemosensitise lung cancer cells in vitro and in vivo.
Methods: The effects of our cytokine on integrins expression in hypoxia and normoxia was investigated using a proliferation, adhesion, invasion, migration, 3D matrigel and colony assays and lung cancer cell lines. The modulation chemoresistance

to Mitomycin, Docetaxel and Doxorubicin by our cytokine on these cells was investigated in vitro and in a xenograft model of lung cancer.
Results: Our phenotypic and functional studies revealed the anti-invasion and anti-metastatic activity of our cytokine on lung cancer cells as treated cancer cells lose their ability to adhere, proliferate, migrate, invade, form colonies, and are significantly less efficient at infiltrating the lungs in vivo. 2-We also demonstrate that this cytokine significantly increases the efficacy of Mitomycin-C, Doxorubicin, and Docetaxel on resistant cancer cells both in vitro (normoxia and in hypoxia) and in vivo.
Conclusion: We propose to combine immunotherapy with currently used low efficient chemotherapeutic agents to potentiate their antitumor efficiency for the treatment of chemoresistant tumors. This would allow the use of lower doses of chemotherapy, and consequently prevents their associated side effects and toxicity. Such combined therapies would efficiently eradicate primary and metastatic resistant lung cancers.
Keyword: Lung cancer, hypoxia , combined chemotherapy

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P2.002 TARGETING MUTANT P53 IN NON-SMALL CELL LUNG CANCER WITH PRIMA-1

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Background: The tumor suppressor protein p53 is a key regulator of cell cycle control, apoptosis, and genomic stability in response to various cellular stresses. Restoration of p53 function in tumors is a potential approach for lung cancer therapy because p53 mutations are found in more than 50% of lung cancers. The small molecule PRIMA-1 (p53-dependent reactivation and induction of massive apoptosis) has been shown to restore the tumor suppression function of p53 and to induce apoptosis in human tumor cells containing mutant p53. This is believed to be mediated by a change in the conformation of mutated p53 protein, restoring DNA binding and activation of p53 target genes.
Methods: We investigated the potential use of the PRIMA-1 in treatment of lung cancers. Human lung cancer cell lines containing mutant (H211, H1155), wild type (A549) or null (H1299) p53 were analyzed with Western immunoblot analysis, TaqMan microRNA Real-Time PCR, MTT and flow cytometry for apoptosis. To evaluate feasibility and preliminary activity of PRIMA-1 on spontaneous lung tumors in vivo, we tested PRIMA-1 in our previously described transgenic mouse lung tumor model in which the human mutant p53(273H) is expressed in a lung specific manner, under the control of the surfactant protein C promoter. We treated the mutant p53 lung tumor bearing mice with PRIMA-1 at a dose of 100 mg/kg every other day for two weeks. Lung tumor bearing mice were identified with a micro–computed tomography (micro-CT) system and pre- and post-treatment tumor volumes were estimated based on the micro-CT images.
Results: PRIMA-1 induced apoptosis in the H211 and H1155 cells, but was less toxic to the A549 and H1299 cells. Western blot analysis showed cleavage of PARP (poly [ADP-ribose] polymerase) in H211 and H1155 cells following treatment of PRIMA-1. In contrast, no cleavage of PARP was observed in the A549 and H1299 cells. TaqMan microRNA assay showed that the expression of microRNA 34a was increased in the H211 and H1155 cells post treatment, whereas no significant increase was found in the A549 and H1299 cells. In addition, five lung tumor bearing mice received the PRIMA-1, and a control group of 4 lung tumor mice received PBS every other day for two weeks. A repeat CT scan was obtained the week after the last treatment. In the control group tumor volume increased more than 25% during the treatment cycle in all cases. However, in treated mice, tumor volume increased more than 25% in one mouse, and decreased less than 50% in two mice, with a more than 50% reduction in two mice.
Conclusion: The above results suggest that PRIMA-1 is a highly selective small molecule toxic to p53 mutant cells in vitro and in vivo which could serve as a prototype for the development of effective systemic p53-targeting agents. The study on animal lung tumors suggests the potential feasibility of using p53 restoring activity small molecules to treat lung cancer.
Keywords: PRIMA-1, p53 mutation, Non-small cell lung cancer

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P2.003 A NOVEL PRIMARY CULTURE SYSTEM OF CANCER CELLS FROM LUNG CANCER PATIENTS

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Background: Primary culture of cancer cells has been expected to be useful for investigating biology of lung cancer or predicting chemosensitivity for individual patients, although it is hampered by the technical difficulties up to the present. Recently, we established a novel primary culture system for colorectal cancer.
Methods: Surgical specimens were mechanically and enzymatically digested into fragments. These fragments (organoids) spontaneously formed spheroids. We named the spheroid as CTOS (cancer tissue-originated spheroid). CTOS consisted of pure epithelial cells without trace of the host cells, including fibroblasts, endotherial cells, macrophages, and other blood cells. CTOSs were able to be prepared in high efficiency. The cancer cells in CTOS were stable only when the cell-cell contact was maintained. CTOS was able to be cultured and propagated in vitro, and formed xenograft tumors in immunodeficient mice. The characters of the original patient tumors, including morphology, KRAS mutations, and p53 staining pattern was preserved in the xenograft tumors. Here we applied the method to the lung cancer.
Results: We obtained CTOS from 54 out of 72 (75.0%) non-small cell lung cancer (NSCLC) patients. CTOSs consisted of pure epithelial cells, were stable in the spheroid form, able to be expanded in vitro. The tumors in immunodeficient mice preserved the characters of the original patient tumors. We performed chemosensitivity assay using CTOS in vitro and in vivo. Sensitivity for CDDP or erlotinib was differed among patients. The results of the in vitro assay were in parallel with those of the treatment of the mice with corresponding xenograft tumors. In addition, change of pathway activation can be analysed with CTOS for molecular targeted reagents, such as erlotinib. We obtained CTOS from the tumors with or without EGFR active mutations, and examined the effect of erlotinib treatment on intracellular signal transduction. Phosphorylation of EGFR was high in the CTOSs with active EGFR mutations even in the starvation culture conditions. Erlotinib was able to diminish the phosphorylation of EGFR. In terms of the intracellular signalling, phosophorylation of AKT was observed in the EGFR mutants in the starvation conditions, while AKT was activated only after treatment with EGF in the CTOSs with wild type EGFR. Downregulation of AKT phosphorylation by erlotinib was well correlated with the sensitivity of CTOSs to the drug.
Conclusion: Accessing the intracellular signalling from patient tumor samples might be useful for predicting sensitivity of molecular targeting drugs for individual patients, and give an excellent platform for investigating the mechanism of resistance to these drugs.
Keywords: chemosensitivity, primary culture, Non-small cell lung cancer

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P2.004 62CUATSM AND 62CUPTSM PET IS A USEFUL IMAGING TOOL FOR HYPOXIA AND PERFUSION IN LUNG CANCER

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Background: Hypoxia is a characteristic of many tumors and portends a worse prognosis in several tumor types including lung, cervical, prostate, and rectal cancers. Unlike cervical, prostate, and rectal malignancies, lung cancers present a unique challenge in measuring hypoxia, given difficulty of invasive biopsies and rate of post-biopsy complications. Noninvasive imaging studies detecting hypoxia using isotopes of copper-diacetyl-bis (N4-methylthiosemicarbazone), CuATSM, have predicted prognosis and treatment outcomes in a few small feasibility cervical cancer and lung cancer trials. Although PET scans imaging hypoxia are helpful, these images may not identify all the areas of hypoxia. Hence, we hypothesize that

another PET imaging agent, copper-pyruvaldehyde-bis(N4-methylthiosemicarbazone), ^{62}CuPTSM, can detect areas of perfusion, which would augment the information obtained in ^{62}CuATSM PET scans.
Methods: In order to characterize tumors based on both perfusion and hypoxia, we have studied ten patients with localized or advanced lung cancer using both novel ^{62}CuATSM and ^{62}CuPTSM PET scans. In addition, proteomic arrays looking at specific targets important for proangiogenic, survival, and proinflammatory responses were assessed.
Results: Our initial experience of characterizing lung cancer hypoxia using ^{62}CuATSM and ^{62}CuPTSM PET scans showed that with kinetic analysis of the ^{62}CuATSM and ^{62}CuPTSM scans, visualization of areas with hypoxia and perfusion is feasible. Within this patient group, all tumors exhibited some degree of hypoxia. Despite the small sample size, a positive relationship was noted between VEGF and sFLT-1 levels and noninvasive ^{62}CuATSM and ^{62}CuPTSM PET imaging.
Conclusion: This initial series of the ^{62}CuATSM and ^{62}CuPTSM PET scans demonstrate that evaluating localized or advanced lung cancer by visualization of hypoxia and perfusion is feasible and noninvasive. The novelty of having both perfusion and hypoxia imaging markers allows for more comprehensive analysis of these tumors. This imaging modality, along with future proteomics analysis, could potentially be useful as biomarkers for lung cancer treatment and prognosis. Further investigation will be undertaken to assess the potential role of ^{62}CuATSM and ^{62}CuPTSM PET imaging techniques combined with proteomics as alternatives to invasive biopsy techniques in routine clinical care.
Keywords: PET imaging, Perfusion, Lung cancer, Hypoxia

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P2.005 THE ANTICANCER EFFECT OF HISTONE DEACETYLASE INHIBITORS AND COMBINATION WITH THE CYTOTOXIC AGENTS IN LUNG CANCER CELLS: BIOLOGICAL ANALYSES FOR FUTURE CLINICAL APPLICATION

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Background: It is consequently desirable to find more appropriate therapeutic opportunities for NSCLC. Recently, molecularly targeted therapy for cancer has made substantial progress. HDAC inhibitors, including suberoylanilide hydroxamic acid (SAHA), have demonstrated therapeutic benefits as monotherapy in hematologic, breast, and bladder malignancies, as well as mesothelioma and NSCLC, without evidence of severe adverse events. Recently, it has been demonstrated that combinations of HDAC inhibitors with well-established chemotherapeutic agents have synergistic antitumor effects via the modulation of biomarkers by HDAC inhibitors. We clarified the predictive markers to select patients receiving this treatment and found a new strategy against lung cancer by using S-1, a novel oral fluorouracil anticancer drug for clinical use against NSCLC in Japan.
Methods: To assess the potential for HDAC-inhibitor-based treatment in NSCLC, we analyzed the antitumor effects of trichostatin A (TSA) and SAHA (vorinostat) in a panel of 16 NSCLC cell lines via MTT assay. To identify a molecular model of sensitivity to HDAC inhibitor treatment in NSCLC, we conducted a gene expression profiling study with cDNA arrays on the same set of cell lines and related the cytotoxic activity of TSA to corresponding gene expression patterns by means of a modified NCI program and pathway analysis.
Using the MTT assay, we analyzed the growth-inhibitory effect of 5-FU/S-1 and SAHA against lung cancer cells. The mRNA and protein expressions of Thymidylate synthase (TS), Dihydropyrimidine dehydrogenase (DPD) and Orotate phosphoribosyltransferase (OPRT), which are metabolites of 5-FU, were analyzed in these cells. In order to clarify the mechanism of the synergistic effect of SAHA and 5-FU, we examined the change of the 5-FU metabolism expressions and their regulator including p21waf1/cip1 and Rb-E2F1 pathway.
Results: There was a strong correlation between the responsiveness to TSA and SAHA ($P<0.0001$). We used 9 genes including PDCD4 to regulate p21 waf1/cip1 activity, which were identified with gene-drug sensitivity correlation and pathway analysis, to build a support vector machine algorithm model, by which

sensitive cell lines were distinguished from resistant cell lines.
Combined treatment with low-dosage SAHA enhanced 5-FU/S-1 mediated cytoxicity and the synegistic effect in 5-FU-resistant cells. 5-Fluorouracil-resistant lung cancer cells displayed high expression of TS mRNA and protein. SAHA down-regulated TS mRNA and protein expression, as well as repressed the rapid induction of this factor during 5-FU treatment, in all examined cell types, also examined the status of the Rb-E2F1 pathway, with SAHA up-regulating p21waf1/cip1 expression via promoter histone acetylation; this, in turn, blocked the Rb-E2F1 pathway.
Conclusion: In conclusion, our results suggest that HDAC inhibitors may be promising anticancer drugs for NSCLC and that the 9-gene classifier is useful for predicting the sensitivity of NSCLCs to HDAC inhibitors and may contribute to achieving individualized therapy for patients with NSCLC. SAHA enhanced S-1 sensitivity in lung cancer cells, and this combination therapy may be effective against lung cancer.
Keywords: SAHA, HDAC, NSCLC, S-1

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P2.006 GDC-0449, A HEDGEHOG (HH) PATHWAY INHIBITOR CAN ATTENUATE EPITHELIAL MESENCHYMAL TRANSITION (EMT) PHENOTYPE IN NON-SMALL CELL LUNG CANCER (NSCLC) CELLS LINES AND CAN ENHANCE THE EFFECTS OF ERLOTINIB AND CISPLATIN.

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Background: EMT, characterized by low E-cadherin, has been proposed as a mechanism for tumor invasion, metastases and resistance to therapeutic agents in many cancers, including NSCLC. The Hh pathway may play a role in inducing EMT. An important ligand of the pathway is Sonic hedgehog (Shh). GDC-0449, an inhibitor of Hh pathway, has shown promising activity in tumors with activated Hh pathway such as basal cell carcinoma.
Methods: We assessed the effects of GDC-0449 (20 nM) and down regulation of Shh via siRNA on the EMT features of A549-M (A549 cells exposed to TGF-β1 for 21 days) and of H1299 cell line, which is known to have EMT features. Assessment included the effects on the mRNA levels of E-cadherin and Zeb1 a regulator of EMT, clonogenic growth (colony formation assay), cell motility (wound healing assay) and invasion (matrigel assay) and the influence on the activity of erlotinib and cisplatin in these cell lines (MTT assay).
Results: A549-M cells had significantly higher rate of clonogenic growth, cell motility and invasion compared to A549 cells and showed higher resistance to erlotinib and cisplatin. A549-M cells had higher mRNA levels of Shh and Zeb1 and reduced levels of E-cadherin than A549 cells. GDC-0449 reduced clonogenic growth, cell motility and invasion of A549-M and H1299 cells and reduced the mRNA levels of Zeb1 and increased the levels of E-cadherin in both cell lines. Pre-treatment with GDC-0449 significantly enhanced the activity of erlotinib (5 and 10 mM) and cisplatin (1mM-10mM) in both cell lines ($p < 0.05$). Similar results were observed in each of the cell lines with down regulation of Shh by siRNA.
Conclusion: GDC-0449, a hedgehog inhibitor can attenuate EMT features in NSCLC cell lines. It can also enhance the activity of erlotinib and cisplatin in NSCLC cell lines that are intrinsically resistant to these agents.
Keyword: EMT and hedgehog and GDC-0449

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P2.007 COMPARISON OF POTENTIAL VALUES OF HYALURONIC ACID AND VASCULAR ENDOTHELIAL GROWTH FACTOR IN THE PLEURAL FLUID OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive neoplasm strongly

associated with asbestos exposure, primarily arising from the surface serosal cells of the pleura. Patients with MPM often develop pleural fluid as initial presentation. However, cytological diagnosis with the pleural fluid is usually difficult and has limited utility. Useful molecular marker for the diagnosis especially is urgently needed. The aim of the present study is to compare the clinical value of hyaluronic acid (HA) and vascular endothelial growth factor (VEGF) in the pleural fluid of MPM.
Methods: Pleural fluids were collected from 47 patients with MPM, 65 with lung cancer (LC), 57 with benign asbestos pleurisy (BAP), and 37 with other pleural diseases (others). HA and VEGF concentrations were determined. All data were analyzed by using non-parametric two-sided statistical tests.
Results: The median concentrations of HA in MPM, LC, BAP, and others were 67900 (range, 7920-2630000), 19500 (2880-147000), 27300 (900-118000), and 23000 (2690-108000)ng/mL, respectively. HA concentration was significantly higher in MPM than in other groups (P=0.001). The area under the ROC curve (AUC) values of MPM diagnosis was 0.795 for differential diagnosis from other groups. The median concentration of VEGF in MPM, LC, BAP, and others were 321.9 (range, 13.5-2222.7), 286.6 (15.6-2221.0), 457.7 (23.3-2222.7), and 209.6 (26.6-1321.7)ng/mL, respectively. VEGF concentration was significantly higher in MPM than in others (P=0.031), but it demonstrated no difference between MPM and LC or BAP. HA was higher in earlier clinical stages (I and II) than in advanced stages (III and IV)(P=0.011); otherwise, VEGF was higher in the advanced stages (P=0.043). HA was higher in epithelioid subtype of MPM than in sarcomatoid subtype (P=0.033); otherwise, VEGF tended to be higher in sarcomatoid subtype than in epithelioid subtypes (P=0.094). VEGF value in the sarcomatoid subtype of MPM was significantly higher than in LC (P=0.019).
Conclusion: HA and VEGF in the pleural fluid of MPM demonstrated different features. HA seems to be more useful for the differential diagnosis of MPM with other diseases than VEGF. VEGF might be useful as a diagnostic marker for sarcomatoid subtype of MPM.
Keywords: mesothelioma, asbestos, VEGF, hyaluronic acid

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P2.008 ADENOSINE AND A2B ADENOSINE RECEPTOR IN REGULATION OF TUMOR-INFILTRATING MYELOID CELLS

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Background: Adenosine, a naturally occurring nucleotide, exerts its biological effects by interacting with a family of adenosine receptors A1, A2A, A2B, and A3 all associated with important physiological processes. The endogenous adenine nucleotides and adenosine are normally present at low concentrations in the extracellular milieu. However, metabolically stressful conditions, including inflammation and hypoxia characteristic for solid tumors, result in dramatic increase in extracellular concentrations of adenosine. Our data demonstrate that adenosine signaling through adenosine receptor A2B strongly modulates differentiation and function of tumor-infiltrating myeloid cells.
Methods: Using in vitro cell culture model, we investigated the effects of adenosine and A2B adenosine receptor signaling on differentiation and function of dendritic cells and CD11b+Gr1+ myeloid cells. The role of host A2B receptor in the regulation of recruitment and function of tumor-infiltrating immune cells was examined in mouse tumor model experiments.
Results: Stimulation of A2B adenosine receptor skews dendritic cell (DC) differentiation diverting them from normal immune protective phenotype toward less mature immune suppressive DCs with pro-angiogenic and tumor-growth promoting properties both in vitro and in vivo. We have also identified adenosine as an important metabolite that induces generation and tumor recruitment of myeloid derived suppressor cells (MDSC) via activation of A2B receptor. Significantly higher proportion of CD11b+Gr1high cells was generated in vitro from hematopoietic progenitors in the presence of adenosine, which mostly induced generation of Ly-6G+CD11b+Gr1high cells. Adenosine differentially regulated production of arginase, iNOS, and reactive oxygen species (ROS) in subsets

of CD11b+Gr1+ cells. CD11b+Gr1high cells isolated from mouse tumors or generated in vitro expressed predominantly A2B and A2A receptors. The key feature of these cells was high expression of 5'-nucleotidase/CD73 that converts AMP into adenosine. The ability of CD11b+Gr1high cells to produce adenosine from AMP presents a novel mechanism of immune suppression by MDSC: upon interaction with T cells CD11b+Gr1high MDSC generate adenosine from AMP present at high levels in inflamed tumor tissue, the generated adenosine inhibits T cell proliferation and function via activation of A2A receptor expressed on T lymphocytes. There were significantly higher numbers of CD11b+Gr1high MDSC in tumors of wild type mice compared to A2B-/- knockout animals, thus indicating the role of A2B receptor in their generation and tumor accumulation. Tumor-bearing A2B-/- knockout mice exhibited significantly attenuated tumor growth and longer survival compared to wild type controls. Tumors in these mice contained significantly lower levels of VEGF and displayed decreased vascular density compared to tumors growing in wild type animals. **Conclusion:** Adenosine is an important metabolite increased in solid tumors; its secretion benefits tumor by inducing tumor immune infiltrate to produce factors that promote tumor angiogenesis and suppress anti-tumor immunity. A2B receptor is a primary mediator of the adverse effects of adenosine on tumor-infiltrating myeloid cells. Given the profound effect that adenosine signaling through A2B receptor has on differentiation and cytokine secretion of tumor infiltrating immune cells as well as tumor growth and vascularization, it is conceivable that the A2B adenosine receptor might be an important therapeutic target in cancer. This receptor is an especially attractive target for therapy, as due to its low affinity to adenosine it stays silent under normal conditions and becomes active only at pathologically high adenosine levels.

Keywords: Adenosine, A2B adenosine receptor, Cancer, Immune infiltrate

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P2.009 5-AZA-2'-DEOXYCYTIDINE/ VALPROATE COMBINATION INDUCES CTL RESPONSE AGAINST MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor of the pleura, usually associated with chronic asbestos exposure. MPM treatments include chemotherapy, radiotherapy and surgery, but are of limited efficacy, urging the development of new therapeutic strategies. Numerous preclinical and clinical studies have proved that epigenetic drugs have a potent anti-cancer activity and promising therapeutic potential. The aim of this study was to evaluate the anticancer effect of a DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (5-azaCdR), and two histone deacetylase inhibitors, valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA).
Methods: Human mesothelioma cell lines, derived from pleural effusions, were treated with each epigenetic drug, either alone or in combinations. The cytotoxic effects on treated cells, and the expression of specific tumor antigens, were evaluated. The recognition of treated cells by a specific CD8+ T-cell clone was also measured. Additionally, the effect of combined treatments was tested in a murine model of mesothelioma.
Results: We showed that VPA and SAHA synergized with 5-azaCdR to kill MPM cells and to induce tumor antigen expression (such as NY-ESO-1, MAGE-A1 and MAGE-A3) in the remaining living tumor cells. As a consequence, tumor cells expressing these antigens were recognized and lysed by specific CD8+ cytotoxic T-cells. In vivo, treatment with 5-azaCdR/VPA inhibited tumor growth and promoted lymphocyte infiltration and an immune response against tumor cells.
Conclusion: Appropriate epigenetic drug combinations, in addition to inducing mesothelioma cell death, also affect the immunogenic status of these cells. This property could be exploited in clinical investigations to develop MPM treatments combining chemotherapeutic and immunotherapeutic approaches.

Keywords: immunotherapy, mesothelioma, epigenetic drugs, tumor antigen

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P2.010 PHARMACOLOGICAL CHARACTERIZATION OF A HISTONE DEACETYLASE INHIBITOR AND TUMOR CELL-GROWTH INHIBITION PROPERTIES OF NEW BENZOFURANONE COMPOUNDS.

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Background: Epigenetic modifications, such as DNA methylation or histone acetylation, are early events in cell tumorigenesis. The consequences of these modifications are repression of gene transcription and, notably, of tumor suppressor gene transcription. New therapeutic strategies aim to normalize the epigenetic status of cancer cells. Histone deacetylase inhibitors (HDACi) have shown promising effects against proliferation and resistance to apoptosis of a large number of cancer cells. Vorinostat, a hydroxamate HDACi, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of refractory cutaneous T-cell lymphoma (CTCL). However, HDACi are poorly specific, present toxicities and many have very low half-lives in the plasma. Thus, the development of new compounds is necessary in order to increase the potential of HDACi in cancer treatment.
Methods: We designed an assay, based on bioluminescence resonance energy transfer (BRET) technology, to screen and characterize HDACi activity in living cells. Using our specific and reproducible BRET assay, we characterized the pharmacological properties of a benzofuranone HDACi for the induction of histone acetylation and performed a comparison with the properties of suberoylanilide hydroxamic acid (SAHA) and valproic acid (VPA). Evaluation of cancer cells growth inhibition by HDACi was evaluated using viable cell counting reagent.
Results: We defined a benzofuranone HDACi compound that induced histone acetylation at nanomolar concentrations and showed an increased duration of histone acetylation. These properties correlated with the pharmacological properties of this HDACi for the growth inhibition of cancer cells.
Conclusion: We, thus, demonstrated the applicability of BRET technology for the screening and characterization of new HDACi compounds in living cells, and identified a very interesting benzafuranone HDACi.
Keywords: Cancer, HDAC inhibitors, BRET

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P2.011 AN IMMUNOCOMPETENT ORTHOTOPIC MOUSE MODEL OF MALIGNANT PLEURAL MESOTHELIOMA PERMITS PLEURAL TUMOR IMMUNE MICROENVIRONMENT CHARACTERIZATION AND INTRAPLEURAL INTERLEUKIN-12 THERAPY

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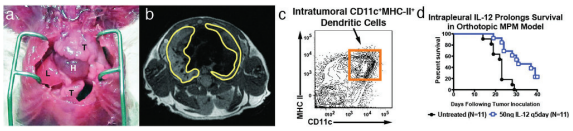
Background: Malignant pleural mesothelioma (MPM) is a regionally aggressive disease localized to the pleura. Pre-clinical immunotherapy in mouse MPM models provide the basis for immunomodulation of the tumor microenvironment and are typically performed in heterotopic flank or peritoneal tumor models. To better recapitulate and characterize pleural tumor immune cell infiltration and assess intrapleural therapy, we seek to establish an orthotopic MPM mouse model.
Methods: BALB/c mice were intrapleurally inoculated with AB12 (murine mesothelioma) and assessed for tumor burden by MRI tumor volume averaging. To determine the biokinetics of intrapleural therapy, mice were intravenously or intrapleurally injected with recombinant murine interleukin-12 (0-100ng rmIL-12) and serial serum rmIL-12 levels were measured. Pleural tumor-bearing mice were treated with intrapleural rmIL-12 (0,10, 50ng) and monitored for survival. Tumors were examined for immune cell infiltration by

immunohistochemistry (IHC) and flow cytometry (FCM).
Results: In this immunocompetent, orthotopic, MPM model, gross pleural disease resembling human MPM is first detectable within 7-14 days by MRI (encasing the heart, lungs, and diaphragm; Figure 1a and b). Mice succumb to disease in 20-30 days (median survival 23 days). IHC confirmed pleural tumor immune cell infiltration of T lymphocytes, tumor-associated neutrophils, and tumor-associated macrophages. Harvested pleural tumors revealed cells associated with immunostimulation (dendritic cells, helper and cytotoxic T cells) and immunosuppression (regulatory T cells, tumor-associated macrophages, myeloid-derived suppressor cells) by FCM (Figure 1c). Intrapleural rmIL-12 resulted in 4-fold lower systemic rmIL-12 levels when compared to intravenous dosing one hour after administration. Furthermore, repeated intrapleural injections of rmIL-12 result in prolonged survival (31 vs. 23 days, n=22, p=0.0003; Figure 1d).



Conclusion: Our immunocompetent, orthotopic, murine MPM model resembling human disease facilitates (a) non-invasive tumor burden imaging, (b) harvesting pleural tumor to characterize tumor-associated immune cells, (c) multiple intrapleural injections, and (d) intrapleural therapy. Our preliminary results suggest that intrapleural rmIL-12 therapy increases survival in this MPM mouse model.
Keywords: mesothelioma, Orthotopic Immunocompetent Mouse Model, Tumor/Immune Microenvironment, Pleural therapy

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P2.012 ONCOLYTIC ACTIVITY OF COXSACKIEVIRUS A21 IN HUMAN LUNG CANCER: A NOVEL TARGETED ANTI-CANCER STRATEGY.

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Background: Oncolytic virotherapy is a novel targeted therapeutic approach that utilises direct tumour lysis and generation of secondary anti-tumour immune responses. Coxsackievirus A21 (CVA21) is a naturally occurring "common cold" virus that within pre-clinical studies displays both in vitro and in vivo oncolytic activity across a wide spectrum of cancers. Natural infection by CVA21 is usually self-limiting within the upper respiratory tract. CVA21 targets human cancerous cells by binding to the N-terminal domain of surface expressed human intercellular adhesion molecule-1 (ICAM-1). Subsequent infection, viral replication and rapid cytolysis of the targeted cell results in systemic release of progeny virus. ICAM-1 is highly expressed on the surface of numerous human cancers including lung, pancreatic, breast, prostate, head/neck cancer and melanoma. ICAM-1 expression levels often correlate with the degree of metastatic spread of the malignancy. CAVATAK™ is the name of a proprietary formulation of Coxsackievirus A21 and it is currently being evaluated in Phase I trials in patients with late stage melanoma, prostate cancer, breast cancer and recurrent Head/Neck cancer.
Methods: In vitro cultures of NSCLC (n=3) and SCLC (n=2) lines were assessed for surface ICAM-1 expression levels and for relative susceptibility to challenge by varying input multiplicities of CVA21. To assess the oncolytic capacity of CVA21 in vivo, human NSCLC cancer xenografts were propagated as subcutaneous flank tumours in SCID Balb/C mice and administered the CVA21 viral formulation (~10^8 $TCID_{50}$) via a single intratumoural injection.
Results: Moderate to high levels cell surface ICAM-1 expression were observed following flow cytometric analysis of a panel of both human NSCLC and SCLC in vitro cultures. High lCAM-1 expressing NSCLC and SCLC cells displayed significant susceptibility to rapid multi-cycle replication and cell cytolysis following in vitro challenge with CVA21. Intratumoural injection of a single dose of CVA21 in subcutaneous xenografts of the NSCLC line H157 in SCID Balb/C mice resulted in rapid cancer cell destruction and subsequent reductions in tumour burden. The viral-mediated oncolysis of the H157 xenografts was accompanied by the release of progeny virus as observed by increases in the systemic load of infectious CVA21.
Conclusion: Coxsackievirus A21 displays significant pre-clinical oncolytic activity against human lung cancer cells both within in vitro and in vivo environments. The presented pre-clinical

findings establish proof of concept for the potential application of oncolytic virotherapy with CVA21 as a novel targeted anti-lung cancer therapeutic within the clinical environment.
Keywords: Viral oncolysis, Coxsackievirus A21, Virotherapy

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P2.013 ANTITUMOR ACTIVITY OF MEK INHIBITORS IN HUMAN LUNG CANCER CELLS WITH ACQUIRED RESISTANCE TO DIFFERENT TYROSINE KINASE INHIBITORS AND WITH EPITHELIAL TO MESENCHYMAL TRANSITION

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Background: Despite impressive clinical successes with different kinase-targeted therapies, most cancer patients with an initially responsive disease eventually experience relapse as a result of acquired drug resistance to these agents. The aim of the present work was to examine the cellular alterations and the molecular mechanisms which are correlated with acquired resistance induced by four different TKIs, such as erlotinib, gefitinib, vandetanib and sorafenib.
Methods: An in vitro model of acquired resistance to these TKIs was developed by continuously treating the human lung adenocarcinoma cell line CALU-3 with escalating doses of each drug. Tascritional profiling was performed with Agilent whole genome microarrays.Western blot, MTT, ELISA,migration, invasion and anchorage-independent colony growth assays were conducted in vitro and in vivo in sensitive (WT) and TKI-resistant CALU-3 cell lines.
Results: As compared to WT CALU-3 cells, in TKI-resistant CALU-3 cell lines a significant increase in the expression of activated, phosphorylated MET, IGF-1R, AKT, MEK, MAPK, and of survivin was observed. Down-regulation of E-cadherin and amphiregulin mRNAs and up-regulation of vimentin, VE-cadherin, HIF-1a and VEGFR-1 mRNAs were observed in all four TKI-resistant CALU-3 cell lines. All four TKI-resistant CALU-3 cells showed increased invasion, migration and anchorage-independent growth. Together, these data suggest epithelial to mesenchymal transition (EMT) in TKI-resistant CALU-3 cells. Treatment with several agents which target AKT, MET or IGF-1R did not affect TKI-resistant CALU-3 cell proliferation.
In contrast, treatment with MSC19363669B and selumetinib, two selective MEK inhibitors, caused inhibition of cell proliferation, invasion, migration, anchorage-independent growth in vitro and of tumor growth in vivo of all four TKI-resistant CALU-3 cell lines.
Conclusion: data suggest that resistance to four different TKIs is characterized by EMT, which is MEK-inhibitor sensitive in human CALU-3 lung adenocarcinoma.
Keywords: acquired resistance, EMT, Lung cancer, erlotinib

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P2.014 RECOMBINANT HUMAN ENDOSTATIN NORMALIZES TUMOR VASCULATURE AND ALLEVIATES HYPOXIA IN LEWIS LUNG CARCINOMAS

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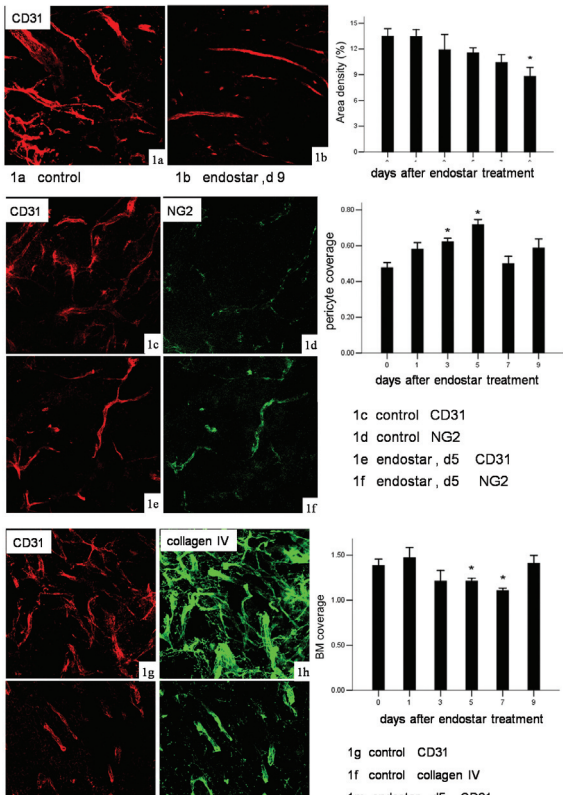
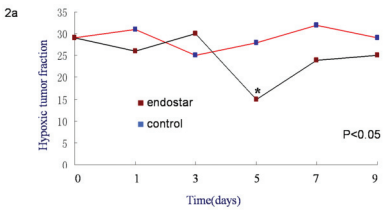
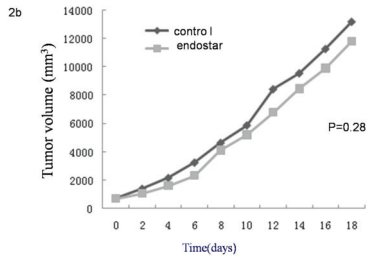
Background: Tumor vessels are structurally and functionally abnormal with defective endothelium, pericyte coverage, and basement membrane. Most antiangiogenic cancer therapies focus on the destruction of solid tumors by eradication of their supporting vasculature. However, antiangiogenic therapy may "normalize" the tumor vasculature for a short period of time, thereby providing a window of opportunity for enhanced sensitivity to radiation treatment.We investigated whether recombinant human endostatin created a "vascular normalization window" within tumors prior to vascular pruning to alleviate hypoxia in Lewis lung carcinomas in mice.
Methods: (1)Kinetic changes in morphology of tumor vasculature in response to treatment with recombinant human endostatin were detected under

a confocal microscope with immunofluorescent staining in Lewis lung carcinomas in mice.(2)The time course of hypoxic tumor fraction was assessed with immunohistochemical staining.(3)Effects on tumor growth were monitored as indicated in the growth curve of tumors.

Results: Vascularity of the tumors was reduced over time by recombinant human endostatin treatment and significantly regressed for 9 days relative to the control group (Fig 1a-b). During recombinant human endostatin treatment, pericyte coverage increased by day3, increased markedly by day 5, and fell again by day 7 (Fig 1c-f). The vascular basement membrane (BM) was thin and closely associated with endothelial cells after recombinant human endostatin treatment, but appeared thickened, loosely associated with endothelial cells in control tumors (Fig 1g-n). The decrease in hypoxic tumor fraction on the 5th day after treatment was also found (Fig 2a). Tumor growth was not accelerated 5 days after recombinant human endostatin treatment (Fig 2b).







Conclusion: Recombinant human endostatin can normalize tumor vasculature within day 3 to 7, leading to improved tumor oxygenation. The results provide important experimental basis for combining recombinant human endostatin with radiation therapy in human tumors.

Keywords: endostatin, tumor vascular normalization, Radiation Therapy, anti-angiogenesis

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Poster Session 2 – Preclinical Models Tuesday, 5 July 2011 12:15-14:00

P2.015 ONCOLYTIC ACTIVITY OF MEASLES VIRUS AGAINST MESOTHELIOMA AND LUNG CANCER: POTENTIAL ROLE OF HSP70, CALRETICULIN AND HMGB1 IMMUNOGENIC MOLECULES

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Background: Cancer virotherapy has recently emerged as a hopeful alternative therapeutic strategy in the aim of better responding to the diversity of cancerous pathologies. It is based on the preferential tropism of certain viruses for tumor cells; such property is exhibited naturally by an attenuated vaccine strain of measles virus (MV). We

previously showed that MV was able to efficiently infect and kill mesothelioma tumor cells. Infected mesothelioma cells were able to induce spontaneous maturation of dendritic cells and subsequently to prime cancer antigen-specific T CD8 response.Thus, danger signals are probably expressed after measles vaccine infection of the cancer cells. These signals would be involved in the immunogenic properties of such oncolytic strategy.

Methods: Meso11, Meso13, Meso47, Meso56, Meso96 epithelioid mesothelioma cell lines and ADK3, ADK117, ADK153 lung adenocarcinoma cell lines were established and characterized in our laboratory from pleural effusion collected by thoracocentesis of cancer patients with their informed consent. A549 lung adenocarcinoma cell line and MSO-1 normal mesothelial cells were purchased from tebu-bio (Le Perray-en-Yvelines, France). All cell lines were exposed to Measles vaccine infections, performed at MOI=1.0 for 2 hours at 37°C. Cell death was determined 3 days after infection using Apoptosis Detection Kit.Three days after infection, tumor cells were analyzed for intracellular HSP70expression, membrane bound calreticulin (flow cytometry), and HMGB1 release into cell supernatant (ELISA)

Results: We found that MV infection ofis specific for cancer cells but not on healthy ones. The MV vaccine demonstrated oncolytic properties and induced an immunogenic apoptosis. The dead cells are associated with synthesis of HSP70, translocation of calreticulin to cell surface and release of HMGB1 in these cells lines in vitro.

We also demonstrated that MV exhibited comparable properties in vivo against human mesothelioma and lung cancer xenografts.

Conclusion: These molecules are expected to play an essential role in the activation of the adaptive immune response by acting on dendritic cells that spontaneously matured after having been co-cultured with MV-infected tumor cells. The immune side of cancer virotherapy remains poorly documented, but it opens exciting outlooks in order to combine direct viral oncolysis with long-term protection by enhancing a potential cancer-specific immune memory. Specific targeting of CD46 complement regulatory protein would also offer an alternative approach to complement-based strategies against tumor cells resistant to complement.

Keywords: oncolytic properties, mesothelioma, lung adenocarcinoma, measles vaccine

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P2.016 COMBINATION THERAPY WITH VORINOSTAT AND ADENOVIRUS-FASL IN LUNG CANCER CELL LINES

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Background: FasL (CD95L), a membrane protein of TNF family, induces strong apoptosis in cancer cells by binding with Fas receptor. Systemic toxicities of FasL limit the clinical use for cancer therapy. To avoid the systemic toxicities of FasL, we performed adenoviral gene therapy of FasL with vorinostat that can enhance the adenoviral transduction and its transcription in lung cancer cell lines.

Methods: Adenovirus expressing FasL (ad-FasL) was replication-defective by E1 deletion and driven by CMV promoter. Vorinostat (SAHA), a HDAC inhibitor, was provided by Merck. Production of FasL from lung cancer cell lines was measured by ELISA kit after transduction of ad-FasL along with vorinostat. The interaction of ad-FasL and vorinostat was analyzed by Calcusyn software. The effects of ad-FasL and vorinostat on apoptotic pathway were analyzed by NF-κB assay and Western blot assay for apoptosis related proteins.

Results: Transduction with ad-FasL produced FasL from lung cancer cells and the addition of vorinostat increased FasL production by 10 fold. Strong synergism of ad-FasL and vorinostat in antitumor effect was found in all lung cancer cell lines tested. Cells showing early apoptotic change were significantly increased by combining ad-FasL and vorinostat. Addition of vorinostat effectively suppressed NF-κB activation induced by ad-FasL. Enhanced phosphorylation of Akt, increased cleavage of caspase-3 and PARP and suppression of antiapoptotic molecucle, Bcl-2 were found by combining ad-FasL and vorinostat in lung cancer cell lines.

Conclusion: Combination of ad-FasL and vorinsostat showed a strong synergistic interaction on antitumor activity. This synergistic interaction was mediated by enhanced FasL production and enhanced induction of apoptosis.

Keywords: adenovirus, FasL, Vorinostat, gene therapy

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P2.017 MODULATION OF PRO-SURVIVAL AND PRO-APOPTOTIC SIGNALING IN NON-SMALL CELL LUNG CANCER (NSCLC) BY 22β-HYDROXYOLEANONIC ACID.

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Background: Lung cancer is the leading cause of cancer-related deaths all over the world. Prevailing treatment options have limited therapeutic success in lung cancer, particularly non-small cell lung cancer (NSCLC), as it becomes resistant to therapy. Hence, better therapeutic options are immediately required for lung cancer. 22β-hydroxyoleanonic acid is a semisynthetic triterpenoid, which is synthesized from pentacyclic triterpenoid Lantadene A and been recently examined for its anticancer effect on different cancers
Methods: To determine the anticancer effect of 22β-hydroxyoleanonic acid on NSCLC cell lines H460 and A549, cell viability, apoptotic, Western blot and reporter assays were performed.
Results: 22β-hydroxyoleanonic acid significantly inhibited the growth of H460 cells compared to A549 cells and down-regulated the expression of EGFR/Neu and its downstream signaling (Akt, NF-ϰB, Bcl-2 and survivin) in H460 cells. In addition, 22β-hydroxyoleanonic acid up-regulated the expression of p53 and p21 causing cell cycle arrest in the G_2/M-phase by down-regulating G_2/M regulatory proteins (cyclinB1 and Cdc25B) in H460 cells. Furthermore, it activated the JNK/p38 signaling, leading to caspase-3 activation resulting in the induction of apoptosis.
Conclusion: 22β-hydroxyoleanonic acid exerted anticancer activity on NSCLC cells by modulating the pro-survival and pro-apoptotic signaling that causes induction of apoptosis.
Keywords: apoptosis, cyclinB1 and Cdc25B, JNK/p38 signaling

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P2.018 RGD-LIPOSOMES: PROSPEROUS CHEMOTHERAPY DRUG CARRIERS EXERTING ANTITUMOR EFFECT VIA TWO WAYS

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Background: Angiogenesis is crucially required for solid tumor growth and metastasis, tumor vasculature has been considered to be an ideal target for cancer treatment. Arg-Gly-Asp (RGD) containing peptides with high affinity to av-integrins are promising ligands for the generation of vascular targeting agents. RGD containing peptides themselves were reported had the ability of tumor growth inhibition by blocking the angiogenesis pathway. Liposomes have been proved to be good drug-delivery systems because of their property of safety, biocompatibility and biodegradability. They were FDA approved and available for cancer treatment. In present study, a kind of RGD containing lipopeptide was conjugated to the surface of stealth liposomes for the purpose of developing active targeted antitumor drug carriers to inhibit tumor growth via both peptides themselves and the loaded drugs.
Methods: A 12-mer peptide containing a cyclic RGD sequence was selected to be the targeting molecular, which was coupled with a KGG-palmitic acid conjugate to make up a kind of lipopeptide. Lipids, cholesterol and the lipopeptide were then mixed together in chloroform to prepare RGD-liposomes with thin-film hydration method. RGD-paclitaxel liposomes were also prepared in the same way. Cell growth inhibitory study and scratch migration experiment were performed to access the toxicity of the RGD containing peptide. The IC50 value and cellular uptake of RGD-paclitaxel liposomes were determined to confirm the peptide mediated cellular internalization.
Results: While cultivated in the media supplemented with 400 200μmol/L RGD containing peptide 72h, the growth rate of A549 (a human lung carcinoma

cell line) cells and human umbilical vein endothelial cells (HUVEC) were reduced 37.3% and 43.3% individually. RGD-paclitaxel liposomes exhibited the greatest cytotoxicity than conventional marketed paclitaxel (Taxol) and non-targeted paclitaxel liposomes. Reduced migration ability was observed in both cell lines after 24h incubation in media containing RGD-paclitaxel liposomes than Taxol or non-targeted paclitaxel liposomes. The IC50 value of Taxol, paclitaxel liposomes and RGD-paclitaxel liposomes were 6.03mg/mL, 3.37mg/mL, 1.46mg/mL individually in A549 cells(P 0.05) and 6.56mg/mL, 4.56mg/mL, 3.40mg/mL individually in HUVEC(P 0.05). Cellular uptake of liposomal paclitaxel was higher than that of Taxol. Moreover, RGD-paclitaxel liposomes showed a 1.5-fold increase in uptake in A549 cells and a 2-fold increase in uptake in HUVEC (P 0.05) than non-targeted paclitaxel liposomes.

Conclusion: RGD-paclitaxel liposomes could exert strengthened antitumor effect both by blocking the integrin pathway and targeting delivery of paclitaxel. RGD based strategy could be used to enhance antitumor effect of chemotherapy drugs encapsulated in nanocarriers.

Keyword: targeted liposomes

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P2.019 BERRY ANTHOCYANIDINS SYNERGISTICALLY SUPPRESSES NON-SMALL-CELL LUNG CANCER CELL GROWTH AND METASTASIS AND ENHANCES SENSITIVITY TO THE CHEMOTHERAPEUTIC DRUG PACLITAXEL

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Background: Lung cancer still continues to represent the largest cause of cancer mortality, thus making the search for new anti-cancer agents imperative for their use in cancer therapy and/or as adjuvants to existing chemotherapeutic options. Lately, berry anthocyanidins (delphinidin, cyanidin, malvidin, peonidin and petunidin) have received increasing attention for their anticancer effects. While these anthocyanidins have been tested individually, their combinatorial effects as a mixture (as present in blueberry, bilberry and Indian blackberry Jamun) has not been explored. Also, their use as adjunctive therapeutic agents is largely unknown. In this study we assessed the effect of these anthocyanidins and their mixture to inhibit the proliferation and metastasis of a highly aggressive NSCLC cells. Furthermore, their ability to sensitize the NSCLC cells to conventional chemotherapeutic drug paclitaxel was also explored.

Methods: The H1299 cell line, established from a metastatic lung cancer, was treated in vitro with individual anthocyanidins and their equimolar mixture and cell viability, cell cycle progression, apoptosis and cell migration was measured through standard assays. Western blot and miRNA analysis were employed for the determination of the molecular targets. In-vivo anti-tumor effects of the most potent anthocyanidin, delphinidin and the anthocyanidin mixture, isolated from black currant and bilberry, respectively were also determined using nude mouse xenograft model. Finally, chemosensitizing effects of the anthocyanidin mixture were assessed by measuring cell viability after treatment of cells with anthocyanidin mixture in combination with paclitaxel.

Results: We demonstrate that all the five anthocyanidins resulted in inhibition of H1299 cell proliferation and migration, however, an equimolar mixture of all five at lower concentrations elicited significantly higher antiproliferative and antimetastatic effects, indicating synergism. The induction of cell cycle arrest and apoptosis was also significantly greater with the mixture than either agent alone. Notably, both the mixture of anthocyanidins and the most potent anthocyanidin delphinidin reduced the H1299 tumor xenograft growth by ~ 60%; however, the effective dose of anthocyanidin mixture (0.5 mg/dose) was 3-times lower than delphinidin (1.5 mg/dose) further emphasizing synergism. The superior antiproliferative and apoptotic effects of the combinatorial treatment seemed to result from attack on different or overlapping molecular targets associated with cell proliferation, apoptosis and metastasis viz the oncogenic NOTCH1, WNT1, c-myc, cyclin D1 and cyclin B1 proteins, the cell survival kinase pERK and the metastatic mediators MMP9 and VEGF. All this was coupled with

enhanced cleavage of the antiapoptotic molecule Bcl2 and PARP protein. The anthocyanidin mixture also induced the expression of four miRNAs (miR-126, miR125a-5p, miR200c and miR-34a) frequently downregulated in NSCLC and implicated in lung cancer growth, metastasis and chemoresistance. Additionally, the combination of low concentrations of anthocyanidins (1:1 mixture) was sufficient to induce 50 percent growth inhibition and enhanced apoptosis in combination with low dose Paclitaxel (1 nM), thus reducing the IC50 dose of paclitaxel by 5-8 folds.

Conclusion: Our results suggests that increased consumption of bilberry, blueberry, or Indian blackberry (jamun) rich in this mixture of anthocyanidins would be useful for the prevention/ treatment of NSCLC or as adjuvants to enhance the effects of existing chemotherapeutic options.

Keywords: Growth & Metastasis, Lung cancer, Anthocyanidins, Chemotherapeutic Adjuvant

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P2.020 EVALUATION OF THE FIBROBLAST GROWTH FACTOR RECEPTOR AXIS AS POTENTIAL THERAPY TARGET IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy with poor outcome and limited therapeutic options. Fibroblast growth factors (FGF) and their receptors have been identified as potential therapy targets in several tumor types but have not been systematically investigated in MPM so far. Aim of the present investigation was to provide a systematic analysis of the expressed FGF as well as FGFR molecules in MPM and to investigate the impact of blocking FGFR-mediated signals with genetic constructs and specific tyrosine kinase inhibitors on MPM cell growth and signalling pathways.

Methods: Expression of FGF/FGFR molecules was screened by qRT PCR in MPM cell lines (n=10) and one normal mesothelial cell line. FGFR inhibition was achieved with FGFR-specific tyrosine kinase inhibitors and by adenoviral transduction with dominant-negative FGFR constructs fused to green-fluorescence protein (dnFGFR1). The impact of inhibition and stimulation of FGF/FGFR molecules was investigated by MTT and clonogenic assays as well as by spheroid formation assays and videomicroscopy. The effect on downstream signal transduction was assessed by immunoblotting with phosphorylation site-specific antibodies. In addition, potentially additive or synergistic antineoplastic activity of FGFR1 inhibitors in combination with clinically applied chemotherapeutics and other targeted drugs against MPM were evaluated.

Results: Expression analysis revealed high overexpression of FGFR1 in all investigated MPM cell lines compared to all other receptors. Concerning the expression of the ligands, high transcript levels of FGF2 and FGF18 were detected, whereas FGF3 and FGF4 were generally undetectable in all cell models. Inhibition of FGFR1 by the specific Inhibitor PD166866 lead to decreased proliferation and migration in all cell lines tested, which was further confirmed in selected cases by adenoviral expression of dnFGFR1. In contrast, stimulation with FGF2 showed remarkably increased migration and significant changes in morphology accompanied by distinct changes in cellular signal transduction pathways. Inhibition of FGFR signals also markedly reduced spheroid formation ability of MPM cell lines. Combination of FGFR inhibition with chemotherapeutic agents e.g. cisplatin, trabectedin, temsirolimus, lead to increased efficacy with respect to cell viability.

Conclusion: Taken together these data suggest that FGFR signals are important for proliferation, survival, migration and chemoresistance of mesothelioma cells and their inhibition should be further evaluated as a potential new treatment strategy in MPM.

Keywords: pleural mesothelioma, Fibroblast growth factors, receptor tyrosine kinase

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P2.021 AURORA-A KINASE AND EGFR INHIBITION ACT SYNERGISTICALLY IN NON-SMALL CELL LUNG CANCER (NSCLC) CELL LINES

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Background: NSCLC is the leading cause of cancer related death in the US. Inhibitors of the epidermal growth factor receptor (EGFR) are active in only a subset of patients. Capitalizing on our recent observation of synergistic activity of combined inhibition of EGFR and Aurora-A pathways1, we investigated combined activity of Aurora-A and EGFR antagonists in several refractory lung cancer cell lines in culture and xenograft models.
Methods: The Aurora-A gene copy number in five human lung cancer cell lines (A549, H322M, H358, H1299 and PC-9) with known EGFR and KRas status was determined by genomic qPCR. The cytotoxcity of erlotinib (E) and MLN8237 (MLN, Millennium) were determined for each cell line using Cell Titer Blue assay. We used the Chou-Talalay method2 to establish combined activity of MLN and E. Animal xenograft studies with A549 and H322M lung cancer cell lines were conducted by sub-Q inoculations of 4M cells and treatment given on daily (E) or BID (MLN) basis. Tumor sizes were monitored thrice weekly. Activity of Aurora A and EGFR effectors: AKT and RalA, was determined in tumor tissues.
Results: The AURKA copy number was 4.37 in PC-9 cells, the other cell lines had normal or low (A549 1.8) copy numbers. PC-9 was most sensitive to both E and MLN with IC50 0.031 uM and 3.05 uM, respectively. Contrastingly, A549 was resistant to either of the drugs (IC50, E=24.4 uM and MLN= 30.5 uM). Combined treatment of A549 xenografts with erlotinib (10 mg/kg/day) or MLN8237 (20mg/kg/bid) showed tumor regression while either agent alone were less effective. Similar tumor blocking effect was observed in H322M xenografts. Western blot analysis of the tumor lysates to investigate signaling inhibition in the combined treatment group is ongoing and data will be presented at the meeting.
Conclusion: Combination therapy with erlotinib and MNL8237 has synergistic activity in lung cancer cell lines in vitro and in vivo. Western blot analysis to investigate signaling events is ongoing. A clinical trial in patients with advanced NSCLC testing this combination is now ongoing at our center.
Keywords: EGFR, Lung cancer, aurora a

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P2.022 ANTIPROLIFERATIVE EFFECT OF ARSENIC TRIOXIDE IN NON-SMALL CELL LUNG CARCINOMA (NSCLC)

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Background: Arsenic trioxide (ATO) has been proven to be an effective treatment in acute promyelocytic leukemia and its activity has also been noted in some other solid tumors. The objectives of this study were to examine the in vitro effects of ATO in cell proliferation and the molecular mechanisms underlying the ATO induced cellular responses in NSCLC cell lines.
Methods: A panel of seven NSCLC cell lines (obtained from ATCC) was employed for our experiments. Effects of treatment (48 hours) with ATO at different concentrations were studied using standard MTT assay (cellular viability), PE-conjugated annexin-V and 7-amino-actinomycin (7-AAD) assay (apoptotic fractions by phosphatidylserine (PS) externalization), and JC-1 staining (mitochondrial transmembrane potential). Expression of pro-apoptotic and anti-apoptotic proteins were studied by Western blotting.
Results: ATO inhibited the growth of NSCLC cell lines H23, H358, HCC827, H1650, H1975, HCC2935 and HCC4006 with an IC50 value of 1.9 μM, 16.5 μM, 2.0 μM, 3.6 μM, 2.8 μM, 10 μM and 5.2 μM, respectively. Only H23 cells treated with 2 μM ATO displayed PS externalization (increased by 10.7%, $p<0.05$). After incubation with 5 μM ATO for 24 hours, H23, H358, HCC827, H1650, H1975, HCC2935 and HCC4006 cells undergoing mitochondrial membrane depolarization were increased by 12.4%, 18.4%, 6.9%, 20.3%, 18.6%, 6.2% and 4.8%, respectively ($p<0.05$). From our preliminary result, Bcl-2 (anti-apoptotic factor) was down-regulated in all NSCLC cell lines except HCC4006. The level of Bax (pro-apoptotic factor)

remained unchanged.
Conclusion: ATO, at clinically achievable concentrations, can induce apoptosis in NSCLC cell lines. Further exploration of its mechanisms and in vivo studies for treatment of NSCLC are warranted.

Funding support: Simon K.Y. Lee Foundation research grant
Keywords: arsenic trioxide, Non-small cell lung cancer

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P2.023 IN-VITRO STUDY OF ARSENIC TRIOXIDE AND CHEMOTHERAPEUTIC AGENTS IN SMALL CELL LUNG CARCINOMA

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Background: Arsenic trioxide (ATO), an anti-tumor agent with multi-faceted mechanisms of action, has become a breakthrough treatment for acute promyelocytic leukemia in recent years. There have been preliminary data about the potential activity of ATO in solid tumours, including small cell lung cancer (SCLC). As SCLC is considered a chemo-sensitive malignancy, we conducted an in-vitro study examining the cytotoxic effects as well as the mechanisms of ATO, clinically effective chemotherapeutic agents, or a combination of both in a SCLC cell line model.
Methods: Six SCLC cell lines (H-187, DMS-79, H-526, H-69, H209 and H841) obtained from ATCC were treated with drugs (ATO, cisplatin and/or etoposide [VP-16]). The cell viability after treatment was assessed by MTT assay. The effects of combination treatment were determined by isobologram analysis (combination index, CI) using standard computer software (CalcuSyn, Biosoft, USA). The proportion of cells undergoing early apoptosis was detected by annexin-V/7-AAD assay with flow cytometry. Mitochondrial depolarization was determined by JC-1 staining. Western Blotting was utilized to measure the apoptotic factors (caspase-3, caspase-8, Bcl-2, Bax).
Results: ATO, cisplatin and VP-16 induced cell death in time- and dose-dependent manner. Cells were sensitive to ATO (IC50 < 5 μM), as well as cisplatin and VP-16 (IC50 < 10 μM) except DMS79 cells for 48hrs exposure. After treatment of ATO and cisplatin, moderate synergistic cytotoxicity and additive effect were found in resistant and sensitive cell lines respectively (CI = 0.5-0.9). On the other hand, antagonism was shown in the combination of ATO and VP-16 in all cell lines (CI = 0.9-2). When combined with standard chemotherapeutic doublet (cisplatin and VP-16), ATO did not potentiate the cytotoxic effect with CI >=1. Using H841 (adhering cell line) as a model, there was time- and dose-dependent increase in apoptotic fractions upon ATO treatment. Mitochondrial depolarization was induced in ATO-treated cells. The combination of ATO and VP-16 resulted in diminished cell death and mitochondrial depolarization when compared with single treatments. The ratio of GSH/GSSG (reduced/oxidized glutathione) decreased in H841 cells treated with ATO, cisplatin or VP-16 in a dose-dependent manner, but increased by 10 folds when treated with both ATO and VP-16. ATO induced up-regulation of cleaved caspase-3 (pro-apoptotic) and down-regulation of Bcl-2 (anti-apoptotic). However, combined treatment with ATO and VP-16 failed to alter Bcl-2 expression.
Conclusion: ATO induced cell death in SCLC cell lines through apoptosis. There is potential synergism between ATO and cisplatin, while antagonism is evident in combination of ATO and VP-16. Future studies to explore the role of ATO as single agent or in combination with cisplatin in treatment of SCLC are warranted.

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Keywords: arsenic trioxide, Small cell lung cancer

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P2.024 CLINICOPATHOLOGIC AND MOLECULAR FEATURES OF YOUNG CHINESE PATIENTS WITH PRIMARY LUNG CANCER

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Background: Incidence and prevalence of lung cancer was on the rise in young adults. This study was to investigate the clinical characteristics and molecular features of these young patients.
Methods: The study was a retrospective review of young patients with primary lung cancer referred to Guangdong General Hospital over a 6-year period from 2004 to 2010. Data regarding demographics, histology, tumor staging, and treatment efficacy were obtained from all patients. EGFR and KRAS mutation was detected on tumor samples by direct sequencing.
Results: 63 patients of the age from 17 to 35 were enrolled. The average age of the population was 30.0. None of them was exposed on chemical contact. One patient had family history of malignancy. 11.1% (7/63) of these patients were students. 10 patients were light smokers, and the rest were non-smokers. 54 cases (85.7%) were diagnosed as adenocarcinoma. And only 6.3% (4/63) of these patients were diagnosed as early stage disease in the first hospitalization. EGFR and KRAS mutations were detected in 16 cases; four patients (25.0%) with active EGFR mutation were found. 40 patients received platinum-based doublet chemotherapy in the first line setting. The chemotherapy achieved disease control rate as 77.5% (18 SD and 13 PR). 22.5% (9/40) of these young patients were refractory to chemotherapy. 2 cases with EGFR active mutation received EGFR TKI treatment, and 1 case achieved PR, another patient was assessed as SD. 12.7% (8/63) patients refused any anti-cancer treatment after the established diagnosis.
Conclusion: The study implies that genetic background or exposure to first-hand cigarette could not fully explain the prevalence of primary lung cancer in Chinese young adults. Adenocarcinoma was predominant in young patients. Early detection was warranted and social support was required as many young patients quit treatment.
Keywords: young adult, primary lung cancer

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P2.025 CISPLATIN RESISTANT NSCLC CELLS BLOCK ACID SPHINGOMYELINASE DEPENDENT CASPASE 8 ACTIVATION BUT CONSERVE DEATH RECEPTOR SIGNALLING

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Background: Failure to efficiently induce apoptosis contributes to multidrug resistance in NSCLC. Although mitochondrial BAX and BAK cooperate in enabling mitochondrial apoptosis, their requirement has not been robustly established in relation to cisplatin, the most widely used drug in the treatment of NSCLC. Here we show that cisplatin bypasses mitochondrial apoptosis via activation of the extrinsic death pathway. This route is blocked in cisplatin resistance, however death receptor signalling remains intact.
Methods: We engineered mitochondrial apoptosis defective NSCLC cells by stably silencing BAX and BAK using short hairpin RNAs in H460 and H1299 cells. Apoptosis signalling in response to cisplatin was assessed using western blot and by cell cycle analysis of PI stained ethanol fixed cells. Functional dependence of components of the apoptotic pathways was determined using RNA interference.
Results: Apoptosis block in NSCLC cells stably expressing BAX and BAK short hairpin RNAs in H460 and H1299 cells was confirmed by resistance to BID BH3 peptide, and lack of caspase 9 cleavage following staurosporine, bortezomib and cisplatin. However, apoptosis still occurred as evidenced by caspase 3/PARP cleavage and hypodiploidy. Cisplatin potently induced the extrinsic pathway initiator caspase 8. Silencing caspase 8 expression by RNA interference, rescued from cisplatin but only in BAX BAK silenced cels. Caspase 8 cleavage induced by cisplatin was dependent on DR4, DR5 and FADD, and required acid sphingomyelinase. In contrast, cisplatin resistant cells, although undergoing cell cycle arrest, H2AX phosphorylation and p53 stabilisation in response to cisplatin, failed

induce caspase 8 and undergo apoptosis. However, these cells conserved sensitivity to death receptor signalling mediated by TRAIL or FLIP silencing.
Conclusion: Cisplatin mediates apoptosis through a redundant pathway involving acid syngomyelinase dependent caspase 8. This signalling is lost in cisplatin resistant NSCLC but can be bypassed by death receptor activation or FLIP silencing. Strategies to effectively target this conserved pathway should bypass platinum resistance to restore apoptosis signalling.
Keywords: caspase 8, Non small cell lung cancer, apoptosis, Cisplatin

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P2.026 TREATING LUNG TUMOUR THROUGH ALKALIZATION

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Background: Many solid human tumors generate an acidic and hypoxic microenvironment due to altered metabolic pathways and aberrant tumor vasculature. These acidic conditions reportedly activate proteases which digest the extracellular matrix and allow phagocytosis of non-tumor cells, leading to invasiveness and metastatic behaviour. In has been suggested that tumor acidosis affects chemotherapy by promoting resistance to (i) weakly basic chemotherapeutic agents by altering their intracellular/extracellular partition coefficient and (ii) radiation therapy by suppressing early steps of apoptotsis and reducing the degree of radiation induced fixation. LDOS47, an immunoconjugate cancer therapeutic, targets this unique tumor microenvironment by localizing urease to lung tumor using a specific antibody. Urease coverts the abundant metabolite urea to ammonia, increasing the local pH and exerts a cytotoxic effect on cancer cells in culture and xenograft models.
Methods: Production LDOS47: LDOS47 is constructed by covalently linking a single urease hexamer to AFAIKL2 (a recombinant camelid single domain antibody directed against CEACAM6 (Carcinoembryonic antigen-related cell adhesion molecule 6). Urease, sourced from jack beans (Canavalia ensiformis), is a hexameric enzyme consisting of six identical subunits of approximately 91 kDa each. LDOS47 tumour suppression activity: Varying amount of LDOS47 was injected in A549 xenograft and the growth of the tumour is monitored. In a separate experiment, LDOS47 is premixed with A549 and the complex is injected through the tail vein of the mice. Groups of mice were sacrificed at the third and tenth week. Lung nodules formed by A549 colonization were counted. LDOS47 Imaging: Varying amounts of LDOS47 labelled with Cy5.5 were injected into A549 xenograft mice. At various time intervals, animals were anaesthetized and transferred to a specially constructed light tight box equipped with CCD camera, laser diode to capture images. Tumour pH measurement: Tumour bearing mice were positioned vertically in a 11.7T magnet and a custom built surface coil is used to acquire 1H-MRI and 32P-MRS signal. Pi, PME, PDE and ATP signals were used to monitor, tumour pH, growth, and tissue energetic. The pH of the tumour was also measured separately using a microelectrode.
Results: LDOS47 tumour suppression activity: LDOS47 suppresses A546 tumour in a dose dependent manner. Effective dose was observed at 35U/kg. Premixing LDOS47with A549 cells prior to injection significantly reduced the ability of A549 cells to colonize the lungs. At ten weeks most of the inhibition is overcome. LDOS47 Imaging: LDOS47 fluorescence peaked at 48 hours post injection. Calculations indicated that the maximal fluorescence is seen at 48 hours. Free dye injected into control or tumour bearing mice is not accumulated in any tissues examined upon necropsy and is cleared from the mice within 2 hours. Tumour pH measurement: Preliminary data showed the magnet/coil set up was effective in measuring tumour pH. The effects of LDOS47 on tumour alkalization are being studied.
Conclusion: LDOS47 is able to target tumour in vivo and reduces tumour growth. Fluorescence imaging data showed the molecule was retained at the tumour for a signifciant period of time and LDOS47 prevented tumour cells to colonize distant organ. Tumour pH data are being collected.
Keywords: Tumour microenvironment, Tumour alkalization, Imaging, MRS

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P2.027 LOVASTATIN INDUCES METABOLIC STRESS THROUGH LKB1/AMPK ACTIVATION: POTENTIAL THERAPEUTIC IMPLICATIONS

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Background: Cellular stress responses trigger signaling cascades that inhibit proliferation and protein translation to help alleviate the stress or if the stress cannot be overcome induce apoptosis. In recent studies, we demonstrated the ability of lovastatin, an inhibitor of mevalonate synthesis, to induce the integrated stress response as well as inhibiting epidermal growth factor receptor (EGFR) and AKT activation. In this study, we evaluated the effects of lovastatin on the activity of the AMPK/LKB1 pathway that is activated upon cellular energy shortage and can interact with the above pathways.
Methods: The activity of LKB1 and AMPK were assessed employing phosphospecific antibodies to these proteins and visualized through Western blot analysis. Affects on tumour cell cell viability coincident with lovastatin and metformin treatments were determined by the MTT assay. ADP/ATP ratios were also determined following treatments. Cell lines evaluated included NSCLC, squamous cell carcinomas and murine embryonic fibroblasts, both wild type and gene knockout LKB1 variants.
Results: In the NSCLC and squamous cell carcinoma cell lines , lovastatin treatment (1-25microM, 24hrs) induced LKB1 and AMPK activation similar to metformin (1-10nM, 24hrs), an inducer of this pathway. Lovastatin treatment also decreased cellular ADP/ATP ratios, a trigger for LKB1/AMPK activation. The cytotoxic effects of lovastatin were attenuated in LKB1 null MEFs indicating a role for this pathway in regulating lovastatin-induced cytotoxicity. Similarly, in the LKB1 deficient cells, the cytotoxic effects of both lovastatin and metformin were also attenuated. Of clinical relevance, lovastatin induces synergistic cytotoxicity in combination with the EGFR inhibitor gefitinib. In two LKB1 deficient (A549, HeLa) and expressing (SCC9, SCC25) cell lines, metformin enhanced gefitinib cytotoxicity that was limited to the expressing cell lines while both groups showed enhanced cytotoxic effects with lovastatin treatments.
Conclusion: The ability of lovastatin to target multiple stress pathways enhances its ability to co-operate with gefitinib enhancing the potential therapeutic benefit of this combination of agents.
Keywords: lovastatin, LKB1/AMPK, metabolic stress

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.028 MECHANISM(S) OF ACTION AND POTENCY OF HSP90 INHIBITOR GANETESPIB IN SMALL CELL LUNG CARCINOMA CELLS

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Background: Ganetespib (formerly STA-9090, Synta Pharmaceuticals) is a second generation Hsp90 inhibitor, which is a resorcinol-containing compound with a novel structure that is unrelated to the geldanamycin class of Hsp90 inhibitors. It binds to the ATP-binding domain of Hsp90 and is a potent Hsp90 inhibitor through degradation of Hsp90 client onco-proteins in cancer cells. At low nanomolar concentrations, ganetespib potently inhibits cell proliferation and induces apoptosis in a variety of cancer cell lines including many receptor tyrosine kinase inhibitor- and 17-AAG (geldanamycin class of Hsp90 inhibitor)-resistant cell lines, and in several tumor xenograft models. Based on preclinical activity of other Hsp90 inhibitors, small cell lung cancer appears like a promising tumor target for this class of agents.
Methods: IC50 was determined by MTS assay according to the manufacturer's instructions. Cell cycle profiling and cell viability were analyzed by flow cytometry on propidium iodide stained cells and by trypan blue exclusion on Auto T4 Cellometer (Nexcelom Bioscience) respectively.
Results: Using 12 small cell lung carcinoma (SCLC) cell lines, we demonstrate that ganetespib (IC50: 30.9$\pm$ 16.6 nM) is much more potent than 17-AAG (IC50: 16$\pm$47 uM) in MTS assays. In addition, at the concentrations of IC50 or 3-60 times over IC50, ganetespib exhibits cytostatic effect by arresting cells

at G2/M on all the SCLC cell lines studied so far. Cells survive for as long as 6 days in the presence of ganetespib. Intriguingly, cell viability precipitously drops upon ganetespib withdrawal following 48-72 h treatment. We are investigating the mechanism of cell death occurring after drug withdrawal (mitotic catastrophe after release from G2 arrest or cell death in the next cell cycle). In addition we are evaluating the molecular mechanism(s) of ganetespib action in xenograft models of SCLC.
Conclusion: Our study suggests that ganetespib is a potent inhibitor of SCLC cell growth via induction of G2/M arrest. The fact that ganetespib withdrawal induces precipitous cell death suggests that ganetespib intermittent treatment strategy might be considered for the ongoing phase II studies in SCLC.
Keywords: Ganetespib, Hsp90 inhibitor, SCLC

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P2.029 MECHANISMS OF ACQUIRED BORTEZOMIB RESISTANCE IN NON-SMALL CELL LUNG CANCER: OVEREXPRESSION OF THE PROTEASOME AND MUTATIONS IN THE β5 PROTEASOME SUBUNIT.

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Background: The proteasome inhibitor bortezomib (Velcade®) is registered for the treatment of multiple myeloma and is being investigated for activity in solid tumors such as non-small cell lung cancer (NSCLC). Bortezomib predominantly inhibits proteasome subunit β5 and mutations in this subunit were recently associated with bortezomib resistance in leukemic cell line models. We studied the molecular mechanisms underlying intrinsic and acquired bortezomib resistance in NSCLC cells.
Methods: A panel of NSCLC with differential intrinsic bortezomib sensitivities was used; H460, A549 and SW1573 NSCLC cells displaying IC_{50} values of 12.6, 8.7 and 1.7 nM, respectively. In addition, we established a model for acquired bortezomib resistance in these cells by exposing cells to gradually increasing concentrations of bortezomib starting from 5nM to 80 or 200 nM for H460, 40 or 100 nM for A549 as well as 30 or 150 nM for SW1573. These bortezomib-resistant cell lines, named $H460BTZR_{80}$, $H460BTZR_{200}$, $A549BTZR_{40}$, $A549BTZR_{100}$, $SW1573BTZR_{30}$ and $SW1573BTZR_{150}$, displayed 8 to 70- fold bortezomib resistance. Expression of the proteasome subunits was determined by Western blot. Proteasome activity was examined using a cell based proteasome activity assay and in gel digestion of the suc-LLVY-amc substrate. FACS analysis was used to determine cell cycle analysis. Furthermore, sequence analysis was performed to detect mutations in the β5 subunit. In addition, other proteasome inhibitors were used to examine cross resistance in the bortezomib-resistant cells.
Results: Examinations into the mechanisms of intrinsic bortezomib resistance revealed that high basal chymotrypsin- and caspase-like proteasome activities are correlated with intrinsic bortezomib resistance in wild type cell lines (R^2=0.99, P<0.05). However, no marked differences were detected in the expression levels of the β5-subunits of the proteasome. Characterization of the acquired bortezomib-resistant cells showed that higher bortezomib concentrations were required to accumulate ubiquitinated proteins, induce G2/M cell cycle arrest and cell death when compared to their parental counterparts. Overall the amount of cell death reduced even at higher bortezomib concentrations when compared to parental cells treated with equitoxic drug doses. Furthermore, augmented levels of the constitutive β-subunits and the α7 subunit were detected in bortezomib-resistant cells which corresponded to increased formation of the proteasome. However, basal proteasome activity was markedly reduced in bortezomib-resistant cells when compared to the parental cells. Moreover, sequence analyses of the bortezomib binding pocket encoded by exon 2 of the PSMB5 gene revealed Ala49Thr, Met45Val and Cys52Phe mutations which have never been described for solid tumor cells. Additionally, we observed cross-resistance to other proteasome inhibitors that specifically target the β-subunits of the proteasome. Interestingly, no cross-resistance was found to 5-amino-8-hydroxyquinoline (5AHQ), a novel non-competitive proteasome

inhibitor that targets the α-subunit.
Conclusion: Taken together, these findings establish a correlation between bortezomib-sensitivity and low basal levels of proteasome activity. In addition, acquired resistance to bortezomib in NSCLC was associated with increased proteasome formation and mutated β5-subunits that may compromise bortezomib binding as well as the binding of protein substrates. Furthermore, α-subunit-specific proteasome inhibitors can efficiently used to bypass bortezomib resistance.
Keywords: bortezomib resistance, β5 proteasome subunit, Mutations

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P2.030 ROLE OF SRC FAMILY KINASES (SFK) IN THE CONSTITUTIVE ACTIVATION OF THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) IN NON-SMALL CELL LUNG CANCER (NSCLC) CELL LINES.

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Background: Constitutive activation of EGFR signaling has a prominent role in driving NSCLC tumor cell proliferation. Gene mutations, amplification and overexpression of EGFR account for some but not all cases of its constitutive activation. In preclinical studies we investigated signaling pathways to determine the mechanisms of EGFR constitutive activation in the absence of its mutation, amplification and overexpression in a representative NSCLC line, Calu3. Other NSCLC cell lines were surveyed including one with both an activating and TKI resistance mutation, H1975.
Methods: Protein lysates were prepared from NSCLC cancer cell lines obtained from and cultured according to ATCC guidelines. These lysates were used for immunoprecipitations, Western blotting and luminex bead assays. Cells were cultured with medium alone or in a variety of kinase inhibitors including EGFR, c-Met, and SFKs before lysates were harvested. Cells were transfected with a pool of either four Lyn gene targetted silencing (si)-RNAs or negative control si-RNA for 2-6 days to measure the effect of specific SFK inhibition on cell proliferation and signal transduction. EGF served as the ligand to trigger EGFR. Cell proliferation was measured using Calcein AM added during the last 2 hours of culture. Signal transduction was measured by Western blotting with specific antibodies directed against phosphorylated amino acids of signaling molecules such as anti-EGFR Y845 or Y1068 of protein lysates separated on SDS-PAGE.
Results: Our findings revealed the promiscuity of EGFR in association and dimerizations with other receptor chains including erbB3, erbB2, and c-Met. Heterodimerization with EGFR led to their activation by EGFR as revealed by phosphorylation on activation sites and Inhibition thereof with EGFR kinase inhibitors. SFK were determined to be critical to the constitutive activation process as the pan-src family kinase inhibitor PP2 inhibited EGFR phosphorylation. In the constitutively activated Calu3 cell line, Lyn a SFK known for its critical role in B-cell lymphomas was found to be expressed and was determined to be critical to the activation of EGFR. Immunoprecipitation studies revealed that Lyn was present in a complex with its regulatory proteins Cbp, Lsk, along with RACK1, a component of lipid rafts in cell membranes. Silencing (si)-RNA experiments demonstrated that the loss of Lyn translation and decreased expression resulted in decreased phosphorylation of EGFR and decreased cell proliferation. Lyn si-RNA further down-regulated ligand mediated- EGF signaling as evidenced by decreased EGFR and c-Met phosphorylation.
Conclusion: Constitutive activation of EGFR in NSCLC cells that lack activation mutations is driven by SFK. In Calu3 cells Lyn is responsible for EGFR activation and downstream signaling. Lyn was found in complexes with src-kinase regulatory proteins and RACK1. RACK1, a component of lipid rafts, probably serves as scaffolding in tumor cell membranes for an EGFR-Lyn activation unit which is responsible for its constitutive activation. Drawing other growth factor receptors into these membrane units result in a significant expansion of growth pathways triggered. Preventing constitutive activation of EGFR with a SFK inhibitor in conjunction with EGFR TKI inhibitors would prevent its association with other growth factor and dramatically decrease the signaling pulse driving NSCLC cell survival.
Keywords: Src family kinase, c-Met, si-RNA, EGFR activation

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P2.031 SAHA SENSITIZES MESOTHELIOMA SPHEROIDS TO BORTEZOMIB-INDUCED APOPTOSIS BY RESTORING LEVELS OF PRO-APOPTOTIC NOXA.

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Background: Mesothelioma displays a stubborn chemoresistance that can be modeled in 3D cell culture (spheroids) where cells acquire multicellular resistance to chemotherapy. Acquired multicellular resistance of spheroids is mediated by the Bcl-2 family of proteins at the level of mitochondria, where apoptotic signals are integrated and executed. Proteasome inhibitors, such as bortezomib, are thought to induce apoptosis via the alteration of Bcl-2 protein expression. We considered that the underlying molecular mechanism of bortezomib resistance could be studied in 3D spheroids.
Methods: We asked whether mesothelioma spheroids were resistant to bortezomib and if so, whether resistance derived from the Bcl-2 repertoire of mesothelioma spheroids. We then investigated ways to restore the apoptotic sensitivity of spheroids to bortezomib.
Results: Mesothelioma cells grown as spheroids acquired resistance to bortezomib and, compared to cells in monolayers, showed a lack of upregulation of pro-apoptotic Noxa. Among many agents tested, SAHA, a histone deacetylase inhibitor, was able to restore Noxa protein levels in spheroids upon treatment with bortezomib and eliminated all acquired multicellular resistance. Ablation of Noxa by siRNA confirmed that SAHA sensitization of bortezomib-induced apoptosis relies on Noxa. Furthermore, while it did not induce significant apoptosis when given alone, SAHA proved to be very effective in 3D when combined with other non-toxic agents such as ABT-737 (a Bcl-2 inhibitor) and tunicamycin (an inducer of the unfolded protein response), suggesting new intriguing avenues to treat mesothelioma.
Conclusion: In sum, studying 3D mesothelioma spheroids allowed us to uncover a potentially therapeutic role for SAHA in ablating multicellular resistance to bortezomib and other non-toxic agents. SAHA may prove effective in novel treatment combinations.
Keywords: apoptosis, 3D cell culture, mitochondria, Chemotherapy

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P2.032 THE EFFECTS OF VITAMIN D ON THE TUMORIGENESIS OF LUNG SQUAMOUS CELL CARCINOMA IN A CARCINOGEN INCDUCED MOUSE MODEL.

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Background: Lung cancer accounts for the majority of cancer mortality. The need for further knowledge for prevention and treatment of lung cancer is crucial as no preventive agents and few screening guidelines have been established for lung cancer. Epidemiological studies indicate that low serum levels of 25(OH)D3 are strongly associated with increased risk and poor prognosis of lung cancer. In addition, calcitriol, the active metabolite of vitamin D, induces cell cycle arrest, apoptosis and differentiation with few toxicities, which makes vitamin D an attractive agent for chemoprevention of lung cancer. To investigate the preventive effects of vitamin D on lung SCC pre-clinical studies are being conducted using a carcinogen-induced (CI) mouse model of lung SCC. The CI model uses N-nitroso-tris-chloroethylurea (NTCU) applied topically to the back of a SWR/J mouse twice weekly. Following 15 weeks of NTCU treatment, these mice begin to develop bronchial epithelial hyperplasia and with time disease progresses through metaplasia, carcinoma in situ, and ultimately forming lung SCC by approximately 35 to 40 weeks. Previous studies by Yian Wang et al. demonstrate that 100% of SWR/J mice develop microinvasive lung SCC by 40 weeks; no other histologies are noted.

Methods: We are investigating the effects of vitamin D on cancer progression in the CI model by examining the effects of a vitamin D deficient diet, as well as a a sufficient diet with weekly intraperitoneal (IP) injections of calcitriol (80 ug/kg). Disease state is determined by histological evaluation using hematoxylin and eosin staining and immunohistochemical staining of cytokeratin 5/6 and p63. Changes in vitamin D receptor (VDR) status and the expression of VDR regulated genes and proteins involved in cell cycle arrest, apoptosis and differentiation are being examined.
Results: AAnimals treated with NTCU and are on a vitamin D deficient diet, sufficient diet or sufficient diet with IP of calcitriol, have average serum 25(OH) D3 levels of 15 nmol/L, 70 nmol/L and 75 nmol/L respecitvly. The average serum level of a mouse on a normal mouse chow is 70- 90 nmol/L, thus demonstrating that the mice on a deficient diet are deficient. The NTCU treated mice who were on a diet sufficient in vitamin D and received calcitriol maintain their weight and are better groomed than mice on a sufficient diet who did not receive calcitriol and even more so than those on the deficient diet. Preliminary histological evaluation of the NTCU treated sufficient groups at 15 weeks indicated the presence of bronchial epithelial hyperplasia regardless of calcitriol treatment. The histology of lungs from the NTCU treated mice on the vitamin D deficient mice taken at approximately 15 weeks of treatment, revealed more advanced disease (hyperplasia, metaplasia and carcinoma in situ) than those on a sufficient diet alone.
Conclusion: This study indicates that mice deficient in vitamin D may develop disease at a more rapid rate. These studies provide evidence that vitamin D status may play an important role in progression of lung SCC. Supported by NIH/NCI R01-CA-067267.
Keywords: Lung Squamous Cell Carcinoma, Pre-Clinical study, Vitamin D

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P2.033 EVIDENCE OF SIGNIFICANT EFFICACY OF THE ONCOLYTIC VIRUS, REOVIRUS, FOR THE TREATMENT OF LUNG CANCER

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Background: Lung cancer is the leading cause of cancer mortality worldwide. It is estimated that approximately 1,529,560 people were diagnosed with cancer in 2010, resulting in approximately 569,490 deaths. Surgical resection and aggressive chemotherapies prove to be only marginally effective as five-year survival ranges from 13% in men and 17% in women. Reovirus (RV), a double-stranded RNA virus, has been shown to be effective against a myriad of cancers through its ability to preferentially lyse cancer cells with aberrant Ras or other pathway signaling. In this study, we investigate the potential of RV (serotype 3, strain Dearing) as a novel treatment for both non-small cell and small-cell lung cancer in vitro and in vivo.
Methods: RV-induced cytotoxicity was assessed by WST-1 viability assays for both NSCLC cell lines: (A549, H460, H1299, HCC4006, H1975, H226, HCC827, HCC2935) and SCLC cell lines: (DMS-53, and H69) in vitro. RV and chemotherapy combination studies were conducted for the DMS-53, H69, HCC827 and H226 cell lines, evaluating the cytotoxic effects of reovirus in combination with each of the following: cisplatin, pemetrexed, etoposide, and erlotinib using the constant-ratio design and combination index method of Chou Talalay. In order to further evaluate the potential of RV as novel therapeutic for lung cancer, three xenograft models (H460, H1299 and DMS-53) were utilized to test RV-induced cytotoxicity alone and in combination with chemotherapy in vivo.
Results: RV induces cytotoxic effects at a multiplicity of infection (MOI) of 40 within 48h for both NSCLC cell lines: (A549, H460, H1299, HCC4006, H1975, H226, HCC827, HCC2935) and SCLC cell lines: (DMS-53, and H69) in vitro. These findings are particularly unique for SCLC, in that effective therapies are limited. Interestingly, preliminary data also suggests that RV

in combination with chemotherapy has potentially synergistic cytotoxic effects in vitro. In addition, current xenograft data indicates that both the H460 and H1299 cell lines are intrinsically sensitive to RV in vivo. Updated results will be presented.
Conclusion: These preclinical results suggest that RV holds promise as a novel therapeutic for both non-small cell and small cell lung cancer and that it warrants further investigation in clinical trials. There is currently a phase III clinical trial for RV in combination with carboplatin for the treatment of NSCLC. These results may suggest that other combinations should be examined and that RV may have the potential to revolutionize therapy for SCLC.
Keywords: Chemotherapy, Reovirus, Non-small cell lung cancer, Small-cell lung cancer

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P2.034 THE INHIBITOR OF SURVIVIN EXPRESSION, YM155, SHOWS SUBTYPE-SPECIFIC ACTIVITY IN MALIGNANT MESOTHELIOMA CELLS

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Background: Survivin is a member of the inhibitor of apoptosis (IAP) family of proteins. Through inhibition of caspase activity, it is a negative regulator of apoptosis. Expressed highly in most tumours, including mesothelioma, but not in normal tissues, survivin is a target for cancer therapy. YM155 is a small molecule that selectively suppresses survivin expression at the transcription level. It inhibits growth of a range of tumours, both in vitro and in vivo, and is currently being tested in early clinical trials. This molecule has not yet been investigated in malignant mesothelioma (MM).
Methods: The mRNA expression of survivin, other IAPs, and genes related to YM155 toxicity were measured by RT-pPCR in a series of MM cell lines. The importance of survivin in the same cell lines was assessed by proliferation and cell cycle analysis following siRNA-mediated knockdown. Growth inhibitory effects of YM155 were measured by standard proliferation assays.
Results: Survivin mRNA expression was found to be similar in a range of MM cells, and siRNA-mediated knockdown led to > 90% knockdown of mRNA and growth inhibition. YM155 treatment led to growth inhibition in all cell lines tested. Interestingly, toxicity was more pronounced in cell lines of epithelioid origin (IC50 from 1 to 12 nM) than those derived from biphasic tumours (IC50 175 and 810 nM). Expression analysis revealed no significant differences in mRNA levels of any IAP family in any of the cell lines, but there was a general trend towards lower OCT1 and higher ABCB1, ABCG2, ABCA6 and ABCA10 expression in the biphasic lines. Further studies with specific inhibitors and siRNA-mediated knockdown of these transporters revealed their involvement in YM155 toxicity.
Conclusion: YM155 is effective in inhibiting growth of MM cells, with cells of epithelioid origin more sensitive. Biphasic cell lines display higher ABC transporter expression and were more resistant to YM155 suppression of survivin. Further pre-clinical testing is needed to determine whether YM155 is a potential therapeutic option for epithelioid MM.
Keywords: Malignant mesothelioma, survivin, ABC transporters

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P2.035 SILENCING OF TYMS AND PLK1 SENSITISES MALIGNANT MESOTHELIOMA CELLS TO GEMCITABINE

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Background: Pemetrexed with cisplatin is considered the chemotherapy standard for malignant mesothelioma (MM). The antimetabolite gemcitabine has also demonstrated some activity in MM. In other solid tumours the cytotoxicity of gemcitabine is increased by inhibiting DNA damage checkpoints. We have used RNAi to identify gemcitabine sensitising genes in MM.
Methods: We used an RNAi-based chemogenetic screen to investigate the ability of 100 genes to modulate the sensitivity of MM cell lines to gemcitabine treatment. In the primary screen, cells

were transfected individually with 200 siRNAs (2 per gene) at a final concentration of 1 nM, and 24 h later they were treated with 10 nM gemcitabine. Effects on proliferation were assessed and combination therapy was compared with siRNA and gemcitabine treatment alone. Hits from the primary screen were further investigated with a full dose response curve for gemcitabine.
Results: The knockdown of a several genes sensitised MM cell lines to gemcitabine. This included genes previously shown to be involved in gemcitabine cytotoxicity, such as CHK1, RRM1 and RRM2. RRM1 knockdown increased gemcitabine sensitivity by 4- to 5-fold, and CHK1 and RRM2 knockdown reduced IC50 values by 2- to 2.5-fold. As expected the inhibition of DCK1, the kinase responsible for phosphorylation of gemcitabine to its active form, led to 3-fold resistance of cells and provides internal validation of the assay. Interestingly, PLK1 and TYMS silencing also increased the toxicity of gemcitabine by greater than 2-fold. This phenomenon was seen in all MM cell lines but was not observed in the lung cancer cell line A549. Additional studies investigating the combination of small molecule inhibitors of these target genes with gemcitabine will be presented.
Conclusion: A chemogenetic RNAi-based screen identified a number of genes involved in the sensitivity of MM cells to gemcitabine. Small molecules specific for these targets can be combined with gemcitabine and warrant further testing in pre-clinical models. Similar screens could be used to identify targets to synergise with pemetrexed and cisplatin, and could lead to new treatment options for MM.
Keywords: gemcitabine, polo-like kinase, Malignant mesothelioma

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P2.036 ALTERNATIVE DOSING REGIMENS WITH TARCEVA IN A PRECLINCAL BREAST CANCER MODEL: EFFECTS ON EFFICACY AND POTENTIAL EFFECTS ON TOXICITY. IMPLICATIONS FOR LUNG CANCER TREATMENT

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Background: The EGFr inhibitors (e.g. Tarceva) have been effective in preventing cancer in multiple animal models including lung cancer, ER+ and ER- breast cancer, head and neck and urinary bladder cancer. Although Tarceva is less toxic than most classical cytotoxic therpaies,, the development of a skin rash in >50% of patients is a significant impediment to its use in an adjuvant setting or any preventive setting. We therefore tested whether alternative dosing regimens would still achieve efficacy in a preclinical model.
Methods: Female Sprague Dawley Rats were administered a single IV dose of methylnitrosourea at 50 days of age. Prevention Study: Beginning 5 days later rats were administered Tarcebva (6 mg/ KgBW) by gavage. In the first study three proteocls were employed : 1) dosing with Tarceva (6mg/ KgBW) 7 days per seek, 2) Dosing with Tarceva (6mg/KgBW) for 2 days followed by 2 days of vehicle treatment. 3) Weekly treatment with a 42 mg/ KgBW dose of Tarceva. Therapy Study: Beginning when palpable mammary tumors first appeared (roughly 5-8 weeks after MNU) tumor bearing rats were randomized to treatments 1 or 3 above. Pharmacokinetic Study Following treatments 1 or 3 listed above serum levels of Tarceva and an active hydroxylated metabolite were deterimened in the serum of tumor bearing rats.
Results: Prevention Study: Preventive treatments 1 daily) 2 2days on/2 dasy off 3 weekly dosing reduced the multiplcity of tumors by 85%, 67% and 89% respectively. They were even more effective in reducing total tumor volume [No of tumorsxsize of tumors]. Therapy Study: Therapeutic Studies 1) daily (6mg/KgBW) 2) Weekly dosing [42 mg/ KgBW] both caused >50% reductions of tumor size over 42 days. In contrast tumor size increased >200% in vehicle treated controls. Pharmacokinetic Studies Determination of serumo levels of Tarceva and an active hydroxylated metabolite showed that following daily dosing active Tarceva levels were achieved for roughly 16 hours per day. In contrast for the weekly dosing effective serum levels were achieved for <54 hours.
Conclusion: These data show that a profoundly altered dosing of Tarceva in a preclinical model is highly effective The results are surprising since the PK data would imply that we probably achieved effective serum levels for only 2-21/2 days out

of 1 week. The more important clinical question, which we cannot address in animals, is whether this alternative dosing may strikingly decrease the rash which is associated with Tareceva treatment in humans. This will have to be addressed clinically but may have impliications for the use of this agent both in adjuvant and potentially preventive settings.
Keywords: EGFr Inhibitors, Prevention, Altered Dosing

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P2.037 EFFICACY OF THE RXR AGONIST BEXAROTENE IN PRECLINICAL MODELS OF ADENOCARCINOMA OF THE LUNG AND SMALL CELL LUNG CANCER

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Background: The RXR agonist Bexarotene is effective in the prevention and lung adenomas in the standrd A/J model of lung adenoma formation. Furthermore it has shown activity in NSCLC in clinical settings as well. We examined the efficacy of Bexarotene in two models of lung cancer in mice . In the first model vinyl carbamate is employed in A/J mice with a grem line P53 mutation which then develop both adenomas and adenocarcinomas with Ki Ras mutations i. In the second model a transgenic mouse with localized KO of both RB and P53 were employed to generatre mice with small cell lung cancer.
Methods: Treatment Of Lung Adenomas/ Carcinomas A/J mice bearing a a dominant negative P53 mutation . Six week old A/J mice were treated with vinyl carbamate i.p. At 16 weeks after treatment with vinyl carbamate a time at which treated mice have multiple adenomas and potentially a limited number of microscopic adenocarcinomas they were treated for a period of 12 weeks (16-28 weeks post vinyl carbamate) with Bexarotene (100 mg/KgBW) by gavage on a daily basis. mice were sacrificed at 28 weeks after dosing with vinyl carbamate. Prevention Of Small Cell Lung Cancers We employed an adenovirus Cre virus to specifically knock out in lung floxed copies of both TrpP53 and RB1. This model was initially developed by Meuwissen and co workers [2003]. Adenovirus Cre Virus was administered to mice via the trachea. Mice develop multiple dysplasias within 5 months following virus treatment and large small cell lung cancers within 7-9 months. In the present study mice were treated with the RXR agonist Bexarotene beginning at the time of treatment with the Adenovirsu Cre virus at a dose of 1000mg/KgBW per day 5 days per seek. Animals were kept for a period of 9 mosths foloowing traeatment with adeno-Cre virus and sacrificed at that time. Tumor incidence and size were determined at sacrifice.
Results: Therapeutic Study Of Adenocarcinomas. At the time that Bxarotene treatment was intiated most mice had multiple adenomas and possibly an ocassional microscopic adenocarcinoma. Twelve weeks of treatment at this more treatment decresed the imultiplicity of adenomas roughly 40%, tumor volume 50% and reduced development of adenocarcinomas >50%. Prevention sTudy Of Bexarotene In Samll Cell Lung Cancer: Exposure of mice to bexarotene beginning at the time of exposure to the Adenovirus-Cre virus administration resulted in profound prevention of development of small cell lung cancer. Tumor multiplcity was decreased roughly 80% and tot al tumor volume[multiplcity x size] was decreased almost 90%.
Conclusion: Bexarotente wa relatively effective in blocking the growth and progression of lung tumors (adenomas/adenocarcinomas) when initated at a time when adenomas already exist. The agent appeared relatively effective in blocking progression of these tumors . Furthermore Bexarotene was effective in preventing the development of small cell lung cancer in a transgenic model in which an Adenovirus -Cre virus is used to KO P53 and RB1 in floxed mice. The efficacy of this agent must be determined when treatment is intiated at later time periods.
Keywords: Small cell lung cancer, transgenic model, RXR agonist (Bexarotene)

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P2.038 TARGETING MET-INDEPENDENT EARLY-RESISTANT LUNG CANCER CELLS EVADING ERLOTINIB BY BH3-MIMETIC ABT-737 TO DISRUPT THE BCL-2/BCL-XL SIGNALING DEPENDENCE

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Background: The recent clinical use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in lung cancer represents a new paradigm of personalized targeted cancer therapy. Nonetheless, molecularly-targeted therapy is still largely limited by the inevitable recurrent resistant disease even in initially responders, ultimately diminishing the impact on their long-term clinical utility. Both mutational (e.g. T790M-EGFR) and non-mutational mechanism (e.g. MET genomic amplification) have been found to partially account for acquired tumor resistance against small molecule EGFR-TKI after chronic exposure. Other resistant mechanisms enabling tumor cells to escape the efficacy of gefitinib/erlotinib remain elusive. Better insights into previously unknown resistance mechanisms would be crucial to further discover novel therapeutic strategies to overcome therapeutic.
Methods: With emphasis on early molecular changes within the residual tumor cells post-treatment, we investigated drug-sensitive lung adenocarcinoma cell lines using EGFR inhibitors, alone or in combination with MET inhibitors, using both in vitro and in vivo short-term treatment models. We investigated the effects of EGFR-TKI treatment on Signal Transducer and Activator of Transcription 3 (STAT3) and B-cell lymphoma protein 2 (BCL-2)/BCL-XL family members in lung cancer cell lines and murine xenografts model. We also tested the therapeutic efficacy of BCL-2 Homology Domain 3 (BH3)-mimetic, such as ABT-737, to eradicate the early resistant tumor cells that emerged in TKI evasion.
Results: Using HCC827, PC-9 (erlotinib-sensitive) and H1975 (CL-387,785-sensitive) lung cancer cells under corresponding TKI treatments, we identified and characterized the adaptive emergence of resistant survivor cells that functionally evaded targeted inhibitors early by day 9 in treatment. These early resistant tumor cells exhibited MET-independent BCL-2/BCL-XL prosurvival-antiapoptotic signaling dependence, a cellular quiescence-like state, and TKI-resistant phenotype having IC_{50} viability as high as 100-fold above the parental cells. In vitro culture and in vivo xenograft model verified that reactivated BCL-2/BCL-XL signal path and its transcriptional activator p-STAT3[Y705] were present within the residual tumor survivor cells after initial tumor response to targeted TKI therapies. Finally, our study results showed that disrupting the mitochondrial BCL-2/BCL-XL pathway machinery as "Achilles' heel" of the HCC827 early survivor cells evaded erlotinib, using BCL-2 Homology Domain 3 (BH3)-mimetic such as ABT-737, eradicated the early-resistant tumor cells. RNAi studies verified that dual RNAi knockdown of BCL-2/BCL-XL (but not BCL-2 alone) recapitulated the results seen with ABT-737 inhibition. Our in vivo HCC827-luc lung tumor xenograft assay with preemptive use of ABT-737 in conjunction with EGFR inhibitor in NSCLC demonstrated that the "early" TKI-resistant tumor evader cells were susceptible to the BH3-mimetic and can be eradicated to ultimately achieve more durable response with prolonged remission.
Conclusion: Taken together, our results revealed a role of reactivated STAT3, and BCL-2/BCL-XL as potential markers for early tumor resistance evading targeted inhibitors in lung cancer. We also provide evidence to support targeting the intrinsic BCL-2/BCL-XL antiapoptotic pathway machinery in the resistant evader cells using BH3-mimetic, which can overcome or prevent early resistance emergence against TKI. Further prospective clinical investigations using BH3-mimetic combined with targeted TKIs are warranted for optimized therapy and to impact on long-term clinical outcome.
Keywords: erlotinib, Resistance, Bcl-2, ABT-737

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P2.039 EVALUATION OF KRAS GENE MUTATION AND COPY NUMBER GAIN IN NON-SMALL CELL LUNG CANCER

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Background: Recent studies for the characterization of the lung cancer genome have suggested that Kras gene was frequently amplified and correlated with activating mutations of Kras, which occur in approximately 5-10% of Japanese lung cancers.
Methods: We analyzed Kras mutation and Kras copy number in 172 Japanese non-small cell lung cancer (NSCLC) cases and their relation to the survival of patients. We also studied using fluorescence in situ hybridization (FISH) to provide direct evidence of Kras amplification in 40 clinical specimens.
Results: In 172 NSCLC cases, increased Kras copy number was existed in 19 (11.0%) cases. Increased Kras gene copy number was correlated with Kras mutation. However Kras gene copy number gain was not correlated with gender, pathological subtypes, stages and smoking status. Increased Kras copy number was not associated with overall survival in these 172 cases, however, increased Kras copy number plus Kras mutant patients were significantly worse prognosis when compared with the Kras wild type and Kras not increased patients. From the FISH analysis, Kras polysomy or amplified patients showed significantly worse prognosis when compared to Kras disomy patients.
Conclusion: Kras mutation plus increased copy number was a predictor of poor clinical outcome in patients with NSCLC.
Keywords: Kras, Lung cancer, copy number, FISH

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P2.040 VASCULAR ENDOTHELIAL GROWTH FACTOR AND HIS RECEPTORS, VEGFR-1 AND VEGFR-2, IN AIRWAYS OF PATIENTS WITH NSCLC.

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Background: Angiogenesis has been proven to be a process related to the migration, proliferation and metastasis of cancer cells. Its predominant moderator is the VEGF which imposes its angiogenetic action through the transmembran receptors VEGFR1 and VEGFR2. The prognostic value of the measurement of these factors in the blood serum of patients is still controversial while their evaluation in the washing has not been studied sufficiently.
Methods: We try to define the VEGF, VEGFR1 and VEGFR2 and the ratios of VEGF/VEGFR1 and VEGF/VEGFR2 in the blood serum and the bronchial washing of patients with newly diagnosed non-small cell lung cancer (NSCLC) and their correlation with the basic clinical characteristics of the patients and the tumors, the treatment response of those who had chemotherapy, the progression free survival (PFS) and the overall survival (OS) of the patients. We will also investigate the correlation of positive VEGF immunohistochemistry with concentration of angiogenic markers in serum and washing. Forty patients with newly diagnosed NSCLC participated in the current study. The measurement of the circulating and washing levels of VEGF, VEGFR1 and VEGFR2 was carried out with the sandwich enzyme-linked immunosorbent assay (ELISA). For immunohistochemistry we have used specific anti- VEGF (Biogenex, San Ramon, CA).
Results: Circulating VEGF levels is correlated with T descriptors in TNM staging system (P=0.021), as well as the ratio VEGF/VEGFR2 in serum and washing (P= 0.03. and P=0.040 relatively). From those who were treated with chemotherapy, best responses were observed in lower concentrations of VEGF in serum and washing (P<0.001). Higher concentrations of VEGF in washing are correlated with worse overall survival (HR 2.208, 95%CI 1.132-4.308, P=0.020) and PFS (HR 2.265, 95%CI 1.145-4.483, P=0.019). Similar results for OS and PFS were observed with high values of the VEGF/ VEGFR2 ratio in washing (HR 3.056, 95%CI 1.483-6.297, P=0.002 for survival and HR 3.067, 95%CI 1.508-6.236, P=0.002 for PFS). Multivariate Cox analysis revealed as independent markers for overall survival VEGFR2 levels in serum and washing (P=0.017 και P=0.004 relatively), while for PFS independent markers were VEGFR1 (P= 0.004),

VEGF/VEGFR1 (P=0.033) and VEGF/VEGFR2 (P=0.007) in washing. No correlation was noted between IHC-VEGF and circulating or washing angiogenic markers.
Conclusion: The circulating VEGF levels are controversial. Nevertheless, the definition of angiogenic markers in bronchial washing could recognize a high risk group of patients who could benefit from an aggressive initial therapeutic approach.
Keywords: angiogenesis, prognostic markers, Non-small cell lung cancer

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P2.041 EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION ANALYSIS OF NON-SMALL CELL LUNG CANCER IN SOUTH KOREA: SUMMARY FROM A NATIONWIDE SURVEY

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Background: Epidermal growth factor receptor (EGFR) mutation analysis is a primary test for predicting the response to EGFR-tyrosine kinase inhibitor. The overall EGFR mutation rates of Korean patients were reported to be lower than in other East Asian countries. To provide comprehensive data of EGFR mutation status of lung cancer in Korea, The Cardiopulmonary Pathology Study Group of Korean Society of Pathologists initiated a nationwide survey.
Methods: We summarized 1,753 EGFR mutation reports from 15 hospitals made between January 2009 and December 2009. We compared EGFR mutations with patient age, gender, history of smoking, histologic diagnosis, specimen type, procurement site, tumor cell dissection, and laboratory status.
Results: The overall EGFR mutation rate was 34.3% in non-small cell lung cancer. Adenocarcinoma histologic type showed a 43.3% EGFR mutation rate. EGFR mutation rates were significantly higher in woman, patients who never smoked, adenocarcinoma, and excisional biopsy specimen. EGFR mutation rates did not differ with patient age, laboratory status, tumor dissection, or procurement site.
Conclusion: EGFR mutation rates and status were similar to those in published data from other East Asian countries.
Keywords: lung, Cancer, Epidermal growth factor receptor, Mutation

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P2.042 URINE DIACETYLSPERMINE AS A NOVEL TUMOUR MARKER FOR LUNG CANCER

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Background: Serum carcinoembryonic antigen(CEA) , cytokeratin 19 fragment(CYFRA21-1) and pro-gastrin-releasing peptide(Pro-GRP) have been used as tumour markers for non small cell lung cancers(NSCLC) and small cell lung cancer (SCLC). A novel urine tumour marker,diacetylspermine, was compared with the three conventional serum tumour markers in 308

patients with lung cancer.
Methods: The series consisted of 308 patients with lung cancer who were treated in Hamanomachi General Hospita, Fukuoka, Japan from August 2003 to September 2010. The 308 patients were 199 men and 109 women and their age ranged from 25 to 89 years with a mean of 66.9±10.4 years. 296 patients with NSCLC and 12 patients with SCLC were enrolled in this study. Urine diacetylspermine(DiAcSpm) , serum CEA, CYFRA21-1 and Pro-GRP were examined in these patients. A urine tumour marker, DiAcSpm was measured by using ELISA system, which was created by Transgenic Co.Ltd, Kumamoto, Japan. The cut off level was set at 325nmol/g Creatinine. The serum levels of CEA, CYFRA21-1 and Pro-GRP were measured in the Clinical Laboratory of Hamanomchi General Hospital. Their cut-off levels were 5.0ng/ml, 3.5ng/ml and 45.9pg/ml respectively. The clinical stage of lung cancer was determined according to TNM Classification of Lung Cancer by the IASLC 2009.The 98 patients were Stage IA, 68 patients-Stage IB, 12 patients-Stage IIA, 20 patients-Stage IIB, 41 patients-Stage IIIA, 39 patients-Stage IIIB and 30 patients-Stage IV, respectively. Mean values were compared by McNemar test and $P<0.05$ was considered as statistically significant.
Results: The sensitivity of urine DiAcSpm was 46.4% and was higher than that of serum CEA(32.7%) and serum CYFRA21-1(23.7%). The specificity of urine DiAcSpm(90.6%) was higher than that of serum CEA(85.7%) and lower than that of serum CYFRA21-1(93.7%). The sensitivity of urine DiAcSpm and other markers was compared among lung cancer patients grouped according to tumour stage. The proportion of positivies with respect to each marker increased with the progression of the cancer, but the sensitivity of DiAcSpm was higher than the snesitivities of CEA and CYFRA21-1 at every clinical stage. Especially, DiAcSpm was elevated in 48.2% of early-stage(stage IA+IB) lung cancers in patients , whereas 24.2% and 11.4% of these patients were CEA- and CYFRA21-1-positive, respectively. Pathologically, the sensitivities of DiAcSpm were 39.5% in patients with adenocarcinoma, 62.0%(SCC), 53.8%(Ad-SCC) and 66.7%(SCLC) , whereas the sensitivities of CEA and CYFRA21-1 were 31.3% and 17.3% in adenocarcinoma, 33.0% and 47.6% in SCC, 15.4% and 38.5% in Ad-SCC respectively, and the sensitivity of Pro-GRP was 88.9% in patients with SCLC.
Conclusion: These results indicate that urinary DiAcSpm is a more sensitive marker than CEA, CYFRA21-1 and that it can efficiently detect lung cancer at early stages.
Keyword: urine diacetylspermine, tumour marker, lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.043 THE POTENTIAL BIOLOGICAL ROLE OF FIBROBLAST GROWTH FACTOR-9 IN MALIGNANT MESOTHELIOMA

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Background: Malignant mesothelioma (MM) kills one patient every 4 hours in the UK and 800 patients each year in Australia. Currently, there are no effective treatments for MM and the median survival period is ~9 months. Identifying novel key molecules in the pathobiology of MM is urgently needed in order to develop new therapies and biomarkers.
Methods: cDNA (Affymetrix) microarray was used to profile 22 prospectively-collected, well-characterised human thoracoscopic pleural tissue biopsies to assess the differential regulation of genes in MM. The over-expression of novel genes in pleural biopsies was confirmed using RT-PCR. Pleural fluid FGF-9 levels in patients and cytokine levels from in vitro experiments were measured using commercially available ELISA kits. Proliferation was measured using a surrogate WST-1 assay while cell invasion was assessed using Matrigel assay.
Results: From our microarray data, we found that fibroblast growth factor-9 (FGF-9) was the leading novel candidate gene with a median overexpression of 17 fold in MM over metastatic pleural carcinomas and benign pleuritis. The over-expression of FGF-9 was confirmed in pleural biopsies from a second

patient cohort (n=24) with a median of 35-fold increase. In addition, in the Oxford cohort of 273 prospectively-collected undiagnosed pleural fluids, pleural fluid FGF-9 levels in MM patients (n=43) were 7.2 fold and 4.6 fold higher than in metastatic pleural cancers (n=137) and benign pleuritis (n=103), p<0.05 for both. Similarly, we found that in an independent cohort (Perth, Western Australia), pleural fluid FGF-9 levels in MM patients (n=205) were 12.5 fold and 11.3 fold higher than metastatic pleural cancers (n=210) and benign pleuritis (n=224), p<0.05 for both. The sensitivity and specificity for this novel protein at a cut-off value of 559 ng/mL was 77% and 85% respectively. The area under the curve was 0.859, which is comparable to that of other MM biomarkers such as mesothelin. FGF-9 is important in the pathobiology of MM. Exogenous FGF-9 (at 100 ng/mL) induces dose- and time-dependent proliferation of both human and murine MM cells up to 2 fold over serum-free control. Furthermore, exogenous FGF-9 (100 ng/mL) induces a dose- and time- dependent release of IL-8 (or MIP-2), VEGF and MCP-1 from human and murine MM cells by 3, 2 and 2.5 fold respectively over serum-free treated controls. These cytokines are known to be playing a role in the MM pathobiology and they were significantly inhibited with the addition of ERK inhibitor, PD98059, JNK inhibitor, SP600125, and p38 inhibitor, SB203580 (p<0.05 for all). In addition, FGF-9 induces MM cell invasion (Matrigel assay) in vitro. The addition of pleural fluid containing high levels of FGF-9, to human MM cells (as an ex-vivo model), significantly induces the release of the above-mentioned cytokines thereby further supporting a role for FGF-9 in cytokine release important in MM pathobiology.
Conclusion: MM produces high levels of FGF-9 which potently induces MM cell proliferation and cytokine release.
Keywords: FGF-9, mesothelioma

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P2.044 ELEVATED CIRCULATING PLATELET AND ENDOTHELIAL MICROPARTICLES IN PATIENTS WITH LUNG CANCER

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Background: Microparticles (MPs) are small membrane vesicles shed from the cell surface in response to various stimuli and are considered to be involved in the pathophysiology of disease. In cardiovascular disease, platelet-derived microparticles (PMPs) are a marker of platelet activation and associate with thrombotic events. Endothelial microparticles (EMPs) are associated with endothelial activation in various vascular diseases. Most cancer patients have activated circulating platelets and high levels of angiogenesis. The aim of this study is to evaluate the levels of circulating PMPs and EMPs in patients with lung cancer and investigate their correlation with the activation of angiogenesis and coagulation.
Methods: This study included 44 consecutive patients with newly diagnosed lung cancer and 19 control subjects. MPs were measured in platelet-poor plasma and stained using cell specific fluorescence-labeled monoclonal antibodies: anti-CD42b-phycoerythrin and anti-VE-cadherin -PE on a flow cytometer. Plasma concentrations of vascular endothelial growth factor (VEGF), thrombin-antithrombin complexes (TATs) and prothrombin activation fragment (F_{1+2}) were measured by enzyme-linked immunosorbent assay.
Results: There were no differences between the lung cancer and control groups in age (P= 0.511) or gender (P=0.095). The percentages of those with hypertension and diabetes mellitus were not significantly different between groups. Twenty-eight patients had adenocrcinoma, 7 squamous cell carcinoma, and 9 small cell carcinoma. Thirty-eight patients (86%) had advanced stage (III and IV) disease. Platelet counts were significantly higher in patients than controls (290± 19 x10^3/μl versus 215± 11 x10^3/μl, P=0.034). The median concentrations of CD42b+ PMPs and VE-cadherin+ EMP were higher in patients than controls (1964/μl vs 1148/μl, P=0.006; 365/μl vs 256/μl, P=0.04; respectively). The median levels of plasma VEGF and TATs in patients were significantly higher than in controls (61.7pg/ml vs 44.8pg/ml, P= 0.006; 3.66μg/l vs 1.2μg/l, P=0.003; respectively). The circulating PMP and EMP levels significantly correlated with the

plasma levels of VEGF (r=0.495, P=0.001; r=0.395, P=0.01) in the patients. PMP levels negatively correlated with TATs and F1+2(r = -0.74, P= 0.642; r = -0.117, P= 0.461) but were not significantly different. There was no significant association between TATs or F1+2 and VE-cadherin+EMP.
Conclusion: We demonstrated the levels of circulating PMPs and EMPs are significantly elevated in patients with lung cancer. Our results highlight a potential link between PMPs and plasma VEGF levels. This possibility may be the expression of complicated interaction between platelet activation and tumor angiogenesis. VE-cadherin^{+}MP might be a potential marker of endothelial activation during tumor angiogenesis.
Keywords: platelet microparticles, endothelial microparticles, Lung cancer

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P2.045 PROGNOSTIC VALUE OF THE PROTEIC EXPRESSION PROFILE IN LOCALLY ADVANCED NON-SMALL CELL LUNG CARCINOMA.

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Background: Lung cancer is the most common cause of death from cancer worldwide. Identifying potentially predictive cellular markers of prognosis in non-small cell lung cancer (NSCLC) is becoming increasingly relevant. This study evaluated the prognostic impact of the expression of cellular and molecular markers in the determination of overall survival.
Methods: This is a retrospective study of 64 patients with locally advanced NSCLC, treated with radiotherapy alone or associated with chemotherapy. Tumor samples were analyzed through immunohistochemistry (IHC) for the proteic markers: p21, p27, p53 and pRb. Normal or abnormal expressions were correlated with survival by univariate and multivariate analyses that also included potential prognostic factors as age, sex, histology, clinical stage and treatment modality.
Results: Clinical stage showed significant correlation with median overall survival (IIIA: 34 months, IIIB: 13 months - p=0.01). Median overall survival correlated with p21-marker expression (normal p21 expression: 14 months, abnormal p21 expression: 21 months - p=0,02). The other markers did not show significant correlation with survival. Multivariate analysis showed an independent prognostic role for clinical stage and for the expression of p21.
Conclusion: In the present study, clinical stage and the p21 expression correlated with poor outcome in patients with locally advanced NSCLC.
Keywords: Non small cell lung cancer, prognostic value, proteic expression

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P2.046 BLOOD-BASED BIOMARKERS ASSOCIATED WITH OUTCOMES IN ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH BEVACIZUMAB PLUS CHEMOTHERAPY

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Background: It's difficult to identify which patients will benefit most from the bevacizumab treatment. So we sought to find blood-based biomarkers that can be used to predict efficacy in advanced non-small cell lung cancer patients treated with bevacizumab plus chemotherapy.
Methods: Blood was collected before treatment and after six weeks of therapy from patients who were participating in an phase 4 trial. Plasma vascular endothelial growth factor (VEGF) levels were evaluated by ELISA.
Results: A total of eight single nucleotide polymorphisms in four candidate genes were analyzed by PCR and sequencing. A total of 45 patients enrolled in a clinical trial at Guangdong General Hospital between August 2007 and March 2008 were used as subjects. The median OS were 25.6 and 13.4 months in the low and high groups respectively, when the median posttreatment plasma VEGF level (46.63pg/ml) was used as the cut-off point (P=0.0284). Patients carrying the AA genotype at the -6C>A polymorphism in laminin 5 (LN5) were more likely to exhibit reduced hemoglobin compared

to patients carrying the CA/CC genotype (OR=8.364, x^2=5.34, P=0.021). Similar associations were found at the -89A>G and -260C>A polymorphisms in LN5. Patients with the CC genotype at the -6C>A polymorphism in LN5 had an increased risk of neutropenia than those with the CA/AA genotype (OR=4.444, X^2=5.116, P=0.030).
Conclusion: Our results show improved survival in patients with lower posttreatment plasma VEGF levels treated with bevacizumab plus chemotherapy; thus, the posttreatment plasma VEGF level may be a promising biomarker to predict clinical benefit early in the course of therapy. Polymorphisms in LN5 were associated with a reduced level of hemoglobin and neutropenia.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.047 MUTATION STATUS OF EGFR, K-RAS AND P53 IN SORTED ADENOCARCINOMA CELLS

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Background: Recent evidence indicates that tumors contain a small population of cancer cells that are responsible for tumor maintenance and spreading. Lung cancer was reported to contain a rare population of CD133 positive cancer cells able to self-renew and generate an unlimited progeny of non-tumorigenic cells. The presence of somatic mutations in the kinase domain of the epidermal growth factor receptor (EGFR) correlates with tumor sensitivity to the EGFR inhibitors, erlotinib and gefitinib. Some modifications of EGFR gene that causes resistance to gefitinib is reported to be sometimes present in a minor population of tumor cells. We hypothesize that small proportion of the tumor cells that have specific gene mutation affect clinical tumor behavior, such as drug resistance. We aim to examine whether there is any difference of gene mutation in EGFR, K-ras and p53 between CD133 positive cells and negative cells in lung adenocarcinoma.
Methods: Lung adenocarcinoma samples were obtained from consenting 10 patients who underwent pulmonary resection for treatment of lung cancer. The study is to be approved by the Research Ethics Board at Kansai Medical University. Tumor tissues were mechanically dissociated and incubated with Collagenase/Dispase (Roche) and DNase I (Roche), followed by magnetic bead separation to remove dead cells (Miltenyi Biotec). The lung cancer cells were magnetically labeled and separated by antibodies. Cancer cells in 5 specimens were sorted with antibody of CD133 and 5 samples were separated with antibody of EGFR. CD133 Cell Isolation Kit (Miltenyi Biotec) were used in cell separation of CD133 positive cells and EGFR antibody conjugated to magnetic beads (R&D) were used in EGFR positive cells. Exons 18 through 22 of EGFR are were assessed by quantitative real-time polymerase chain reaction, and exon 1 of K-ras and exon 5 through 8 of p53 by sequencing.
Results: In CD133 analysis, CD133 expression of cancer cells in five lung cancer samples ranged from 1.8% to 24.8% (1.8, 2.7, 5.6, 10.4 and 24.8). Two cases of bronchiolo-alveolar carcinoma showed lower levels of CD133 expression (1.8% and 2.7%) than three cases of papillary adenocarcinoma. Among five cases, there were four cases that had EGFR mutation, no case of K-ras mutation, two cases of p53 mutation. There was no difference in mutation status of EGFR, K-ras and p53 between CD133 positive cells and negative cells. In EGFR analysis, there was no difference in mutation status of EGFR, K-ras and p53 between sorted cells by EGFR antibody.
Conclusion: In our analysis, sorted cancer cells of lung adenocarcinoma by CD133 and EGFR did not have any difference in gene mutation status of EGFR, K-ras and p53.
Keywords: Adenocarcinoma, EGFR, Kras, P53

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P2.048 NOVEL BIOMARKERS IN NON-SMALL CELL LUNG CANCER DISTINGUISH SQUAMOUS-CELL CARCINOMA AND ADENOCARCINOMAS SAMPLES.

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Background: Despite advances in early detection and standard treatment, non-small-cell lung cancer is often diagnosed at an advanced stage and carries a poor prognosis. Greater knowledge of the molecular origins and progression of lung cancer may lead to improvements in the treatment and prevention of the disease.
Methods: Microarray analysis was performed on a set of 46 tumour samples and 45 paired non-tumour samples of non-small cell lung cancer (NSCLC) samples in order to establish gene signatures in primary adenocarcinomas and squamous-cell carcinomas, determine differentially expressed gene sequences at different stages of the disease and identify sequences with biological significance for tumour progression. After the microarray analysis, the expression level of 92 selected genes was validated by qPCR and the robust Bonferroni test in an independent set of 70 samples composed of 48 tumour samples and 22 non-tumour samples. Kaplan Meier survival curves for patients were analyzed for the microarray samples
Results: The differentially expressed gene sequences validated by qPCR distinguished tumour phenotype (tumour vs. non-tumour samples); adenocarcinoma vs. squamous-cell carcinomas (including stages I and IB) and differentiation grades [FDR≤0.05; Bonferroni≤0.05]. An acceptable agreement (CCC)15 was found between microarray and qPCR results.
The Breslow (generalized Wilcoxon), Tarone-Ware and Log-Rank (Mantel-Cox) tests yielded highly significant differences ($p<0.001$), showing short survival times for patients with tumour recurrence.
Conclusion: Besides confirming the significant NSCLC-related gene changes previously reported in gene expression profile analyses (e.g., genes for keratins), our study has identified further differentially expressed genes of importance in NSCLC.
Keywords: Microarray/qPCR, NSCLC, Biomarkers, Expression profiling

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P2.049 ANALYSIS OF SINGLE NUCLEOTIDE POLYMORPHISMS AND RADIATION SENSITIVITY ASSESSED WITH AN OBJECTIVE RADIOLOGICAL ENDPOINT

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Background: It is clinically apparent that some cancer patients are more sensitive to the adverse effects of radiation therapy (RT) than others. This variation may be due, in part, to underlying genetic make-up. Recent studies have shown that single nucleotide polymorphisms (SNPs) within genes involved in DNA damage recognition, DNA repair, and chronic inflammation are associated with adverse effects after RT. The endpoints studied have been largely subjective. Herein we report a study evaluating SNPs in 24 candidate genes and their association with RT sensitivity using an objective radiological endpoint.
Methods: As part of an IRB-approved prospective clinical study, patients undergoing thoracic RT for lung cancer had pre-RT and serial post-RT single photon emission computed tomography (SPECT) lung perfusion scans (providing a 3D map of regional perfusion). Changes in regional perfusion after RT were related to regional RT dose (via image fusion) yielding a patient-specific dose response curve (DRC). The DRC slope is independent of irradiated volume and is taken as a reflection of the patient's inherent sensitivity to RT. The DRC was obtained from the non-tumor bearing contralateral lung to avoid issues related to reperfusion after treatment of central tumors. DNA was extracted from patient blood samples using the QIAamp DNA Blood Mini Kit (Qiagen). Primer pairs for each SNP were designed using the NCBI/Primer Blast program. SNPs were determined using a combination of High Resolution Melting and TaqMan assays. Genotypes were compared against the slope of the DRC using the Kruskal-Wallis test. We evaluated 51 SNPs within 24 genes involved in DNA damage

recognition and repair, fibrosis, and chronic inflammation as well as SNPs that have previously been associated with RT sensitivity. Review of the literature identified the following genes for study: TGFB1, RAD21, RAD51, RAD52, ATM, TP53, XRCC1, XRCC2, XRCC3, ERCC2, ERCC5, NOS2A, SOD2, ATR, APE1, BRCA1, BRCA2, HIF1A, LIG4, GRP, MSH3, MLH1, IL12RB2, and ABCA1.

Results: 39 self-reported Caucasian patients with pre-RT and 3 6 month post-RT SPECT scans and blood samples were identified. Of the 51 SNPs evaluated, 2 exhibited deviation from Hardy-Weinberg equilibrium and in 9 only the heterozygote genotype was observed. Of the remaining 40 SNPs, an association between genotype and increasing slope of the DRC was noted with four including C(-509)T in TGFB1 (rs1800469), G(1301)A in XRCC1 (rs25487), T(1939)C in LIG4 (rs1805386) and G(3748)A in BRCA1 (rs16942).

Conclusion: This small study suggests that polymorphisms within genes involved in repair of DNA damage (XRCC1, LIG4, BRCA1) and fibrosis (TGFB1) are associated with RT sensitivity. Significantly, we used an objective measure of RT sensitivity, which is independent of the dose and volume of normal tissue irradiated. Supported in part by grant NIH R01 CA69579 (LM) and NIH R01 CA115748 (SD)

Keywords: single nucleotide polymorphism, radiation sensitivity, SNP

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P2.050 PROGNOSTIC SIGNIFICANCE OF CANCER STEM-LIKE CELL MARKERS, BLOOD PARAMETERS AND ANGIOGENIC FEATURES IN RESECTED NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related death world-wide and curable solely upon resection. In various tumors, expression of cancer stem-like cell (CSC) markers such as CD133 is prognostically unfavorable. However, in lung cancer data about the prognostic significance of CSC markers are scanty and conflicting.

Methods: We performed an immunohistochemical analysis of the CSC markers CD117, CD133 and breast cancer resistance protein 1 (BCRP1) in a total of 142 completely resected stage I-IIIA non-small cell lung cancer (NSCLC) patients with a median potential follow-up time of 56.5 months. The expression of CSC markers was related to clinico-pathological characteristics, blood parameters, angiogenic features, relapse and survival.

Results: In univariate analysis, BCRP1 expression was associated with the proportion of metastatic lymph nodes (p0.022), CD117 expression with histology (p0.005) and CD133 expression with tumor size (p0.021) and T status (p0.002). Blood parameters showed no association with clinico-pathological characteristics, whereas microvessel density (MVD) was linked to histology (p0.039) and vascular architecture to T status (p0.029). Cox proportional hazards regression analysis revealed no prognostic significance of CSC markers, but an increased risk of disease-related mortality in patients with pretherapeutic anemia [hazard ratio (HR)4.2, 95%CI1.5-12.0, p0.008] or elevated neuron-specific enolase levels [NSE; HR4.3, CI1.4-12.8, p0.009]. Moreover, anemia was associated with an increased risk of relapse [HR3.4, 95%CI1.4-8.4, p0.007].

Conclusion: Expression of CSC markers appeared to be associated with clinico-pathological characteristics, but not with prognosis in resected NSCLC. In contrast, pretherapeutic anemia and increased NSE levels may indicate an unfavorable prognosis.

Keywords: Cancer Stem-Like Cell Markers, Non-small cell lung cancer, Prognosis

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P2.051 VALIDATION OF PURPORTED SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN THE TRANSFORMING GROWTH FACTOR β1 (TGFβ1) GENE AND RISK OF RADIATION PNEUMONITIS (RP).

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Background: A recent study has suggested an association between TGFβ1 single nucleotide polymorphisms (SNPs) rs1982073:T869C and risk of radiation pneumonitis (RP). A validation study was performed to determine if this association existed in our lung cancer population.
Methods: Patients with non-small cell lung cancer (NSCLC) treated with radiation with stored blood samples were identified. All patients received definitive radiotherapy with or without chemotherapy. Three SNPs of the TGFβ1 gene rs1800469, rs1800470 (previously rs1982073) and rs1800471 were genotyped. We genotyped rs1800470 and rs1800471 by direct sequencing and rs1800469 by Taqman assay. Patient characteristics, treatment information, and toxicity were collected retrospectively using the electronic patient charts. RP was graded using the CTCAE V3. Association between the risk of grade ≥ 2 RP and TGFβ1 SNPs as well as the dosimetric parameters were performed using logistic regression. Interactions between the SNPs and the risk of RP were further performed using additive, co-dominant, dominant and recessive models as well as haplotype analysis. The statistical analysis was applied using SAS 9.2.
Results: Of the 103 patients with stored samples, thirty six patients (35%) developed RP (31 patients with grade 2 and 5 patients with grade 3). The median time to develop RP was 8.8 months. The median dose of radiation was 66 Gy and median MLD and V20 were 16.3 Gy and 28.9 % respectively. Of the total 103 serum samples analyzed, genotypes were available from 99 patients. On univariate analysis, RP was correlated with the history of smoking (p = 0.02; OR: 3.4 95% CI (1.3–10.5) and concurrent chemotherapy (p = 0.024; OR: 3.3 (1.2-9.0). Of dosimetric parameters, MLD ≥ 18 had the highest correlation with RP (p = 0.09; OR: 2.2 (0.9-5.6). There was no statistically significant univariate correlation found between the genotypes of each TGFβ1 SNPs and RP. Multivariate regression analysis identified smoking history, concurrent chemotherapy, and MLD as most associated with RP. None of the TGFβ1 SNPs had a significant correlation with RP when included in the modeling.
Conclusion: Our study showed no significant association between development of RP and any of three TGFβ1 SNPs examined when accounting for dosimetric and other clinical factors. Additional studies will be required to identify genetic risk factors for RP.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.052 A NON-INVASIVE SYSTEM FOR MONITORING RESISTANCE TO EGFR TYROSINE KINASE INHIBITORS WITH PLASMA DNA

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Background: EGFR tyrosine kinase inhibitors (EGFR-TKIs) are widely used to treat lung adenocarcinomas with EGFR activating mutations. However, half of patients acquire resistance because of the gatekeeper T790M mutation. Non-invasive mutation detection system is desired considering the difficulty in obtaining tissue specimens during disease progression.
Methods: Sixty-seven plasma DNA samples from forty-nine lung adenocarcinoma patients and thirty healthy volunteers were evaluated. T790M in plasma DNA was determined using the MBP-QP method. The method combines mutation-biased PCR (MBP)

and genotyping, the latter based on analysis of the melting curve of the probe DNA binding the target mutated site using a fluorescence quenching probe (QP) system.
Results: The detection limit was two copies of control plasmid and 0.2 ng of genomic DNA. The mutant plasmid could be detected when it accounted for as little as 0.3% of a mixture of plasmids carrying EGFR exon 20 with or without T790M. The T790M mutation was detected in plasma DNA from ten of nineteen patients (53%) who acquired resistance, but not in non-responders, patients responding to treatment, or those not treated with EGFR-TKI. Other mutation detection systems, such as the nucleic acid-locked nucleic acid PCR clamp (PNA-LNA PCR clamp), the cycleave PCR technique, and allele-specific oligonucleotide PCR, detected T790M in three, four, and six patients, respectively, among ten in which T790M was detected by the MBP-QP method.
Conclusion: The MBP-QP method is simple, sensitive, and—intriguingly—reflective of clinical course, compared with the other three mutation-detection systems. Thus, the MBP-QP method is an ideal non-invasive monitoring system for detecting T790M in plasma samples.
Keywords: T790M, plasma DNA, Lung cancer, EGFR-TKI

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P2.053 AGR2 AS A NOVEL USEFUL BIOMARKER OF HUMAN LUNG ADENOCARCINOMA

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Background: Lung cancer is the leading cause of cancer death in the worldwide. Despite advances in early diagnostic methods and treatment modarities, lung cancer is often diagnosed at an advanced stage and has a poor prognosis. There is a need for the development of new biomarkers for early detection, defining cancer risk, prognosis, and therapy targets. The purpose of this study was to search useful biomarkers for clinical treatment including early detection and prognosis prediction of lung cancer by performing proteome analysis of human lung adenocarcinoma.
Methods: We assessed high frequently overexpressed proteins in 12 lung adenocarcinoma samples compared to adjacent normal tissue samples by LC-MS/MS coupled with iTRAQ technology and validated the expression of target proteins by immunohistochemistry in 268 cases with lung adenocarcinoma. Then, we measured serum levels of biomarker candidate proteins with 111 lung adenocarcinoma patients and 46 non-cancer controls using ELISA method and we evaluated candidate proteins as diagnostic biomarkers of lung adenocarcinoma with ROC curve analysis. Statistical analysis of the association between the expression levels of candidate proteins and clinicopathological variables, and survival analysis using Kaplan-Meier curves for overall survival with log-rank test was also assessed to evaluate as prognostic biomarkers of lung adenocarcinoma.
Results: LC-MS/MS analyses indicated that anterior gradient protein 2 homolog (AGR2) was a potential biomarker of human lung adenocarcinoma and AGR2 was stained in 94% of 268 lung adenocarcinoma tissues. ELISA assay showed that serum AGR2 level of lung adenocarcinoma patients was significantly higher than that of non-cancer controls. The optimal cut-off point was detected with ROC curve (the AUC 0.858), the sensitivity and specificity of this cut-off point was 65.8% and 87%, respectively. Kaplan-Meier curves for overall survival showed that positive serum expression level of AGR2 (above the cut-off point) was significantly associated with poor prognosis compared to negative expression (log-rank test; p=0.037).
Conclusion: In this study, it is showed that AGR2 has possibility to be a novel biomarker for diagnosis and prognosis of lung adenocarcinoma. Further studies are required to clarify the biological significance of AGR2 overexpression in lung adenocarcinoma and finally to evaluate its usefulness as a novel diagnostic or prognostic biomarker to reach adequate therapeutic modality in clinical practice.
Keywords: lung adenocarcinoma, AGR2, biomarker, proteomics

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P2.054 FOLATE PATHWAY IMPLICATIONS IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC): IMPACT OF THYMIDYLATE SYNTHASE (TS) PROMOTER AND METHLYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) C677T AND A1298C VARIANTS EXPRESSION ON PATIENTS' OUTCOME AND CORRELATION WITH P53 CODON 72 MUTATIONS.

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Background: Folate depletion and its resultant reduction of DNA synthesis and DNA methylation must be toxic to malignant cells, resulting in DNA damage and hypomethylation. Paradoxically, inhibition of folic acid metabolism has been used as a mechanism for successful elimination of malignant cells, but insufficient folic acid levels in normal cells have been associated with malignant transformation. TS and MTHFR are involved in folate metabolism. Two functional single nucleotide polymorphisms (SNPs) in the 5,10 methylenetetrahydrofolate reductase gene, C677T and A1298C lead to decreased enzymes activity and affect chemosensitivity of tumor cells. Also TS expression is influenced by a variable number of tandem repeats (VNTR) in TS gene. Hypometylation of the p53 tumor suppressor gene has been described in folate depletion. p53 codon 72 polymorphisms influencing the function of the protein seems to increase the risk of developing lung cancer. We investigated whether MTHFR SNPs and TS tandem repeats were associated with time to progression (TTP) and overall survival (OS) in 50 locally advanced and metastatic NSCLC patients and evaluated the correlations with p53 codon 72 polymorphisms.
Methods: Pts (36 M/14 F) median age was 61.5 (range 45-84). ECOG PS 0/1/2/: 15/21/14. 78% of pts had a metastatic disease and 22% IIIB stage. Histology was: squamous carcinoma 25/50, adenocarcinoma 18/50, bronchiolar-alveolar adenocarcinoma 2/50, undifferentiated 5/50. All pts were treated with one or more therapeutic lines. Clinical and outcome data were collected. Genomic DNA was isolated from peripheral blood lymphocytes of pts, using Puregene Genomic DNA Purification System. Genotyping for MTHFR polymorphisms was carried out by DG-DGGE (double gradient-denaturing gradient gel electrophoresis), for p53 codon 72 (Arg/Pro) with the use of fluorogenic allele-specific oligonucleotide TaqMan probes on a 7900HT Fast Real-Time PCR System and for TS Promoter Polymorphisms with PCR and subsequent electrophoresis on 3% agarose gel. Patients outcome data were compared with TS VNTR, MTHFR SNPs and/or p53 codon 72 polimorphisms expression. A multivariate analysis was performed.
Results: We have recorded no significant correlation among TTP and OS data and the individual expression of MTHFR SNPs, TS tandem repeats, and p53 codon 72 polymorphisms. No difference in TTP were recorded in the multivariate analyses including the TS, MTHFR and p53 codon 72 genotypes. However, the combined MTHFR CT677/AC1298 genotype was significantly associated with longer survival (34,5 months $p<0,05$) also in association of TS genotype homozygous for triple repeats (3R/3R), (29,5 months $p<0,05$).
Conclusion: Although preliminary, these data support the role of MTHFR and TS genotypes as prognostic markers in NSCLC pts. Genotyping for p53 codon 72 polimorphisms do not predict for patients' outcome. Further validation and investigation of the involvement of genotypes of folate metabolizing enzyme are needed to confirm these findings and to evaluate their correlation with chemotherapy metabolism and activity.
Keywords: Non small cell lung cancer, MTHFR polymorphisms, TS promoter variants, p53 codon 72 mutations

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P2.055 PATHOLOGIC COMPLETE RESPONSE TO INDUCTION THERAPY OF NON-SMALL CELL LUNG CANCER IS ASSOCIATED WITH FOXP3+/CD8+ TUMOR-INFILTRATING T CELL RATIO

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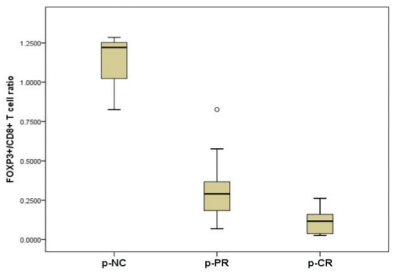
Background: Survival benefits of induction therapy followed by surgery for locally advanced non-small cell lung cancer (NSCLC) have been shown, but factors influencing chemo-sensitivity remain unclear. Anti-cancer agents are suggested to mediate cytotoxic effect not only directly on tumor cells but also through the immune system. We investigated the relationship between T cell distribution in tumor stroma and pathologic responses to chemoradiotherapy in patients with locally advanced NSCLC.
Methods: We chose 20 patients with c-stage IIB to IIIB NSCLC who underwent platinum-based chemotherapy and concurrent radiation followed by surgery from January 2006 to January 2011. Tumor-infiltrating T cells expressing CD8 or FOXP3 were detected by immunohistochemical staining from biopsy and surgically removed specimens. FOXP3+/CD8+ T cell ratio was calculated based on the cell count at 200x magnification.
Results: Patients characteristics were as follows: 18 males, with average age of 60.9 years (range of 42-74), 7 adenocarcinomas, 9 squamous cell carcinomas, 2 adenosquamous carcinomas, and 2 undetermined NSCLCs. Pathologic responses were NC for 3, PR for 11, and CR for 6 patients. The mean values of FOXP3+/CD8+ T cell ratio in operative specimens were 1.11 for p-NCs, 0.32 for p-PRs, and 0.12 for p-CRs (P = 0.004). Pre-treatment TBLB specimens were available in 11 patients (3 p-NCs, 6 p-PRs, and 2 p-CRs). FOXP3+/CD8+ T cell ratios in operative specimens after induction therapies were elevated compared with that of biopsy specimens in p-NC patients, whereas the ratios were decreased in p-PR and p-CR patients.



Conclusion: Tumor-infiltrating T cell distribution suggested by FOXP3+/CD8+ T cell ratio can be a marker for effectiveness of chemotherapy in patients with NSCLC.
Keywords: Non-small cell lung cancer, regulatory T cell, tumor-infiltrating T cells, induction therapy

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P2.056 HIGHLY SENSITIVE DETECTION OF SOMATIC EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) GENE MUTATIONS IN CIRCULATING TUMOR CELLS (CTC) FROM PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH CISPLATIN/PEMETREXED OR AFATINIB

Frank Breitenbuecher[1], Sandra Hoffarth[1], Thomas C. Gauler[1], Sarah L. Stergar[1], Stefan Kasper[1], Jens Köhler[1], Karl Worm[2], Angela Märten[3], Kurt W. Schmid[2], Martin Schuler[1]
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Background: Activating somatic mutations in the EGFR gene define a group of genetically dependent pulmonary adenocarcinoma, which are exquisitely sensitive to treatment with EGFR tyrosine kinase inhibitors (EGFR-TKI). Hence, EGFR mutation status has been established as a biomarker to guide therapeutic decisions in advanced NSCLC patients. The majority of activating mutations cluster in exons 19 and 21 of the EGFR gene. Another type of EGFR mutations leading to a T790M amino acid

substitution has been found in up to 65% of patients acquiring resistance to EGFR-TKI, as well as in rare cases of primary resistance. In clinical practice, EGFR mutations are determined in fresh or archival tumor biopsies, which do not necessarily reflect the status of all current tumor manifestations. Sequential biopsies or biopsies of multiple tumor lesions are not routinely performed for patient safety. The availability of non-invasive methods for repetitive determination of prognostic and predictive genetic biomarkers would greatly facilitate personalized treatment strategies in lung cancer. Against this background we reasoned whether circulating tumor cells (CTC) spreading via the bloodstream, which may be derived from different disease sites (primary tumor, metastases) with potentially diverse genotypes, are suited for EGFR mutation analysis in NSCLC. Potential applications include rapid genotyping prior to EGFR-TKI treatment, monitoring of treatment-induced reduction of the patient's systemic tumor burden, as well as early detection of disease relapse and drug resistance.
Methods: We have developed a highly sensitive "real time" PCR-based method using individually designed probes to detect >90% of all activating EGFR mutations (including the majority of DelEx19 variants) as well as the T790M mutation to analyze CTC isolated from peripheral blood (PB) of EGFR–mutant NSCLC patients treated at our center in an IEC-approved diagnostic pilot study. Written informed consent was obtained from all patients. Sampling of 40ml of PB, isolation of CTC and EGFR mutation analysis was conducted in 10 patients either treated with chemotherapy or the irreversible erbB family blocker afatinib within 7 days prior to start of therapy, and at regular visits thereafter. An additional analysis was performed at clinical progression and/or termination of therapy.
Results: Combining immunomagnetic CTC enrichment with mutation-specific PCR analysis we were able to detect EGFR mutations at sensitivities ranging from 0.2% up to 0.0005% against a background of wild type alleles. In this pilot study, mutations were detected in CTC-derived genomic DNA from all 10 patients suffering from advanced NSCLC with known EGFR mutations. Clearance of peripheral blood from EGFR mutation-positive CTC correlated with clinical and radiological response to afatinib or chemotherapy.
Conclusion: We have successfully developed a diagnostic strategy for highly sensitive detection of EGFR mutations in CTC from NSCLC patients. Mutation signal intensities correlated with clinical treatment response. This technology could be useful for rapid, non-invasive stratification of NSCLC patients for mutation-triggered personalized pharmacotherapies. Sequential analyses may facilitate "online monitoring" of treatment response at a genomic level.
Keywords: circulating tumor cells, epidermal growth factor receptor (EGFR) gene mutations, Non-small cell lung cancer (NSCLC)

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.057 TRANSKETOLASE INVOLVED CANCER CELL PROLIFERATION AND VEGF SECRETION IN LUNG ADENOCARCINOMA ASSOCIATED MALIGNANT PLEURAL EFFUSION

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Background: Transketolase (TKT), the key enzyme in the pentose phosphate pathway, which mediates the conversion of glucose to ribose phosphate, is used in the biosynthesis of nucleic acids and nucleotides. TKT and the isoenzyme of transketolase, transketolase-like (TKTL)-1, have been demonstrated to play a pivotal role in cancer cell proliferation. However, cancers are heterogeneous, representing not only involved in proliferative activity but also the potential for metastasis and angiogenesis and the correlation with TKT were not well demonstrated. Malignant pleural effusion (MPE) accompanying lung adenocarcinoma indicates poor prognosis and early metastasis. Cancer cells that proliferate in MPE are anchorage independent and VEGF plays the key mediator in pleural effusion formation by increasing vascular permeability. In our previous study, we found high TKT expression in MPE in micro-array analysis. In our recent study, we plan to verify the aberrant expression of TKT in primary lung cancer tissue, metastatic pleural tumor, and MPE. We further investigate the effect of inhibition of TKT on lung cancer cell proliferation, anchorage-independent growth, and VEGF secretion.

Methods: Immuno-histochemical and immuno-fluorescence staining were used to confirm the aberrant TKT in tumor cells. Oxythiamine (transketolase inhibitor) was used to investigate the significance of TKT on the proliferation of lung cancer cells via MTT assays. PC14PE6/AS2 cells were transfected with siRNA against human TKT expression (TKT siRNA) and mismatch control oligonucleotides (scramble siRNA). Cell proliferation after transfection was detected by flow cytometry analysis with proliferation-associated antigen Ki-67 and cell colony formation assay. To investigate the significance of TKT on anchorage independent cell growth, PC14PE6/AS2 cells were maintained in ultra-low attachment plate to investigate the effects on cells clusters formation. ELISA of VEGF secretion of the conditioned medium and the in vivo permeability assay (Miles permeability assay) were performed to evaluate if knockdown of TKT can down-regulate VEGF and lead to diminished vessel permeability.
Results: Immuno-histochemical analyses of 48 lung adenocarcinoma specimens showed higher staining scores for TKT in tumor tissue than in adjacent healthy tissue. Oxythiamine inhibited the proliferation of lung cancer cells dose-dependently . MTT assays showed that the IC_{50}s of all cells were around 10-20 mM. The transfection of TKT siRNA into cells suppressed cell clusters formation and proliferation; the proportion of ki-67 staining was lower in cells (54%) than in the scramble control (74%). The rate of colony growth also decreased (20%) by colony formation assay. ELISA of VEGF secretion of the conditioned medium revealed decreased VEGF secretions in si-TKT PC14PE6/AS2 cells compared to the si-scramble controls. Miles permeability assay showed that knockdown of TKT can lead to diminished vessel permeability. The areas of dye leakage induced by conditioned medium from TKT siRNA PC14PE6/AS2 cells were smaller than the leakage area from scramble transfected cells.
Conclusion: Transketolase is important not only in cancer cell proliferation but also in anchorage independent cell growth and VEGF secretion in MPE. This study reveals the significance of the pentose phosphate pathway in MPE formation, which may facilitate the development of new treatment strategies for MPE-associated lung adenocarcinoma.
Keywords: transketolase, Lung cancer, VEGF, anchorage-independent growth

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.058 ALDH7A1 EXPRESSION IS ASSOCIATED WITH RECURRENCE IN PATIENTS WITH RESECTED NON-SMALL CELL LUNG CARCINOMA

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Background: The aldehyde dehydrogenase (ALDH) enzymes are important for detoxification of endogenous and exogenous aldehydes. Expression of ALDH family members has recently been described as a potential marker for tumor-initiating cancer stem cells in a variety of human malignancies, including lung cancer. We were interested to determine whether expression of ALDH7A1, a member of the ALDH family, has prognostic significance in resected non-small cell lung carcinoma (NSCLC).
Methods: Tumor specimens were obtained for 107 patients with completely resected stage I through stage III NSCLC from paraffin-embedded tissue microarrays and stained with an antibody specific for ALDH7A1. Staining patterns were graded by a pathologist based on the intensity of staining and the percentage of cells stained. A staining score index was calculated by multiplying intensity score by the percentage area with positive staining.
Results: Positive ALDH7A1 staining was identified in 46 patients, and negative staining was noted in 48 patients, with 13 tumor sections missing. Multivariate analysis demonstrated that NSCLC patients with positive ALDH7A1 expression had decreased overall survival relative to ALDH7A1-negative tumors, although this did not reach significance (hazard ratio 1.42, 95% confidence interval 0.84 to 2.389; p=0.192). However, patients with ALDH7A1-expressing NSCLC tumors had a significantly higher incidence of lung cancer recurrence compared to patients with ALDH7A1-negative tumors (hazard ratio 6.24, 95% confidence interval 2.06 to 18.86; p=0.001).
Conclusion: These data indicate that ALDH7A1 staining is present in a substantial number of NSCLC tumors and may be a biomarker predictive for

increased incidence of cancer recurrence in patients with surgically resected NSCLC.

Keywords: aldh, stem cell, NSCLC, biomarker

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.059 AMPLIFICATION OF THE ACTN4 GENE IN STAGE I ADENOCARCINOMA OF THE LUNG

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Background: Even if detected at an early stage, a substantial number of lung cancers relapse after surgery. Patients with such tumors are likely to benefit from adjuvant therapy, but no method for discriminating them has been established. Actinin-4 is an actin-binding protein that we originally identified as being associated with enhanced cell motility. Knockdown of actinin-4 suppresses the migration and invasiveness of cancer cells. Conversely, its overexpression in mice increases cell motility and causes metastasis. The expression of actinin-4 protein is closely associated with a poor outcome in patients with cancers of the breast, colorectum, pancreas, and ovary. Here we report that increased expression and gene amplification of actinin-4 can identify a distinct subset of patients with stage I lung adenocarcinoma in whom the outcome will be extremely unfavorable even after complete resection of their tumors. This subset of patients requires intensive medical attention and might benefit from adjuvant chemotherapy.

Methods: We performed a retrospective analysis of multiple cohorts totaling 1744 patients who underwent complete resection of lung adenocarcinoma. The expression of actinin-4 protein in the tumors was evaluated immunohistochemically, and the copy number of the actinin-4 (ACTN4) gene was determined by fluorescence in situ hybridization.

Results: Amplification of the ACTN4 gene was significantly correlated with smoking history ($P = .02$), pathological stage ($P = .002$), and histological differentiation ($P < .001$). Overall survival was significantly worse for patients with all stages from stage I to IV, and stage I lung adenocarcinoma harboring ACTN4 gene amplification than for those whose tumors showed no such gene amplification ($P < .001$ and $P < .001$). Multivariate analysis revealed that ACTN4 gene amplification in all stages from stage I to IV , and stage I lung adenocarcinoma was an independent factor associated with a higher risk of death (hazard ratio, 2.65 ; $P < .001$ and 6.78; $P < .001$). The 5-year survival rate of patients with stage I lung adenocarcinoma showing increased actinin-4 protein expression and ACTN4 gene amplification was 63%, 70% and 55%, whereas that of patients whose tumors lacked gene amplification was 86%, 93% and 87%, and that of patients whose tumors lacked actinin-4 protein expression was 97, 96% and 90% in three independent cohorts. The former had significantly worse overall survival than either of the latter in every cohort ($P < .001$).

Conclusion: Amplification of the actinin-4 gene defines a subset of stage I lung adenocarcinoma with a distinct outcome.

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P2.060 C4.4A IS A PROGNOSTIC INDICATOR IN NON-SMALL CELL LUNG CANCER PATIENTS WITH ADENOCARCINOMAS

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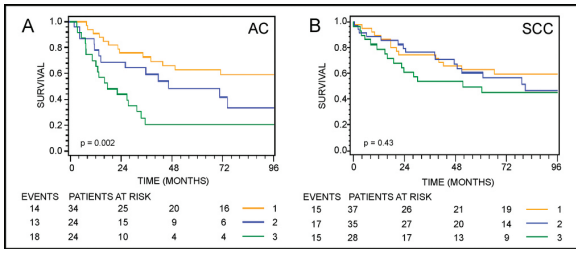
Background: The glycolipid-anchored membrane protein C4.4A is a structural homolog of the urokinase-type plasminogen activator receptor (uPAR) and a member of the Ly6/uPAR/a-neurotoxin protein domain family.[1] We have recently shown C4.4A to be induced in early precursor lesions of non-small cell lung cancer and to be a histologic biomarker for poor prognosis in this disease.[2]
Methods: In the present study, we have undertaken an immunohistochemical, retrospective study on the expression of C4.4A in 229 formalin-fixed, paraffin-embedded non-small cell lung cancer cases. For each patient, one tissue section from the periphery and one from the center of the tumor were stained with our well-characterized polyclonal anti-C4.4A antibody. C4.4A levels were scored semi-quantitatively for intensity and frequency of positive tumor cells (range 0-16) and statistically correlated to survival.
Results: Expression of C4.4A was more pronounced in squamous cell carcinomas (SCC) compared to adenocarcinomas (AC), with median tumor center scores of 8.0 and 1.3, respectively. Consequently, statistical analysis of survival was performed separately for 88 AC and 104 SCC patients. C4.4A score for the tumor center was, together with pathological stage, a highly significant prognostic factor in the AC group both in univariate (p-value = 0.0003; Hazard ratio (95% CI) = 1.48 (1.14-1.91)) and multivariate analysis (p-value = 0.0006; Hazard ratio (95% CI) = 1.72 (1.26-2.35)), demonstrating decreasing survival with increasing score. Only pathological stage was significant for the SCC group. These results validate our earlier observations, now in a larger and independent patient cohort.
Conclusion: Together with recent data demonstrating expression of C4.4A in a fraction of atypical adenomatous hyperplasias, the putative AC precursor lesion, the present results further substantiate the potential clinical value of C4.4A as a prognostic marker in this histologic subtype of lung cancer.



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Keywords: survival, immunohistochemistry, LYPD3, Prognosis

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P2.061 ANALYSIS OF PTEN MUTATION STATUS IN CHINESE PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Tumor suppressor Phosphatase and Tensin Homolog (PTEN) protein is a lipid phosphatase that dephosphorylates PIP3 and negatively regulates PIP3 levels and PI3K/Akt pathway activity that controls cell cycle progression, growth and inhibition of apoptosis. The identification of somatically tumor mutations is increasingly important in the clinical management of cancer. The aim of this study is to detect somatic mutations of PTEN in patients with non-small cell lung cancers (NSCLCs).
Methods: The DNA was isolated from 76 tumor tissues obtained from Guangdong Lung Cancer

Institute's tumor bank. The sequences of exons 1-9 of PTEN gene were assayed using PCR and DNA sequencing methods. The relationship of the PTEN mutation rate with the clinical parameters was analyzed using Fisher's exact test. A two-tailed P-value of <0.05 was considered statistically significant.

Results: Of these 76 patients, 52 were squamous cell carcinoma, 24 were adenocarcinoma; 28 were IB stage, 26 were IIA/IIB stage, and 22 were IIIA stage; 58 were male, 18 were female; The mean age of these patients was 59.37 years, range from 26-82 years. The PTEN mutation rate is 7.9% (6/76) in all of these patients. Of these 6 mutations, 3 in exon 8, 1 in exon 1, 1 in exon 2, and 1 in exon 5. We didn't find mutations in exon 3, exon 4, exon 6, exon 7, and exon 9. The mutation rate in adenocarcinoma and squamous cell carcinoma were 8.3% (2/24) and 7.7% (4/52), respectively (P=1.000); in stage IB, IIA/IIB, and IIIA were 10.7% (3/28), 3.8% (1/26) and 9.1% (2/22), respectively (P=0.664); in male and female were 8.6% (5/58) and 5.6% (1/18), respectively (P=1.000); in non-smokers and smokers were 2.7% (1/37) and 10.5% (4/38), respectively (P=0.358).

Conclusion: The present study indicated that the mutations of PTEN in patients with non-small cell lung cancer are frequently present in exon 8. And the mutation rate is not related with the gender, histology, smoking status, and clinical stages of the patients. These findings need to be verified in a large sample size in the future.

Keywords: PTEN, Mutation, Lung cancer

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.062 ARE BIOLOGICAL FACTORS ABLE TO PREDICT RESPONSE TO CHEMOTHERAPY (CT) IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)? A FEASIBILITY STUDY OF TUMOUR SAMPLINGS.

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Background: There is currently no validated test predicting tumour sensitivity to cisplatin-based CT in advanced NSCLC while the usefulness of some biomarkers (ERCC, RMM1) has been suggested. The primary aim of this prospective study is to identify predictive factors for response to CT in patients with advanced NSCLC using high throughput techniques by comparing the transcriptome (miRNAs and mRNAs) and the genetic background (SNPs) of responders and non responders. This approach allows investigating thousands of molecular markers in a same experiment with a small endobronchial sample.

Methods: Patients with suspected lung cancer were screened for inclusion. Those with pathologically proven advanced or metastatic NSCLC with an assessable lesion and who will receive first-line CT are eligible. Three biopsies from the primary lung tumour, with a control sample from normal bronchial tissue, are prospectively collected during a conventional bronchoscopy. One is formalin fixed and paraffin embedded for pathological diagnosis. The second biopsy is used for miRNAs, mRNAs and DNAs analyses and the third is frozen in liquid nitrogen to store it in a tissue bank. Predictive factors for response to CT will be assessed in successive cohorts of 50 patients, this number allowing enough power to find a discriminant signature among responders and non-responders to conventional first-line CT.

Results: From April 2009 until January 2011, 114 patients with suspected primary lung cancer were registered. As expected, a significant number of patients were ineligible because NSCLC histology cannot be confirmed (n=25) or no tumoural tissue can be obtained during diagnostic bronchoscopy (tumour not accessible n=15, absence of neoplastic tissue in the biopsy n=12, other reason n=7). Nine patients did not receive chemotherapy. At the time of analysis, the status of 2 bronchial samples among 46 eligible patients is pending on ongoing work-up. Forty-four samples were analysed by spectrophotometry for mRNA quantity and purity for microarrays analyses. Thirty-eight were considered adequate. No serious complication occurred during bronchoscopy.

Conclusion: This feasibility study demonstrates the capability to obtain adequate endobronchial lung cancer sampling for mRNA analyses in a substantial number of unselected NSCLC patients without significant complications. The study is recruiting further patients before searching a predictive signature for response to chemotherapy.

Keywords: Non small cell lung carcinoma, Predictive biomarkers, Chemotherapy

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P2.063 ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND SOLUBLE INTERCELLULAR ADHESION MOLECULE-1ON CONTROL OF PLEURAL EFFUSION AND SURVIVAL IN PATIENTS WITH HUMAN LUNG ADENOCARCINOMA

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Background: The mechanisms by which vascular endothelial growth factor (VEGF) and soluble intercellular adhesion molecule-1 (sICAM-1) contribute lung cancer growth have not been fully elucidated. This study aimed to assess the role of VEGF and sICAM-1 in survival and control of pleural effusions (PE) in patients with primary human lung adenocarcinoma.
Methods: Using enzyme-linked immunoadsorbent assay, the concentrations of VEGF and sICAM-1 were measured in pleural effusions and serum from a total of 79 lung adenocarcinoma patients with malignant pleural effusions (MPE) and 24 patients with tuberculosis. Data were correlated with the efficacy of MPE control and survival.
Results: Compared to patients with tuberculosis, the levels of VEGF and sICAM-1 in both PE and serum were significantly higher in patients with lung adenocarcinoma. Statistically significant correlation was observed between PE VEGF levels and MPE control. PE VEGF≥2760 pg/mL was used as a cut-off point for failure to MPE control (odds ratio=7.06; 95% confidence interval (CI), 2.40-20.78; P<0.001). The median progression-free survival (PFS) from response assessment was 3 months. In a multivariate analysis, PE VEGF (hazard ratio [HR], 1.16; 95%CI, 1.02-1.32), serum sICAM-1 (HR, 1.90; 95%CI, 1.17-3.07) were confirmed as independent prognostic factors for PFS.
Conclusion: The level of VEGF in PE appears to be a reliable surrogate marker in evaluating the therapeutic efficacy in the control of MPE and this, together with serum level of sICAM is potential survival factors in lung adenocarcinoma patients with MPE.
Keywords: malignant pleural effusion, lung adenocarcinoma, vascular endothelial growth factor, soluble intercellular adhesion molecule-1

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P2.064 MAINTENANCE BEVACIZUMAB MONOTHERAPY INCREASES HEMOGLOBIN (HGB) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG ADENOCARCINOMA (NSCLC-AD)

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Background: Inhibitors of vascular endothelial growth factor (VEGF) have been widely studied as therapeutics for a range of malignancies. Stringent VEGF inhibition in mice and non-human primates increases hemoglobin (Hgb) due to a combination of plasma volume contraction and increased erythropoiesis. The latter is mediated by elevated hepatic erythropoietin (Epo) production. Studies in renal cell carcinoma (RCC) have documented increased Hgb levels in patients receiving sorafenib and sunitinib, tyrosine kinase inhibitors with anti-VEGF receptor activity. We evaluated the effect of VEGF inhibition on Hgb level in a phase II trial of NSCLC-Ad patients that included maintenance bevacizumab monotherapy.
Methods: Patients with newly diagnosed advanced NSCLC-Ad received 4-6 cycles of carboplatin, gemcitabine, and bevacizumab followed by bevacizumab monotherapy dosed at 15 mg/kg every three weeks until evidence of disease progression (Clement-Duchene et al, JTO 2010.) No patient analyzed received erythropoiesis stimulating agents or red blood cell transfusions while on study. Baseline reticulocyte count, Hgb and Epo levels at the start of chemotherapy were compared to the median reticulocyte count, Hgb and Epo levels calculated from all measurements obtained after two cycles of bevacizumab monotherapy until 3 weeks after discontinuation of maintenance bevacizumab. These timepoints were chosen to minimize the confounding effects from hematologic recovery after induction with myelosuppressive therapy.
Results: Forty patients were consented for this

correlative study. The data from twenty-two patients (55%) who received more than two cycles of maintenance bevacizumab were analyzed. Hemoglobin increased significantly from 12.9 g/dL at the initiation of chemotherapy to a median of 13.8 g/dL (p=0.01) after 2 cycles of maintenance bevacizumab, an increase of 7%. In 7 patients who had both Epo level and reticulocyte count collected before the initiation of chemotherapy, pre-treatment Epo level was 17 mU/mL and after 2 cycles of bevacizumab the median Epo level was not significantly different at 19 mU/mL. Median reticulocyte count was also not significantly different at 72.6 K/μL before chemotherapy and a median of 53.3 K/μL after two cycles of maintenance bevacizumab.

Conclusion: Maintenance bevacizumab led to significantly higher Hgb levels than baseline pre-treatment Hgb. Median Epo level and reticulocyte count were similar at the start of chemotherapy and after maintenance bevacizumab, but the small number of patients who had serum Epo level and reticulocyte count collected before chemotherapy limits the interpretation of this finding. Based on these results showing an increase in Hgb with maintenance bevacizumab in patients with advanced NSCLC-Ad and mouse models where high-level VEGF inhibition increases hepatic Epo and Hgb levels, further investigation of erythrocytic parameters for NSCLC-Ad patients receiving bevacizumab and other VEGF inhibitors are warranted.

Keywords: bevacizumab, hemoglobin

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P2.065 SCREENING FOR MUTATIONS IN COLOMBIAN METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (ONCOLGROUP)

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Background: Driver mutations occur in genes that encode signalling proteins critical for cellular proliferation and survival. In lung cancer, these mutations include EGFR, KRAS, BRAF and EML4/ALK.

Methods: We evaluated the feasibility of screening 228 NSCLC patients in Colombia by analyzing tumor tissue by DNA sequencing.

Results: The study included 152 females (67%) and 76 males (33%) with a mean age of 59 (SD ± 13); 63% of the patients had adenocarcinoma, 6% presented non-specific tumors, 1.8% had large cell carcinomas, 2.6% had squamous cell carcinomas. Histological subtype was non-specific in 12.3%. According to tobacco consumption (n=173), 60%, 20% and 3% were non-smokers, ex-smokers or active smokers respectively. 57 patients had activating mutations (25%) in the EGFR, 40 with E19 deletion (70% of mutated subjects) and 17 with the in-frame L858R mutation (30%). Almost all with the E19 deletion were non-smokers (86%), as well as those affected by the E21 mutation (75%). 11% of tumors were positive for K-ras mutations (n=114), one patient (3.8%) was positive for the ALK/ELM4 fusion gene (n=26). BRAF (V600E) mutations were not detected (n=60).

Conclusion: The frequency of mutations in EGFR in NSCLC patients from Colombia was greater than that reported in other western countries; the distribution favoured the presence of the E19 deletion and the proportion of ALK/ELM4 is in agreement with previous data. To our knowledge, this study represents the first comprehensive analysis of major oncogenic mutations found in a large cohort of lung cancers from Latin America.

Keywords: Latin America, Genetic profiling, Non-small cell lung cancer, Somatic mutations

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P2.066 ASSOCIATION BETWEEN DNA-REPAIR GENE AND GLUTATHIONE S-TRANSFERASE GENE POLYMORPHISMS AND CLINICAL OUTCOME IN PATIENTS (PT) WITH LOCALIZED NON-SMALL-CELL LUNG CANCER (NSCLC) TREATED WITH SEQUENTIAL RADIOCHEMOTHERAPY

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Background: To evaluate the impact of DNA-repair and glutathione S-transferase gene polymorphisms on clinical outcome measured by progression-free (PFS) and overall survival (OS) in patients with localized non-small-cell lung cancer (NSCLC).
Methods: DNA for genotyping was extracted from archived paraffin embedded formalin-fixed tumor tissues. Genotyping was performed using PCR-based methods. Genomic polymorphisms of ERCC1, XRCC1, XRCC2, XPA, GSTP1, GSTT1 and GSTM1 were analyzed using PCR-based methods.
Results: 116 pt with NSCLC Ib-IIIb 85% received cisplatin-based chemotherapy (cx) prior to radiation. Pt demographics: median age 63 years; ECOG 0/1 and 2: 90%, 10%; 87% male/13% female; 90% of pt got local treatment (radiation and/or resection) following cx. Responses: 72 pt (62%) complete or partial remission, 32 pt (27%) stable disease and 14 pt (11%) progressive disease (PD). Median follow up time was 23.1 months (mo). Relapse or PD was observed in 80% of cases. Median OS of all pt was 23.4 mo and median PFS was 9.8 mo. GSTP1-105Val/Val genotype was associated with superior PFS and OS. In this group the median was not reached whereas median OS for heterozygots or homozygous wildtypes was 23.4 mo (p=0.056). Median PFS for GSTP1-105Val/Val was 24.4 mo compared to 9.8 mo (p=0.048). Moreover, all GSTP1-105Val/Val patients (n=8) were responders (R) to cx compared to only 59% R in pt with at least one Ile allele (p=0.023). Pt with a GSTT1 deletion showed shorter OS with 10.7 mo compared 23.8 mo in pt without a GSTT1 deletion (p=0.12). Median OS in the XPD-312N/N genotype group was 69.7 months compared to 23.4 mo in pt with at least one D allele (p=0.08). All XPD-312N/N pt were R (n=6) compared to 63% R in XPD-312D/D or D/N pt (p=0.08). Multivariate cox regression analyses revealed performance status (p=0.006), XPD-312N/N (p=0.038), GSTT1 (p=0.03) and surgical resection (p=0.001) as independent predictors of OS.
Conclusion: DNA-repair and GST polymorphisms may be associated with clinical outcome in NSCLC patients with localized disease and multimodal chemoradiation.
Keywords: pharmacogenetics, NSCLC, polymorphism

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P2.067 N-ACETYLGALACTOSAMINYL-TRANSFERASE-6 AS A POTENTIAL BIOMARKER FOR LUNG CANCER BY IMMUNOHISTOCHEMISTRY.

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Background: Altered O-glycosylation in cancer leads to an aberrant expression of immature carbohydrate structures (Tn, TF and sialyl-Tn antigens). The UDP-N-acetyl-D-galactosamine-polypeptide N-acetylgalactosaminyltransferases (ppGalNAc-T) enzymes regulate the initial steps of mucin O-glycosylation and could be responsible for the altered glycosylation observed in cancer. In recent years the enzyme ppGalNAc-T6 has attracted attention as a new marker for breast and gastric tumors. GALNT6 gene is expressed in a restricted pattern, being mainly in normal placenta, trachea, brain, pancreas and fibroblast cells. We previously found aberrant expression of ppGalNAc-T6 in breast and colon cancer, observing that this glycosyltransferase may be implicated in changes in O-glycan patterns in tumor cells. Considering that abnormal O-glycosylation is frequently observed in lung cancer, the aim of this work was to assess ppGalNAc-T6 expression in malignant lung cells.
Methods: ppGalNAc-T6 expression was evaluated

in a panel of human lung cancer cell lines using both RT-PCR and Westen blot assays. Using the monoclonal antibody T6.3 (Berois, J. Histochem. Cytochem. 2006, 54:317) we determined by immunohistochemistry ppGalNAc-T6 expression in lung cancer and in normal lung tissues.
Results: Expression of ppGalNAc-T6 was found in A549, H526, H838, H1703, H1755, H1650, H1975 and MES1 lung cancer cell lines. We do not observed ppGalNAc-T6 expression in the H69AR small cell lung cancer (SCLC) cell line. In formalin-fixed tissues ppGalNAc-T6 expression was observed in 45/49 (91.8%) lung cancers, and in 0/8 normal lung samples. The staining pattern observed in adenocarcinoma and epidermoid cancer is shown in Figures 1 and 2, respectively.
Conclusion: This report is the first evidence of aberrant expression of ppGalNAc-T6 in lung cancer. We found that ppGalNAc-T6 is a novel immunohistochemical marker for non-small cell lung cancer. In order to determine the potential clinical value of this marker now is necessary to extend our observations in a follow-up study of a larger number of cases.
Keywords: O-glycosylation, Glycosyltransferases, tumor markers, Lung cancer

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P2.068 CLINICAL IMPLICATIONS OF THE TUMOR EXPRESSION OF S100 PROTEINS IN NON-SMALL-CELL LUNG CANCER

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Background: The S100-protein family is a group of proteins that share the same calcium-binding motif but play different roles in a variety of intracellular and extracellular mechanisms, such as increase of cell motility (S100A4), promotion of cell-cycle arrest (S100A7 and S100A11), induction of apoptosis (S100A8/A9), intracellular trafficking of membrane proteins (S100A10) and ultimately, binding to p53 and modulation of its function (S100A2, S100A4 and S100A6). We have previously shown that S100A6 and S100A4 are expressed in a p53-dependent way in lung cancer cells (Orre et al. Mol Cell Proteomics 2007) and that S100A6 levels have prognostic implication in stage I NSCLC (De Petris et al. Lung Cancer 2009). The aim of the present study is to evaluate the tumor expression of diverse S100 proteins in specimens of surgically resected NSCLC in correlation with clinical outcomes.
Methods: Expression of S100A2, S100A4, S100A6, S100A7, S100A8, S100A9, S100A10, S100A11 and p53 was determined by immunohistochemistry on archival formalin-fixed paraffin embedded tumor specimens from 494 patients with node-negative stage I (6th TNM) NSCLC who received curative surgical resection, without peri-operative chemo- or radiotherapy. Tumors were mainly adenocarcinomas (54%) and squamous-cell carcinomas (32%). Half of the cases were on stage IA. Median follow up of censored cases was > 10 years.
Results: Positive immunoreactivity for p53, S100A2, S100A4, S100A6, S100A7, S100A8, S100A9, S100A10 and S100A11 was observed in 45%, 37%, 33%, 65%, 63%, 34%, 49%, 33% and 75% of cases, respectively. S100A8, S100A9 and p53 were significantly more expressed in squamous-cell tumors and in those with a lower grade of differentiation. Conversely, S100A4 and S100A6 were more expressed in adenocarcinomas and in well differentiated tumors. Higher expression of S100A4 and S100A10 was associated with the development of brain metastasis as the first site of tumor recurrence (chi-square p=0.04). In terms of survival outcomes, p53 was a negative prognostic factor of overall survival (log-rank p=0.02), but this was not confirmed on multivariate analysis adjusted by stage, histology and grading (HR for p53 negative vs positive 0.92, 95% CI 0.84-1.04; p=0.1). Further analyses by histology and p53 status showed that in p53-negative adenocarcinomas (n=153) the low/negative expression of S100A2 was an independent prognostic factor of shorter time-to-progression (multivariate analysis, adjusted by stage and grading; HR 1.38, 95% CI 1.00-1.96; p=0.04). In p53-positive squamous-cell tumors (n=88) the low/negative expression of S100A10 was an independent prognostic factor of longer time-to-progression (HR 0.66, 95% CI 0.48-0.91; p=0.01).

Conclusion: In this study we perform a broad evaluation of the clinical significance of the expression of several members of the S100 protein family in NSCLC. In light of recent research on functional relation between S100 proteins and p53, our results may elucidate the prognostic impact and functional effect of p53 in lung cancer by parallel detection of relevant S100-proteins.

Keywords: early-stage NSCLC, Biomarkers, Prognosis, S100 proteins

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.069 THE GEFITINIB LONG-TERM RESPONDER (LTR) – A CANCER STEM-LIKE CELL STORY? INSIGHTS FROM MOLECULAR ANALYSES OF GERMAN LONG-TERM RESPONDERS TREATED IN THE IRESSA EXPANDED ACCESS PROGRAM

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Background: Lung cancer is the leading cause of cancer-related death world-wide and has a poor prognosis. In selected patients with advanced non-small cell lung cancer (NSCLC) the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) gefitinib (Iressa) shows response rates ≥70% and a significant prolongation of progression free survival (PFS). Clinico-pathological and molecular characteristics such as gender, smoking status, histology, EGFR or k-ras mutations are considered to be predictive for response or resistance to EGFR-TKIs.

Methods: In this study, pretherapeutic tissue specimens of German patients with advanced NSCLC, who experienced long-term response to gefitinib (≥3 years) within the International Iressa Expanded Access Program (EAP) were analyzed. Of 1,925 patients enrolled, who had progressive disease after at least one course of chemotherapy or radiation or were ineligible for both, 20 (1.0%) long-term responders (LTR) were identified; 11 with appropriate tissue specimens available. These were analyzed for EGFR and k-ras mutations, EGFR and c-met amplification, and protein expression of EGFR, E-cadherin, CD133 and breast cancer resistance protein (BCRP1). The results were compared to those of intermediate responders (IR) showing a median response of 8.6 months and primary resistant patients (RP). The distribution of gender, histology and smoking status in the LTR, IR and RP group was matched.

Results: Each group consisted of 6 women and 5 men, who had received at least 1 previous therapy. 1 patient had a squamous cell carcinoma (SCC) and 10 patients an adenocarcinoma. 6/11 patients were never smokers. Except for the number of metastatic sites (LTR: 0.8±0.4, IR: 2.2±1.0, RP: 1.7±0.9, $p<0.05$), the clinico-pathological characteristics of the various groups showed no significant differences. All LTR, but the SCC had EGFR mutations. In turn 5/11 RP showed k-ras, but no EGFR mutations. 8/11 IR had EGFR and 3/11 k-ras mutations, of which 2 occurred concomitantly with EGFR mutations. 1 LTR had an EGFR, 1 RP a c-met and 1 IR both, an EGFR and c-met amplification. EGFR and E-cadherin expression was not different between the groups, whereas CD133 was exclusively expressed in LTR (LTR: 4/10, IR: 0/11, RP: 0/11, $p<0.05$) and BCRP1 predominantly in responders (LTR: 7/10, IR: 7/11, RP: 1/10, $p<0.05$). The median PFS to gefitinib was 61.4 months in LTR, 8.6 months in IR and 1.1 months in RP. The median survival was 85.1, 18.0 and 16.1 months, respectively. Remarkably, the LTR showed also a significantly longer median PFS to previous therapies than IR or RP (LTR: 13.6 months, IR: 5.6 months, RP: 7.8 months, $p<0.05$). This suggests not only a predictive, but also a prognostic impact of the molecular properties of LTR.

Conclusion: These data demonstrate that pretherapeutic tissue specimens and established biomarkers predict response to gefitinib in pretreated

patients. Moreover, they suggest that markers indicating cancer-stem like cells, i.e. CD133 and BCRP1 may characterize a subgroup of favorable LTR and thus matter of interest for further evaluation.

Keywords: Non-small cell lung cancer, epidermal growth factor receptor tyrosine kinase inhibitor, cancer stem-like cell, biomarker

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P2.070 DANISH POPULATION BASED STUDY OF THE PREVALENCE OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS IN NON SMALL CELL LUNG CANCER (NSCLC) (DAPPER STUDY)

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Background: Mutations in the EGFR gene in NSCLC identify patients sensitive to tyrosine kinase inhibitors. The mutations are more prevalent in Asian population compared to Caucasian. However estimates of mutation frequencies are only available from selected patient cohorts. The true incidence in an unselected Caucasian (Danish) population is unknown.

The study will assess the incidence of EGFR mutations in a large population based cohort, and the correlation between mutation and gender, age, ethnicity, smoking habits, as well as clinical and pathological data.

Methods: Since June 2010, all patients with NSCLC diagnosed in a well defined population of 1.2 million in the Copenhagen area are included in this single center study. Detailed information regarding type and location of the obtained material is registered. A specific focus is on whether cytologic material (all types included) is suitable for mutation studies. The influence of necrosis and the percentage of malignant tumor tissue necessary for the analysis are registered. Information on smoking habits, treatment, TNM stage and survival is also collected. We aim to include 100 mutated patients. Assuming a mutation rate around 10% 1000 tumors should be tested (95% CI 83-120 patients positive). The mutations will be detected by therascreen EGFR RGQ PCR Kit (selective site-specific detection of 29 somatic mutations in the EGFR oncogene, Qiagen).

Results: 65 patients have been included per month. By February 2011 590 patients were included. We expect to be able to present data for 850 patients with NSCLC tested for EGFR mutations. All data will be presented including an algorithm for optimal selection of patients to be tested for EGFR mutations.

Conclusion: Data for 850 patients with NSCLC tested for EGFR mutations will be presented and an algorithm for optimal selection of patients will be developed.

Keywords: EGFR mutations, NSCLC, population based, test algorithm

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.071 A PHASE IB WINDOW OF OPPORTUNITY CLINICAL STUDY WITH EVEROLIMUS IN PATIENTS WITH RESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Preclinical and clinical correlative studies implicate aberrant mTOR pathway activity in lung cancer. We conducted this study to demonstrate the biologic activity of everolimus, an allosteric

inhibitor of mTOR pathway, in patients with resectable NSCLC.
Methods: Patients with surgically resectable NSCLC (Stage I-III) underwent baseline tumor biopsy and FDG PET scan followed by treatment with everolimus (5 or 10mg daily for 21 to 28 days). Blood samples for pharmacokinetic (PK) assay for drug levels were collected at 0.5, 1, 2, 5, 8 and 24 hours post drug ingestion on Days 1, 8 and 21. A repeat PET scan was obtained within 24 hours prior to surgery. Control group patients did not receive everolimus but also had two PET scans at least 2 weeks apart prior to surgery. Evidence of target engagement and biological activity was assessed in vivo by PET imaging and ex vivo by immunohistochemical detection of markers of mTOR pathway activation (total and phosphorylated mTOR, Akt, S6, eIF4e, EBP1) in baseline tumor tissue and in resected surgical specimens.
Results: Sixteen patients have been enrolled including 14 on the experimental and 2 on the control arm. Age (median 63 yrs; range 44-77), gender: (8/8 –M/F), stage (I - 12; II - 2; III - 2); histology (adenocarcinoma - 10; squamous - 4; others - 2). All patients underwent surgery as planned. Comparison of paired baseline and resected tumor specimens showed consistent upregulation of p-Akt, an upstream event, whereas p-S6 expression, a downstream marker was not consistently downregulated in the initial cohort of patients treated with 5mg dose of everolimus. Analysis of FDG activity within the tumor mass on the baseline and the repeat PET scan showed a reduction in SUVmax in everolimus-treated patients (mean SUVmax reduction of -20%; range -54% to +20%), while control subjects showed a +42% increase in SUVmax in paired PET scans. Preliminary PK analysis in patients treated at the 5mg dose was consistent with previous experience in other population with no significant accumulation over time.
Conclusion: Everolimus showed measurable biologic activity in vivo and ex vivo at the level of the tumor in NSCLC patients. At the commonly studied dose in NSCLC of 5 mg per day, everolimus did not result in consistent downregulation of pS6, an established downstream biomarker of pathway inhibition. Our result raises the possibility that the 5mg dose may be inadequate to completely abrogate aberrant mTOR signaling in NSCLC patients. Ongoing enrolment to the 10mg dose cohort will provide additional insight into dose-dependent pathway modulation. **Acknowledgements:** *This study was supported by NCI grant P01 CA116676. Everolimus was provided by Novartis Oncology. FRK, TKO, SS, and SSR are Georgia Cancer Coalition Distinguished Cancer Scholars.*
Keywords: Lung cancer, mTOR, biomarker, everolimus

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P2.072 CLINICAL SIGNIFICANCE OF IGF-1R AND MMP-7 EXPRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Insulin-like growth factor-1 receptor (IGF-1R) is a tyrosine kinase receptor implicated in the pathogenesis of several malignancies and expected to be a molecular target in non-small cell lung cancer (NSCLC). A number of IGF-1R inhibitors are currently investigated in several clinical trials. A phase II study concluded that figitumumab, a selective inhibitor of the IGF-1R, increases the response rate and progression–free survival benefit of paclitaxel and carboplatin as first-line treatment of patients with advanced NSCLC. In vitro studies showed that expression of IGF-1R correlates with sensitivity to IGF-1R inhibitors. Matrix metalloproteinase-7 (MMP-7) is a member of the MMP family, and plays an important role in tumorigenesis, tumor invasion, and metastasis. Recent studies showed that MMP-7 regulates the bioavailability of insulin-like growth factors. The purpose of this study was to clarify the clinical siginificance of the IGF-1R and MMP-7 in NSCLCs.
Methods: We examined the clinical significance of IGF-1R and MMP-7 expression in 78 postsurgical patients in non-small-cell lung cancer. Immunohistochemistry was used to measure the expressions. The percentage of stained cells (0-100%) was multiplied by the staining intensity (0-3).

The final score ranged from 0-400, The sample was classified as high staining when the final score was above median score

Results: A high staining of IGF-1R and MMP-7 was noted in 41 patients (53%) and in 42 (54%) cases, respectively. IGF-1R expression was associated with pathological stage and recurrence (P=0.03 and 0.006, respectively). Overall survival was significantly lower in patients with IGF-1R-high NSCLCs than in those with IGF-1R-low NSCLCs (P=0.011). Expression of MMP-7 was not significantly associated with survival. Among patients with IGF-1R-low and MMP-7-low, overall survival was significantly better when compared with other groups. Multivariate analysis showed low expression of both IGF-1R and MMP-7 was significantly associated with better overall survival. (HR 3.808; 95% CI 1.586-9.145, p=0.003)

Conclusion: Immunohistochemical expression of IGF-1R and MMP-7 might be a useful biomarker for postoperative prognosis in NSCLCs.

Keyword: IGF-1R

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P2.073 PREDICTING THE EFFECT OF RADIOTHERAPY AND CHEMOTHERAPY IN COMBINED TREATMENT FOR LOCALLY ADVANCED LUNG CANCER BASED ON GENE EXPRESSION ANALYSIS

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Background: Several studies have shown the prognostic and predictive potential of molecular markers in combined therapy for lung cancer. Most of these studies refered, however, to operable early stage NSCLC. The aim of the present study is to corelate the expression of multiple mRNA markers in bronchoscopy obtained cancer specimens with clinical outcome of locally advanced NSCLC and LD-SCLC patients treated with radiotherapy and chemotherapy.

Methods: Between January 2007 and December 2008 bronchoscopy cancer specimens were taken from 110 patients. We were able to isolate RNA and perform gene expression analysis in 90 out of 110 cases (81%), including 53 NSCLC, 22 SCLC and 16 specimens with other or not specified cancer type. The majority of 90 patients were treated with radiotherapy (78%), 62% had platinum-based chemotherapy, only three individuals (3%) had surgery. Quantitative real time PCR was carried out by ABI 7900 HT machine, with Universal Probe Library (Roche) fluorescent probes. The genes selected for the analysis were ERCC1, EGFR, BRCA1, CSF1, CA9, DUSP6, STAT1, ERBB3, MMD, FN1, and CDKN1B. The influence of gene expression on survival was analysed using univariate and multivariate Cox regression model.

Results: The expression of four genes (BRCA1, CA9, CDKN1B and CSF1) differed significantly between NSCLC and SCLC. The difference for two other genes (STAT1, EGFR1) was on the bordrerline of significance. By contrast, there were no significant differences between gene expression in squamous cell cancer (33 patients) vs. adenocarcinoma (11 patients). A multivariate Cox regression model has shown a significant impact of FN1 (p=0.002, RR=3.1) and ERCC1 (p=0.004, RR=0.32) expression on overall survival in a group of 53 patients with NSCLC, while CA9 (p=0.15, RR=1.7) has shown a non-significant trend.

Conclusion: These results support the studies that demonstrate the feasibility of multiple gene expression analysis in bronchoscopy obtained cancer specimens as prognostic and predictive markers in combined radiotherapy and chemotherapy for locally advanced NSCLC and LD-SCLC. Study supported by N N403 2906 36 grant

Keyword: molecular markers, radiotherapy, chemotherapy, bronchoscopy, NSCLC, SCLC

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P2.074 EGFR AND K-RAS ANALYSIS IN CYTOLOGICAL SPECIMENS FROM NON SMALL CELL LUNG CANCER

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Background: EGFR gene mutations in patients with non small cell lung cancer (NSCLC) have been correlated with response to treatment with tyrosine kinase inhibitors. In addition, k-ras mutations may be involved in resistance to anti-EGFR therapy and might therefore be useful for treatment decision making in the future. The paucity of histological material is often the main reason for not being able to perform molecular analyses, and cytological material could be a valid alternative. We evaluated the possibility of determining EGFR and k-ras mutations in cytological samples and compared the sensitivity of this methodology with that used in histological samples.
Methods: Fifty-one patients were prospectively analyzed for EGFR (exons 18, 19 and 21) and k-ras (exon 2) mutations. Cytological specimens were obtained during bronchoscopy using Wang needle aspiration. Needle aspirates were placed on a slide, fixed with cytofix and stained with Fast Quick Rapid (Diapath) or Papanicolau. Non-tumor cells were carefully removed from slides and DNA extraction was only performed on selected cells (> 90% tumor cells). EGFR and k-ras analyses were performed by both direct sequencing and pyrosequencing. Histological specimens were available for 15 patients and molecular analyses were also performed on these samples.
Results: 6 (12%) and 12 (24%) patients had EGFR or k-ras mutations, respectively. EGFR mutations were 1 exon 18 point mutations (G719S), 3 exon 19 deletions (E746_A750) and 2 exon 21 point mutations (L858R, L861Q), whereas k-ras mutations were all on codon12 (7 G12C, 3 G12V, 1 G12D, 1 G12A). When possible, all mutations were further confirmed in histological tissue. None of the wild type cytological specimens was mutated in the histological samples. All mutated cases were adenocarcinoma. In 3 patients with gene mutations, analyses were conducted on a scalar number of cells, and mutations were detected in as few as 20 cells.
Conclusion: EGFR and k-ras analyses proved technically feasible in cytological specimens, which can thus be considered a valid alternative to histological material. As few as 20 cells are required to perform the analysis, thus permitting slide conservation in pathology archives.
Keywords: Non small cell lung cancer, cytological specimens, EGFR, K-ras

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P2.075 PILOT STUDY TO MEASURE CIRCULATING ENDOTHELIAL CELLS (CECS) IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: CECs reflect vascular turnover and are elevated in many patients with cancer. CECs are a potential biomarker for both risk of recurrence following surgical resection and for benefit from antiangiogenic therapies in patients with NSCLC. We utilized CellSearch (Veridex, New Jersey) to quantitate CECs in both early and late stage NSCLC pts before and after stage specific treatment.
Methods: In this pilot study, 10 patients with early stage (AJCC stage I-IIIA) NSCLC had CECs tested within one week prior to surgical resection, and again when possible at the first post-op visit. In addition, 6 pts with metastatic NSCLC were tested prior to initiation of chemotherapy plus bevacizumab and again immediately prior to cycle 3 of treatment. CECs were enumerated as nucleated, CD146+/CD105+/CD45- cells in 4 mL of blood utilizing the CellSearch immunomagnetic selection technology.
Results: Using normal subjects as controls, we established the upper limit of normal for CECs to be 26 with a standard deviation of 4, and ≥38 CECs was considered elevated. 10 pts with early-stage NSCLC were tested prior to surgery (stage IA (n=2), IB (n=5), IIB (n=1), and IIIA (n=2)), while 4 pts to date have had post-op draws. 4 pts (40%) had elevated

CECs prior to surgery (mean 43.7, range 11-162) and all 4 pts (100%) tested approximately 1 month post-op had elevated CECs (mean 110, range 49-173). There was no relationship between stage or histology and elevated CECs. In the advanced NSCLC group, 2 of 6 pts (33%) had elevated CECs immediately prior to initiating chemotherapy plus bevacizumab (mean 42.1, range 11-124) and 2 of 3 pts (67%) prior to cycle 3 (mean 115, range 21-207). One of the post-treatment pts had a normal CEC level at baseline and the level increased post-bevacizumab treatment, and one had elevated CECs at baseline which remained stably elevated. No outcomes data were available at the time of this submission.
Conclusion: CECs are elevated in a substantial proportion of early and late stage NSCLC patients, and can be readily measured throughout treatment. Future studies will attempt to assess CEC numbers as prognostic markers for recurrence after resection and for treatment effect in advanced disease. Because it is semi-automated, validated, and has potential for study reproducibility, we chose to utilize the CellSearch platform for extending studies serially in patients. We realize that CECs with other markers such as CD34 or CD133, different kinetics, or differentiation may of course be missed.
Keywords: prognostic, biomarker, early stage lung cancer, Advanced Lung Cancer

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P2.076 COPY NUMBER ABBERATION IN NON-SMALL CELL LUNG CANCER WITH ALK FUSION PROTEIN

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Background: Lung cancer with ALK fusion protein accounts for 5% of non-small cell lung cancer (NSCLC). The patients with ALK-positive lung cancer are treated by specific inhibitor of ALK. The effect of ALK inhibitor is very good, however reccurence was observed in these patients.
Methods: ALK-positive NSCLC patients were selected by immunohistochemistry and reverse transcription-polymerase chain reaction (RT-PCR) from 404 patients who had undergone surgical resection or bronchoscopy in Chiba Cancer Center from 2007 to 2009. Copy number abberations of the tumors from ALK-positive patients were detected by comparative genomic hybridization (CGH) using oligo array.
Results: There were 15 patients with ALK positive-lung cancer in 404 lung cancers. Of 15 patients, ten tumors were analyzed by array-CGH. Chromosomal instabilities were detected in 9 patients. The number of the regions with copy number abberation were between 4 to 20 in each patient. In one patient with ALK-EML4 lung cancer who was treated by ALK-inhibitor, the copy number abberation was remerkably increased in brain metastases from primary lung tumor.
Conclusion: The additional copy nnumber abberations in metastatic tumor may relate to the mechanism of reccurent in patient with ALK-inhibitor treatment.
Keywords: copy number, ALK

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P2.077 PROGNOSTIC EFFECT OF EPITHELIAL AND STROMAL LYMPHOCYTE INFILTRATION IN NON-SMALL CELL LUNG CANCER.

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Background: The major value of prognostic markers in potentially curable non-small cell lung cancer (NSCLC) should be to guide therapy after surgical resection. In this regard, the patients' immune status at the time of resection may be important and also measurable. The immune system has paradoxical roles during cancer development. However, the prognostic significance of tumor-infiltrating lymphocytes is controversial. The aim of this study is to elucidate the prognostic significance of epithelial and stromal lymphocyte infiltration in NSCLC.
Methods: Tissue microarrays from 335 resected NSCLC, stage I to IIIA were constructed from duplicate cores of viable and representative neoplastic epithelial and stromal areas. Immunohistochemistry was used to evaluate the

epithelial and stromal CD4+, CD8+, and CD20+ lymphocytes.
Results: In univariate analyses, increasing numbers of epithelial CD8+ (P = 0.023), stromal CD8+ (P = 0.002), epithelial CD20+ (P = 0.023), stromal CD20+ (P < 0.001), and stromal CD4+ (P < 0.001) lymphocytes correlated significantly with an improved disease-specific survival. No such relation was noted for epithelial CD4+ cells. Furthermore, a low level of stromal CD8+ lymphocyte infiltration was associated with an increased incidence of angiolymphatic invasion (P = 0.032). In multivariate analyses, a high number of stromal CD8+ (P = 0.043) and CD4+ (P = 0.002) cells were independent positive prognostic factors for disease-specific survival.
Conclusion: High densities of CD4+ and CD8+ lymphocytes in the stroma are independent positive prognostic indicators for resected NSCLC patients. This may suggest that these cells are mediating a strong antitumor immune response in NSCLC.

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P2.078 ABERRANT SIGNAL TRANSDUCTION AND DNA DAMAGE RESPONSE PATHWAYS IN PRIMARY LUNG CANCER

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Background: Because cell signaling and cell metabolic pathways are executed through proteins, characterizing protein signatures in tumor tissues is required to identify key nodes in signaling networks whose alteration is associated with malignancy. This study aimed to determine protein profiles in primary lung cancer tissues.
Methods: Case-matched normal and tumor samples from 101 lung cancer patients, mostly non-small cell lung cancer, were analyzed with reverse-phase protein array assay for 127 proteins and/or protein phosphorylation sites. Differences in signal intensities between normal and tumor tissues and their association with clinical parameters were analyzed with analysis of variance, some of them were validated by Western blot and/or immunohistochemical analyses.
Results: We found that 18 molecules were significantly different ($p<0.05$) by at least 30% between normal and tumor tissues. Most of those molecules play roles in cell proliferation (cyclin B1), DNA damage response (ATM, CHK2, and Ku80), signal transduction (14-3-3zeta, IGFBP2, p38-pT180, IRS-pS307, Src, PI3K-p85, mTOR, and Stat5), or lipid metabolism (COX2 and ACC-1pS79) or function as cell surface/matrix proteins (caveolin 1, CD31, and collagen type VI). Analysis on association with clinical parameters revealed that Ku80 levels were significantly higher in tumors of nonsmokers than in those of smokers. Cyclin B1 levels were significantly higher in poorly differentiated tumors than in well or moderately differentiated tumors. The levels of five molecules were significantly higher in neuroendocrinal tumors than in other types of tumors. A comparison with a separate RPPA profiling on another set of patient samples showed that the results were highly repeatable.
Conclusion: Molecules involved in DNA damage response, signal transductions (in the PI3K/AKT/mTOR, Src/Stat, and MAP kinase pathways), lipid metabolism, and cell proliferation were drastically aberrant in lung cancer tissues and some of those could be useful for molecular diagnosis of lung cancers.
Keywords: DNA damage, primary tumor, Biomarkers, signal transduction

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P2.079 HE4 EXPRESSION IS ASSOCIATED WITH WORSE PROGNOSIS IN PULMONARY ADENOCARCINOMA

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Background: Human epididymis 4 (HE4) gene product, also known as Whey-Acidic-Protein (WAP) four-disulphide core domain protein 2 (WFDC2), was identified as the transcript expressed in the epididymis and respiratory tract. HE4 is also expressed in lung adenocarcinoma, however, the function of this protein in lung adenocarcinoma remains unclear. We investigated the possibility of HE4 to predict survival for patients with pulmonary adenocarcinoma.
Methods: One hundred and forty-one patients with pulmonary adenocarcinoma underwent surgery in our institute from 2000 to 2008. We used immunohistochemical analysis to determine the expression of HE4 and compared with the clinicopathological factors and survival. HE4 expression of lung adenocarcinoma cell lines were investigated by immunofluorescent staining and RT-PCR.
Results: Fifty-seven of 141 cases (40%) were HE4 positive and five of six cell lines expressed HE4 protein and mRNA. We found no correlation between HE4 expression by IHC and clinicopathological factors, however, bronchiolo-alveolar carcinoma subtype was significantly associated with HE4 expression. Five-year disease-free survival in the HE4-positive group (44.6%) was significantly different from that in the negative group (79.3%, p=0.006) by immunohistochemisty. The five-year overall survival rate was 60.1 % in the HE4-positive group, as compared with 86 % in the HE4-negative group (p=0.02). In multivariate Cox regression analysis, positive HE4 protein expression was a worse prognosis factor of disease-free and overall survival (HR =2.6, 95%CI = [1.3–5.3], p = 0.008; HR =2.6, 95%CI = [1.1–6.2], p = 0.04, respectively), in addition to nodal status as a powerful value.
Conclusion: Our study demonstrated that patients with HE4-positive adenocarcinoma had a worse prognosis than patients with HE4-negative adenocarcinoma. HE4 might be a powerful tool to stratify worse candidate groups in lung cancer patients.
Keyword: lung, adenocarcinoma, HE4, prognosis

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P2.080 CLINICAL AND PATHOLOGICAL ANALYSES OF ISOLATED TUMOR CELLS IN NON SMALL CELL LUNG CANCER -CLINICOPATHOLOGICAL PARAMETERS AFFECTING ISOLATED TUMOR CELL MORPHOLOGY IN NON SMALL CELL LUNG CANCER

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Background: The presence of isolated tumor cells (ITCs) in the pulmonary vein (PV) of a lung resected for lung cancer has been reported to be a prognostic factor. Previous investigations noted correlations between prognosis and the presence or amount of ITCs, though few studies have investigated the clinical and histopathological implications of the morphological characteristics of those cells. We assessed the clinical and histopathological implications of ITCs in the PV using a novel enrichment approach that maintained their morphological characteristics.
Methods: We studied 130 consecutive patients with primary non-small-cell lung cancer (NSCLC) who did not undergo preoperative chemo- or radiation therapy (p-stage I in 103, II in 17, III or IV in 10).To examine vessel invasion of primary tumors, surgical specimens were fixed with 10% formalin and embedded in paraffin, then evaluated pathologically by hematoxylin and eosin (HE), and elastic van Gieson (EVG) staining. Blood samples were drawn from the PV draining the lung just after pulmonary resection, and ITCs were enriched with a CD45-negative selection method and density-gradient centrifugation, followed by Papanicolaou staining using 1 ml of PV blood. The ITCs were classified into 4 types based on patterns of cluster formation: no tumor cells (N), singular tumor cells (S), clustered cells (≤0.2 mm) (CS), and bulky clustered cells (>0.2 mm) (BCS). We evaluated the relations between ITC morphology, and clinical data and pathological results of the primary tumor - tumor marker

serum CEA, CT/FDG-PET findings including maximal standard uptake value (SUV max), and histopathological analysis including vessel invasion by primary tumors.
Results: ITCs were detected in 96 patients (73.8%), of which the BCS type was observed in 3, CS in 41, S in 52, and N in 34. Cancer recurrence occurred in 34 cases (26%), 21 in the combined CS/BCS group, 11 in S, and 2 in N. Log-rank analysis revealed that the disease-free survival rate was exclusively worse in patients with clustered ITCs as compared with the other 2 groups ($p<0.01$). As for clinical features, the clustered cancer cell-positive ratio was high in cases with a high levels of serum CEA and SUV max, and a high solid component ratio in CT findings as compared to cases with low levels of those factors. Furthermore, there was a possible strong correlation between the positive ratio of vessel invasion by primary tumors and presence of ITCs in the PV, as the positive ratio of vessel invasion was 79% in the combined CS/BCS group, while that was 40% in S and 9% in N ($p<0.0001$).
Conclusion: Our method was useful to detect and enrich ITCs from the PV, and showed the clinical relevance of their morphology in lung cancer cases. The presence of ITC clusters may be a prognostic biomarker for patients with resected NSCLC. Furthermore, the presence of clustered cancer cells may be strongly related with clinical and histopathological features including vessel invasion of primary tumors.
Keyword: lung cancer, isolated tumor cells, histopathology, vessel invasion

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P2.081 HUMAN ASH-1 EXPRESSION IS ASSOCIATED TO NEUROENDOCRINE DIFFERENTIATION IN VIVO, AND MODULATES PROLIFERATION, INVASION AND DRUG RESPONSIVENESS IN VITRO OF NON-SMALL CELL LUNG CANCER

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Background: Human achaete scute homologue1 (hASH-1) is a transcription factor that regulates neuroendocrine (NE) phenotype, cell growth and apoptosis in cancer models. No data are available on its role in non-small cell lung cancer (NSCLC). Therefore, the aims of this study were to correlate hASH-1 mRNA and protein expression with neuroendocrine phenotype and clinical pathological variables in a consecutive series of NSCLC tumour tissues, and to define the capability of hASH-1 to induce neuroendocrine differentiation and to modulate cell growth, apoptosis, invasive capacity and drug responsiveness in NSCLC cells in vitro.
Methods: H-ASH-1 expression was determined in 81 consecutive NSCLC cases using immunohistochemistry and quantitative PCR; its functional role in vitro was evaluated by means of MTT test, apoptosis assay, matrigel assay, and pharmacological sensitivity tests to pemetrexed and cisplatin onto four wild-type and lentiviral hASH-1-transfected NSCLC cell lines.
Results: H-ASH-1 protein was detected in 15/81 cases, correlated with hASH-1 mRNA and NE phenotype but not with clinical-pathological variables. In vitro, hASH-1 transfection variably induced NE phenotype, promoted cell growth, inhibited invasive capacities and induced resistance to pemetrexed with concurrent increase in NE markers expression.
Conclusion: H-ASH-1 seems to be a relevant player in NSCLC tumor biology since is expressed in a subset of NSCLC, and modulates neuroendocrine phenotype and tumor properties in vitro; moreover, its capability to develop resistance to conventional chemotherapeutic agents identify hASH-1 as a possible target to modulate chemotherapy sensitivity in NSCLC patients

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P2.082 CHARACTERISTICS OF LUNG CANCER IN WOMEN: IMPORTANCE OF HORMONAL AND GROWTH FACTORS.

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Background: The incidence of lung cancer is increasing dramatically in women. Lung cancer occurring in women displays some specific epidemiological, clinical and pathological characteristics suggesting that lung carcinogenesis is, at least in part, distinct in women.
Methods: We aim to analyze the clinico-pathological characteristics of lung cancer and to compare the immunohistochemical expression of hormonal receptors (Estrogen Receptor [ER] a and b, Progesterone receptors [PR]) and growth factors (EGFR, Her2) and the status of EGFR and K-Ras mutations in two groups of surgically treated patients, 50 men and 50 women. We also aim to define the prognostic value of each biomarker.
Results: Lung cancer occurring in women is less associated with tobacco use than in men. EGFR is more frequently mutated in women but also overexpressed by using a 10% positivity threshold score. No significant difference was observed for Her2 expression and K-Ras mutation. ERa expression is more frequently found in women when compared with men. ERb is also more frequently expressed without reaching significance. We then analyzed the prognostic value of all clinical and biological data. After multivariate analysis we found that the presence of lymphatic embols was associated with a worse disease free survival ($p = 0.012$) and that tumors without bronchioloalveolar component have a shorter time to progression. REa expression was associated with a better prognostic ($p = 0.007$).
Conclusion: We identified specific genetic alterations or hormonal profiles in women that may help in defining lung cancer prognosis after surgery and pave the way for a gender-based targeted therapy.
Keywords: Women, Lung cancer, EGFR, Estrogen

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P2.083 CDRS AS AN EARLY DETECTION MARKER FOR NON-SMALL CELL LUNG CANCER USING MASS SPECTROMETRY

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Background: Late diagnosis is the main reason for a high lung cancer mortality rate. Although CT screening has improved the early detection of lung cancer, a more sensitive and specific early detection method is needed. Therefore, biomarker discovery is of great importance for early detection of lung cancer.
Alterations in protein structure or expression in tumors may induce an increase of the immune response resulting in specific antibody production. As this immune response is expected to occur at an early disease stage, specific sequences of the antigen binding sites of antibodies (CDRs) might discriminate lung cancer patients from controls at a stage that effective therapy can be applied.
Methods: Forty lung cancer patients and 40 controls, recruited from the randomized lung cancer screening trial NELSON were used. IgG was isolated from serum and digested with immobilized papain into Fab and Fc. An anti-Fc affinity column was used to purify Fab from the digested mixture and further purified by SDS-PAGE. The Fab containing gel bands were excised and enzymatically digested. The resulting Fab peptides were measured on a nano-LC-Orbitrap-Mass-Spectrometry system. Quantitative analysis was performed by the software package Progenesis. Mascot was used for database searches against the human NCBInr database. De novo sequencing was performed by Peaks Studio software. CDRs were identified by homology to the IMGT database. Statistical analyses were performed in Stata.
Results: From the lung cancer patients, 60% were diagnosed within one year after blood sampling. From these patients, 88% were men and the average age was 64 years. All 40 cases were former smokers, 53%

were current smoker and 25% had a COPD history. Forty-one percent of the cases were diagnosed with adenocarcinoma and 11% with squamous cell lung carcinoma. Forty-eight percent were diagnosed with a different histology, such as large cell neuroendocrine tumors. The control group consisted of 93% men with an average age of 61 years. All controls were former smokers without COPD history.
After Fab purification and mass spectrometry (MS) measurement of Fab samples we were able to observe 477 different CDR1 peptide sequences, 864 CDR2 and 101 CDR3 peptide sequences in all 80 samples measured.
We performed a multivariate analysis, logistic stepwise regression, on the data obtained from the lung cancer patients and controls to search for a statistical prediction model consisting of a set of MS signals (regression model) that could distinguish lung cancer patients from controls. We observed a model consisting of nine masses with a p-value of <0.001. From the nine masses we observed 1 CDR1 sequence, 3 CDR2 sequences and 1 Framework sequence. The four other peptides were not identified yet.
We performed an internal validation of the predictive model by determining the sensitivity and specificity, yielding values of 77% and 92%, respectively.
We also intend to validate this model in a new independent lung cancer and control sample set.
Conclusion: To our knowledge this is a new approach for early detection of lung cancer, which is able to distinguish lung cancer cases from controls with 77% sensitivity and 92% specificity.
Keywords: Early detection biomarker, NSCLC, Immunoglobulin, proteomics

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P2.084 DIFFERENCES IN BIOLOGICAL BEHAVIOR BETWEEN ADENOCARCINOMAS AND SQUAMOUS CELL CARCINOMAS IN NON-SMALL CELL LUNG CANCER: CORRELATIONS AND PROGNOSTIC VALUE OF GLUT1 AND MCT4 EXPRESSION

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Background: Hypoxia leads to changes in tumor cell metabolism such as increased glycolysis. Markers related to hypoxia and glycolysis could be prognostic indicators in non-small cell lung cancer (NSCLC). In this study, glucose transporter 1 (GLUT1) and monocarboxylate transporter 4 (MCT4) expression were correlated with survival in stage I, II and resectable stage IIIA NSCLC.
Methods: GLUT1 and MCT4 expression were determined in 85 NSCLC biopsies using immunohistochemical techniques and a computerized image analysis system. Markers were analyzed for the adenocarcinoma (n=41) and squamous cell carcinoma (n=35) subgroups separately. Patients were retrospectively evaluated for relapse and survival.
Results: Squamous cell carcinomas demonstrated higher GLUT1 expression, relative to adenocarcinomas. In adenocarcinomas, high GLUT1 expression correlated with a poor differentiation grade and positive lymph nodes at diagnosis. The ratio GLUT1:MCT4 was <1 in adenocarcinomas and >1 in squamous cell carcinomas. In squamous cell carcinomas, GLUT1 and MCT4 expression increased with increasing distance from the vasculature, whereas upregulation of MCT4 was already found at closer distance from vessels in adenocarcinomas. High GLUT1 plus high MCT4 expression correlated with a poor disease-specific survival in adenocarcinomas (p=0.032).
Conclusion: A different tumor metabolism was found for adenocarcinomas and squamous cell carcinomas. Adenocarcinomas rely mainly on aerobic glycolysis for ATP production, whereas the behavior of squamous cell carcinomas is more physiological, i.e. mitochondrial oxidation with anaerobic glycolysis where appropriate. High GLUT1 plus high MCT4 expression denoted an aggressive tumor behavior in adenocarcinomas. This subgroup of tumors may benefit from new treatment approaches, such as MCT4 inhibitors.
Keywords: Hypoxia, microenvironment, metabolism, GLUT1

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P2.085 IDENTIFICATION OF NOVEL MARKERS FOR THE DIAGNOSIS OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: Despite recent improvements, the diagnosis and treatment of malignant pleural mesothelioma (MPM) is still a major challenge. Due to the unspecific symptoms and tissue polymorphism of this cancer, MPM can be confused with benign pleural diseases or with pleural metastasis of adenocarcinomas, especially from lung origin. Because an accurate diagnosis is crucial, both for the management of MPM patients and also for the settlement of financial compensation for individuals with a history of asbestos exposure, the development of new tools and the improvement of existing diagnostic procedures are of major interest.
Methods: In order to identify novel markers able to improve diagnostic accuracy, we performed a genome-wide gene expression analysis on tumor cell lines established from pleural effusions. The levels of new markers were assessed in tumor biopsies by immunohistochemistry and in pleural fluids using enzyme-linked immunosorbent assays.
Results: We profiled 51 biological samples corresponding to triplicates of 13 mesothelioma and 4 lung adenocarcinoma cell lines. Our microarray analysis led to the identification of genes encoding novel cellular and soluble markers whose expression was validated by RT-qPCR. Immunohistochemical staining of tumor biopsies with anti-type-III collagen antibodies were positive in mesothelioma cells but not in adenocarcinoma cells. (CCL2) concentration was significantly higher in patients with mesothelioma (n = 61) than in subjects with adenocarcinoma (n = 25) or with benign pleural effusion (n = 15): median (interquartile range) = 2.99 ng/mL (1.76-6.01) versus 0.99 ng/mL (0.51-1.83) and 1.47 ng/mL (0.80-1.56), respectively, P < 0.0001. Conversely, the galectin-3 concentration was lower in mesothelioma: 11.50 ng/mL (6.73-23.53) versus 24.74 ng/mL (20.42-70.35) and 17.64 ng/mL (14.81-24.68), respectively, P < 0.0001. The area under the receiver-operator characteristic curves for CCL2 were 0.8030 (95% confidence interval 0.7061-0.8998) and 0.7716 (0.6429-0.9003) for differentiating mesothelioma from adenocarcinoma or benign effusions, respectively. Similarly, the AUC obtained for galectin-3 were 0.7980 (0.7019-0.8942) and 0.6923 (0.5647-0.8200), respectively.
Conclusion: Type-III collagen, CCL2 and galectin-3 are promising new diagnostic markers for mesothelioma.
Keywords: mesothelioma, Microarray, biomarker, Pleural effusion

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P2.086 AN IMMUNOHISTOCHEMICAL PROFILE FOR PREDICTING RESPONSE TO CISPLATIN/VINORELBINE THERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) has a poor prognosis and only a small minority of patients is diagnosed at an early stage in which curative multimodality-treatment is possible. Inoperable patients receive platinum-based palliative chemotherapy. Customizing chemotherapy based on chemosensitivity prediction may improve outcome in this cancer disease with a generally poor outcome. The cytotoxic effect of cisplatin depends on the formation of DNA cross-links that hinders replication. This effect can be overcome by the DNA repair system that replaces the damaged DNA. Over-expression of key enzymes

in different DNA-repair pathways has been linked to chemotherapy resistance. Nucleotide excision repair (NER) is the main pathway involved in replacing cisplatin-induced DNA damage. Excision repair cross-complementation group 1 enzyme (ERCC1) recognizes and cuts out the damaged DNA. Breast cancer 1 (BRCA1) is a component of multiple DNA-repair pathways and decreased expression is linked to sensitivity towards DNA-damaging agents. BRCA1 may also play a role in mitotic-spindle formation and seems to be required for spindle-poison sensitivity. The aim of the study was to explore the baseline expression of DNA repair proteins in MPM, and their ability to predict survival.

Methods: Fifty-four consecutive inoperable MPM patients were enrolled between February 2003 and September 2006 into a phase II trial with cisplatin and vinorelbine. Formalin-fixed paraffin-embedded histologic tumor specimens were retrospectively evaluated by immunohistochemistry (IHC) for ERCC1 and BRCA1 expression. To assess protein expression we used a semi-quantitative H-score (staining intensity multiplied by a proportion-score based on the percentage of positive tumor cells). For each marker the median value of the H-scores was set as a cut-off point to separate positive (H-score > median) from negative (H-score ≤ median) tumors. Results were correlated to clinical outcome such as response to chemotherapy, progression-free survival (PFS) and overall survival (OS).

Results: Fifty patients had tumor-tissue available for IHC. For ERCC1 the median H-score was 2, yielding 20 positive and 30 negative tumors. There was no significant difference in OS between positive and negative tumors. There was no significant difference in response rate between the two populations. The median PFS was 10.9 months [CI.95% 5.6; 16.7 months] in the ERCC1-negative tumor group and 6.7 months [4.4; 7.2 months] in the ERCC1-positive group (p=0.052). Multivariate Cox regression revealed ERCC1-positive patients to have a significantly higher risk for progression (HR=2.24, 95% confidence limits= [1.16; 4.34], p=0.0163) compared to ERCC1-negative patients. Scoring of immunostainings for BRCA1 and correlation with clinical data are in progress. The results will be available at the time of the 14th WCLC 2011.

Conclusion: Negative immunohistochemical ERCC1 staining predict significant higher PFS in patients with MPM. Analysis of the impact of BRCA1 will be available at the meeting.

Keywords: mesothelioma, ERCC1, BRCA1, Predictive value

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.087 PULMONARY VEIN CIRCULATING TUMOUR CELLS FROM PATIENTS UNDERGOING CURATIVE RESECTION OF NON-SMALL CELL LUNG CANCER.

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Background: Circulating tumour cells (CTCs) are postulated to have a critical role in the development of metastatic disease. Relapse at distant sites remains a major challenge to improved survival in patients with early stage non-small-cell lung cancer (NSCLC) despite curative intent surgery. Standard imaging techiniques are unable to reliably detect micrometastatic disease, therefore detection of CTCs may help identify patients at high risk of metastasis. We have previously reported that the prevalence of CTCs in peripheral blood of patients with advanced stage NSCLC, using the CellSearch system, is low and that CTCs are absent in patients with stage III disease. We hypothesize that CTC numbers are higher in the pulmonary vein of patients with early stage NSCLC and that presence of CTCs will correlate with clinical outcome. We initiated a study to determine the number of CTCs in the tumour draining pulmonary vein in patients undergoing resection of early stage NSCLC. The specific aims of this study are to: 1. Enumerate and compare CTC numbers in peripheral blood (pre-operatively) and tumour draining pulmonary vein (intra-operatively)

2. Compare morphology of CTCs with primary tumour specimens. 3. Examine the association of CTC numbers with clinical characteristics including smoking exposure stage and progression free/overall survival.
Methods: This study is a surgical case series. Inclusion criteria: patients attending the Thoracic Surgical Department of the University Hospital of South Manchester (UK) for curative resection of NSCLC. Exclusion criteria: patients with a prior diagnosis of malignancy or who have received chemotherapy. The aim is to recruit 30 patients into this pilot study. A risk factor questionnaire is completed. Ten ml blood samples are taken pre-operatively from a peripheral site and intra-operatively from the pulmonary vein draining the cancer bearing lobe prior to vessel ligation or resection. Samples are processed using 7.5ml blood according to standard operating procedures with the CellSearch system, at the Clinical and Experimental Pharmacology Group, Paterson Institute for Cancer Research, Manchester, UK. Patients will be followed up for a period of 5 years or until recurrence occurs.
Results: Preliminary data suggests the number of CTCs isolated from the tumour draining pulmonary vein is higher than in peripheral blood. Further data will be presented.
Conclusion: This pilot study supports the hypothesis that higher numbers of CTCs are detectable in the tumour draining pulmonary vein than peripheral blood, in patients with early stage NSCLC. This may have important relevance for clinical outcome, to be determined from ongoing follow-up over 5 year period
Keywords: Circulating tumour cells, Pulmonary vein, Non-small cell lung cancer, Surgery

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P2.088 A RETROSPECTIVE LONGITUDINAL STUDY OF THE CYFRA 21-1 EIA ASSAY AS AN AID IN MONITORING PATIENTS DIAGNOSED WITH LUNG CANCER

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Background: Elevated levels of cytokeratin 19 fragments CYFRA 21-1 are found in serum from patients with lung cancer. Several studies have shown that lung cancer progression leads to an increase in CYFRA 21-1 while the response to therapy leads to decrease in CYFRA 21-1. We investigated if successive 50% increase in serum levels of CYFRA 21-1 can classify patients as suspects for disease progression. Additionally, we evaluated if a one third reduction in CYFRA 21-1 levels from an immediately preceding time point is an indicator of response to therapy.
Methods: This was a retrospective clinical study utilizing remnant serial serum samples from a heterogeneous group of subjects diagnosed with lung cancer at various stages of disease. One hundred patients were followed for an average of 10 months and a maximum of 6 years. On average, each subject provided a baseline and 3.1 follow-up visits, spaced at an average of 101 days. The subject's clinical status was classified as: no evidence of disease (NED), responding to treatment, stable disease, and progression. Blood samples from each visit were assayed for CYFRA 21-1 using CYFRA 21-1 Enzyme Immunometric Assay (EIA) (Fujirebio Diagnostics, Inc.). CYFRA 21-1 EIA is based on 2 monoclonal antibodies specific for cytokeratin 19 (BM 19.21 and KS 19.1). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) values were determined.
Results: A total of 414 samples from 100 subjects were evaluated. The mean age was 59 years (range 34-82) and fifty-seven percent of subjects were male. To assess the performance of CYFRA 21-1 for the detection of disease progression a 50% increase from the immediately preceding draw was considered significant. Out of three hundred and fourteen longitudinal sample pairs 85 were clinically progressing and 229 had no progression from the previous visit. The cutoff of a 50% increase in CYFRA 21-1 offered a sensitivity of 45.9%, a specificity of 87.9%, PPV of 57.4% and NPV of 81.3% for detecting lung cancer progression. To evaluate if a significant reduction in CYFRA 21-1 is an indicator of response to therapy we used 284 samples from 91 subjects. The cutoff of at least one-third decrease in CYFRA 21-1 levels from the previous reading offered a sensitivity of 37.6%, a specificity of 83.0%, PPV of 39.6% and NPV of 81.8% for detecting response to therapy.
Conclusion: Serial measurement of CYFRA 21-1 is a reliable serum biomarker test for use as an aid in

monitoring disease progression during the course of disease and treatment in lung cancer patients.
Keywords: CYFRA 21-1 biomarker, lung cancer monitoring, diagnostic test

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P2.089 DETECTION OF PRENEOPLASIC LESIONS USING BIOLOGICAL AND GENOMIC LUNG CANCER BIOMARKERS IN A HIGH RISK CHILEAN POPULATION

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Background: Lung Cancer (LC) is the leading cause of cancer mortality world wide and the second one in Chile, where every year nearly 2500 persons died from LC, furthermore, between 1990 and 2008 the LC mortality rate for 100.000 inhabitants for the whole country, both genders, increased from 10.8 to 14.6. Although, cigarette smoking is the major risk factor, genetic diversity and exposure to environmental or occupational pollutants must also be considered, especially in those cities highly exposed to environmental carcinogens. Evaluation of risk assessment and early-detection strategies are important for LC control in Chile. Objective: The objective of the study is to evaluate LC risk biomarkers and early LC detection technologies to detect pre-neoplastic lesions and early lung cancer using Genomic Biomarkers (SNPs), DR70® (Onko Sure), Automated Quantitative Cytometry (AQC) of induced sputum cells and Autofluorescence Broncoscopy (AFB).
Methods: A LC Risk Survey was conducted in Metropolitan Santiago and Antofagasta region; the latter has high levels of arsenic exposure in drinking water in the past. Individuals older than 40 years of age who had smoked ≥ 20 pack years, environmental exposure to arsenic and or a family history of LC were selected. Each participants provided an induced sputum sample for AQC, and a blood sample for DR70 and genomic biomarkers studies. Those with AQC DNA index ≥2.3 and atypical nuclei in sputum or DR70 positive test were invited for AFB studies.
Results: AQC was done in 228 voluntaries. A h, indeterminate or low score for malignancy was observed in 18%, 31% and 51 %, respectively. Of 18% who had a high AQC score 2% were positive for DR70. DR70 was positive in 90% of clinically diagnosed LC patients (positive controls). Up until now, 62% of the participants with high AQC scores have been analyzed by AFB. 20.8 % of them were found to have squamous metaplasia or mild dysplasia. Very high frecuency (0.961) for the mutated allele (G) was found, this is the highest frequency described for this SNP in different populations.
Conclusion: Our preliminary results suggest that further work need to be done to evaluate genomic biomarkers, AQC in sputum cells, DR70 and AFB for identification of at risk of LC in Chile. This research was supported by INNOVA CORFO.
Keyword: Lung cancer biomarkers

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.090 MUTATIONS OF THE CATALYTIC SUBUNIT ALFA OF PI3K (PIK3CA) IN ERLOTINIB-TREATED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P) WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS

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Background: Stage IV NSCLC p with EGFR mutations treated with erlotinib had a median progression-free survival (PFS) of 14 months (m) and median survival (MS) of 27 m in our experience. However, EGFR mutations can only imperfectly predict outcome. PIK3CA mutations occur in several tumors and have prognostic and therapeutic implications. We examined the presence and potential influence of PIK3CA mutations on outcome to erlotinib in NSCLC p with EGFR mutations.
Methods: PIK3CA mutation status was assessed in pretreatment paraffin-embedded tumor samples from 118 advanced NSCLC p with EGFR mutations treated with erlotinib. E542K, E545K and H1047R mutations were screened by 5'-nuclease PCR (Taqman) assay and confirmed by standard PCR followed by sequencing.
Results: PIK3CA mutations were detected in 6 of 118 patients (5.1%). 84% of p with PIK3CA mutations had adenocarcinomas vs 50% of p with wild-type (wt) PIK3CA (P=0.01). Response rate was 50% for p with mutations vs 70% for p with wt PIK3CA (P=0.03). There were no other differences between p with and without PIK3CA mutations. 2 of the 6 p with PIK3CA mutations had the uncommon L861Q mutation in exon 21 of EGFR. 1 of the 6 p had complete response; 2 had partial response; 3 had progressive disease. There was a non-significant trend towards shorter PFS for the 6 p with PIK3CA mutations (9 vs 16 m; P=0.59). MS was not reached for the 6 p with PIK3CA mutations, while it was 29 m for p with wt PIK3CA (P=0.09).
Conclusion: PIK3CA mutations can be present in some EGFR-mutant NSCLC p, with lower response and a trend towards shorter PFS. Treatment with EGFR tyrosine kinase inhibitors plus PIK3CA inhibitors should be tested in this small subset of p with double mutations.
Keywords: Non-small cell lung cancer, EGFR mutations, PIK3CA

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P2.091 ASSOCIATION BETWEEN TS EXPRESSION LEVELS AND RESPONSE TO PEMETREXED IN MPM: FACT OR FICTION?

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Background: Malignant mesothelioma is a highly aggressive tumour arising from mesothelial lined surfaces like the peritoneum and, more often, the pleura (malignant pleural mesothelia, MPM). Antifolates are actually considered the most promising cytotoxic drugs for MPM. Pemetrexed, an antifolate mainly inhibiting thymidylate synthase (TS), but also dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT) and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), is the first and only drug approved by the FDA for treatment of mesothelioma but show different response rates. The aim of the study is to find a potential correlation between TS, GARFT and/or AICARFT levels in MPM and their response to pemetrexed, potentially resulting in a reliable predictive factor for MPM treatment.
Methods: 63 patient samples were tested immunohistochemically and via qPCR for TS, GARFT and AICARFT levels. In addition, two enzymes involved in antifolate transport (RFC) and activation (FPGS) were tested immunohistochemically. Distribution patterns were analysed and, if possible, a cut-off was defined. Mortality statistics and clinical data were evaluated to determine a potential effect of pemetrexed application correlated to TS, GARFT and/or AICARFT levels. For IHC a tissue microarray was established. Evaluation of expression levels were done with a commercial TaqMan® Gene Expression-assays (Applied Biosystems®) using

optimized primer and probe concentrations. qPCR and data analysis was performed on a Roche® LightCycler® 480. Immunohistochemistry was done as recommended by the manufacturers, and the reactions were evaluated semiquantitatively by multiplying staining intensity by percentage of positive tumour cells. Correlation analysis was performed using a self-programmed algorithm for the R software.
Results: qPCR analysis did not show a difference in expression pattern of GARFT and AICARFT, TS gene expression rendered two distinct groups. Results of the immunohistochemical investigation showed a heterogeneous staining pattern of all enzymes. Statistical analysis of data did not show any significant correlation between one of the enzyme-expressions and response to pemetrexed treatment.
Conclusion: Our results showed that in MPM, in contrast what might be valid in lung carcinoma, the TS gene and protein expression levels have no influence on a response to pemetrexed therapy. Furthermore, GARFT and AICARFT expression show no deregulation administered over all patient samples, GARFT seems to be a potent house-keeping gene in MPM. Also FPGS and RFC expression can not be used as markers for a response to pemetrexed, a possible influence of several published mutations of these enzymes has to be proven. As pemetrexed nevertheless has proven its therapeutic use, other pathways of drug reaction are being investigated.
Keywords: mesothelioma, biomarker and treatment correlation, thymidylate synthase, GARFT, DHFR, AICARFT

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P2.092 DAB2 INTERACTIVE PROTEIN (DAB2IP) METHYLATION IN SERUM DNA OF NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P) WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS

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Background: DAB2IP loss promotes primary tumor growth by activating Ras and drives metastasis through NFkB, serving as a signaling scaffold to coordinately regulate these pathways. DAB2IP is frequently methylated in lung cancer, and methylation in the m2a region is a key regulatory factor for DAB2IP expression in prostate cancer. We examined DAB2IP methylation in cell lines and in serum from erlotinib-treated NSCLC p with EGFR mutations.
Methods: In human lung, breast and colorectal cancer cell lines, we analyzed DAB2IP promoter methylation in regions m2a and m2b by methylation-specific PCR (MSP) and bisulfite genomic sequencing. In circulating serum DNA from 152 erlotinib-treated NSCLC p with EGFR mutations, we analyzed methylation in the m2a and m2b promoter regions of DAB2IP by MSP. Methylation status was correlated with clinical outcome.
Results: Methylation was detected in the m2a region of 42 (27.63%) p, and in the m2b region in 51 (33.55%) p. There were no major differences in clinical characteristics (age, gender, smoking history, EGFR mutation type, metastatic sites) between p with methylation in the m2a region and p with methylation in the m2b region. Overall progression-free survival (PFS) was 15 months (m), and median survival (MS) 28 m for all 152 p. For the 41 p with bone metastases (mets), PFS was 14 m for 30 p without methylation in the m2a region vs 8 m for 11 p with methylation in the m2a region (P=0.01), and MS was 23 m vs 10 m, respectively (P=0.19). For the 57 p with distant mets but no lung mets, PFS was 18 m for 36 p without methylation in the m2a region vs 10 m for 21 p with methylation in the m2a region (P=0.01), and MS was 24 m vs 16 m, respectively (P=0.03). No differences in either PFS or MS were observed according to the methylation status of the m2b region.
Conclusion: Methylation in the m2a region of DAB2IP in serum DNA correlates with PFS and MS to erlotinib in NSCLC p with EGFR mutations with non-lung mets. Surveillance of DAB2IP methylation status in circulating DNA could be a useful tool

to predict outcome to erlotinib in EGFR-mutated NSCLC p with non-lung mets.
Keywords: DAB2IP, methylation, Non-small cell lung cancer, EGFR

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P2.093 DIFFERENTIAL EXPRESSION OF BRCA1, RAP80 AND GENES INVOLVED IN THE NUCLEAR FACTOR κB (NFκB) AND NOTCH SIGNALLING PATHWAYS IN NON-SMALL-CELL LUNG CANCER (NSCLC) AND SMALL-CELL LUNG CANCER (SCLC) PATIENTS (P)

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Background: Genetic diversity in lung cancer according to histological subtype has not been fully explored. BRCA1 and RAP80 influence response to chemotherapy. Musashi 2 activates HES-1 in the Notch pathway, and HES-1 can abrogate CYLD. A20, AEG-1, EZH2 and TRAF6 are also involved in NFkB activation. We have examined mRNA expression of BRCA1, RAP80 and components of the NFkB and Notch pathways in lung cancer p.
Methods: mRNA expression of Musashi 2, CYLD, HES-1, A20, EZH2, AEG-1, TRAF6, NFKBIA, RelA, BRCA1 and RAP80 was analyzed by quantitative RT-PCR in tumor samples from 85 lung cancer p (77 NSCLC, 8 SCLC).
Results: p characteristics: 51 males; median age, 59; 33 smokers, 26 ex-smokers; 49 adenocarcinoma, 10 large cell carcinoma (LCC), 18 squamous cell carcinoma (SCC), 8 SCLC. Source of tumor sample: 36 primary tumor, metastasis, 15. 11 p had K-ras mutations. There were differences in the expression levels of Musashi 2, BRCA1, EZH2 and RAP80 according to histological subtype. The median Musashi 2 mRNA expression was 4 times higher in SCLC than in NSCLC (adenocarcinoma, SCC, LCC) (P<0.001); BRCA1 expression was 3 times higher (P<0.001); EZH2 was 7 times higher (P<0.001); RAP80 was 2 times higher (P=0.011). There were no differences in expression levels of any of the 11 genes analyzed according to p age, smoking history or source of the tumor sample. NSCLC p with K-ras mutations had higher expression of both AEG-1 and NFKBIA than p with wild-type K-ras (P=0.04).
Conclusion: Musashi 2, BRCA1, EZH2 and RAP80 expression was significantly higher in SCLC p. Further investigation is warranted to examine the potential association between expression of these genes and response to platinum regimens and radiotherapy in SCLC. Elevated AEG-1 levels associated with K-ras-mutant tumors could identify a subgroup of NSCLC p with poor prognosis.
Keywords: RAP80, Non-Small-Cell Lung Cancer, BRCA1, NFkB

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P2.094 FEASIBILITY OF EGFR AND KRAS MOLECULAR TESTING ON CYTOLOGIC SPECIMENS FROM NON SMALL CELL LUNG CARCINOMAS

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Background: Somatic mutations in the epidermal growth factor receptor (EGFR) and KRAS are present in a subset of patients with non-small cell lung cancer (NSCLC), and may be of predictive value for response to treatment with tyrosine kinase inhibitors (TKIs). The recent approval of an EGFR-TKI for the treatment of patients with

unresectable stage IIIB or IV adenocarcinomas of the lung harboring EGFR mutations encourages to develop testing techniques on cytologic specimens, instead of tissue biopsies, which are sometimes unavailable.
Methods: DNA was extracted from cytologic specimens of 39 patients from bronchial brush (n=5), lavage (n=2), transthoracic and transbronchial needle aspiration (TBNA) (n=20), pleural or pericardial fluids (n=9), subcutaneous nodule or peripheral lymph node (n=3). The adequacy of cytologic specimens submitted for EGFR/KRAS molecular testing, including echo-guided TBNA, for direct sequencing method was evaluated.
Results: Tumor cells represented 5-80% of overall cellularity. Confirmed adenocarcinomas were present in 27 patients. Available DNA was extracted from all specimens, both in terms of yielding and quality. DNA recovering ranged from 3.4 to 339.6 ng/ïl and 260/280 OD ratio was > 1.54 in all patients, including those with poor cellularity rate. DNA sequencing was available for EGFR exon-18, -19, -20 and -21 in 37/39, 36/39, 37/39 and 38/39 patients respectively and for KRAs in all patients. Abnormalities were found in 8 (20,5%) of 39 patients. Exon 18 mutations, exon 19 deletions, exon 20 mutations, and exon 21 L858R mutations were detected in 2/37 (5.5%), 4/36 (11%), 1/37 (2.7%), and 1/38 (2.6%) cases, respectively. KRAS mutations in exon 2 were revealed in 11 patients (28%). The overall EGFR/KRAS mutations profile from this small series including only cytologic specimens was consistent with that usually obtained from tissue biopsies except for EGFR exon 21.
Conclusion: Direct sequencing of DNA from cytologic material is accurate for the detection of EGFR and KRAS mutations in patients with NSCLC. Extracted DNA recovering was sufficient despite important variability, whatever the tumoral cellularity. Cytologic specimens may challenge tissues biopsies when needed to check EGFR/KRAS mutational status in patients candidate for TKIs treatment.
Keywords: EGFR mutations, cytology, NSCLC

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P2.095 MOLECULAR PROGNOSTIC FACTORS IN NON-SMALL CELL LUNG CANCER PATIENTS WHO RECEIVED CURATIVE RADIOTHERAPY AND CHEMOTHERAPY

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Background: To determine the molecular prognostic factors which effect treatment results in locally advanced non-small cell lung cancer (LA-NSCLC) patients who received radiotherapy and chemotherapy for curative intent.
Methods: Between January 2000 and December 2008, 76 LA-NSCLC patients whose pathologic slides were available for immunohistochemical analysis were evaluated for ERCC1, RRM1, MMP7, and VEGF expression.
Results: Positive prognostic factors for overall survival in univariate log-rank analysis were weight loss ≤ 5% (p=0.04), epidermoid histology (p=0.04), N0-1 stage (p<0.01), high expression level of MMP7 (p=0.05), good response to treatment (p<0.01). Positive prognostic factors in multivariate Cox regression analysis were high level of Karnofsky Performance Status (p=0.05), epidermoid histology (p=0.02), and good response to treatment (p<0.01). Positive prognostic factors which influenced disease-free survival were epidermoid histology (p<0.01), good response to treatment (p<0.01), high expression levels of ERCC1 (p=0.02) and MMP7 (p=0.02) in univariate analysis, and epidermoid histology (p<0.01), N0-1 stage (p<0.01), good response to treatment (p=0.01) in multivariate analysis. Positive prognostic factors for locoregional recurrence-free survival were concomitant chemotherapy (p=0.03), good response to treatment (p=0.05), high expression levels of ERCC1 (p=0.03) and MMP7 (0.03) in univariate analysis. High expression level of ERCC1 was found to increase treatment response rate (p=0.05), decrease the risk of recurrence (p=0.02), prolong the duration of overall survival but without statistical significance (p=0.32), influence disease-free (p=0.02) and locoregional recurrence-free survival rates (p=0.03). High expression level of

MMP7 did not have an impact on treatment response and recurrence rates however it influences the duration and rates of overall (p=0.05), disease-free (p=0.02) and locoregional recurrence-free survival in a positive way. The expression levels of RRM1 and VEGF did not have impact on treatment response, recurrence rates, and the duration and rates of overall, disease-free, and locoregional recurrence-free survival.

Conclusion: ERCC1 and MMP7 were molecular prognostic factors that influence survival and treatment response in LA-NSCLC patients who receive RT and CT. These findings should be clarified with prospective clinical trials with higher number of patients.

Keywords: Non-small cell lung cancer, molecular prognostic factors

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P2.096 EARLY-PHASE DECISION MODELING IN LUNG CANCER TO PROJECT THE VALUE OF A PROGNOSTIC NSCLC MULTI-MARKER SIGNATURE

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Background: Molecular signatures may provide additional information beyond histological staging about the likelihood of relapse and the benefit of adjuvant chemotherapy in early-stage non-small cell lung cancer (NSCLC).

Methods: We developed a Markov-type decision-analytic model to evaluate the clinical and economic impacts of a predictive multi-marker assay in early-phase development compared to standard care. In the standard care arm, stage I patients were assumed to be observed and stage II patients were assumed to receive chemotherapy. In the testing arm, high-risk patients received chemotherapy and low risk patients were observed. After initial treatment, patients could experience three health states: disease-free, recurrence, and death. Heath-state transitions depended on stage, chemotherapy use, and risk strata. The sensitivity (82%) and specificity (66%) for predicting 5-year recurrence were derived from a meta-analysis of publicly available expression data and laboratory evaluations of stored tumor samples. The model included costs for the multi-marker assay, chemotherapy treatment and administration, disease monitoring, and post-recurrence medical care. Time spent in each health state was adjusted by the commensurate utility value. The model outcomes were expressed in terms of incremental costs, life-years gained, quality adjusted life-years gained (QALYs), and the incremental cost-effectiveness ratio (ICER).

Results: The multi-marker assay provided an average increase in QALYs and costs of 0.13 and $4,312, respectively, with an incremental cost-effectiveness ratio (ICER) of $33,701/QALY. The results were most sensitive to estimates of chemotherapy benefit in high-risk patients and the utility value during chemotherapy treatment. Threshold analyses indicated that the assay would yield an ICER <$50,000/QALY for sensitivity and specificity values ≥ 70% and hazard ratios for the impact of chemotherapy on recurrence risk below 0.8 in high-risk patients. Using baseline test characteristics, the ICER remained below $50,000/QALY for test cost below $5,200.

Results:

Intervention	Test cost	Chemotherapy Cost	Monitoring Cost	Post-Recurrence Cost	Total cost	LYs	QALYs	% Receiving chemotherapy
Multi-marker Assay	$3,200	$3,337	$12,230	$17,721	$25,372	6.47	5.25	52%
No Testing	$0	$1,415	$11,762	$18,607	$21,059	6.31	5.12	22%
Difference	$3,200	$1,922	$467	-$886	$4,312	0.16	0.13	30%
ICER (Incremental cost per LY or per QALY)						$26,449	$33,701	

Abbreviations: LY: life-year; QALY: quality adjusted life-year, ICER: incremental cost-effectiveness ratio

Conclusion: A predictive multi-marker assay with moderate accuracy has the potential to efficiently improve outcomes in early-stage NSCLC. Early-phase decision analyses can provide useful target test characteristics for development programs. As part of test validation, it is essential to understand levels of chemotherapy benefit by patient risk strata.

Keywords: Early Stage NSCLC, recurrence, Multi-marker assay, prognostic

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Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.097 CLINICOPATHOLOGICAL FEATURES OF LUNG ADENOCARCINOMA WITH KRAS MUTATIONS

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Background: KRAS and epidermal growth factor receptor (EGFR) mutations are thought to play an important role in the carcinogenesis of lung adenocarcinoma. The occurrence of these two oncogenic mutations is mutually exclusive, and they exhibit many contrasting characteristics, such as gender, smoking history, pathological features, response rate to molecular-targeted agents, and prognostic implications. KRAS mutations have been widely hypothesized to be related to direct tobacco exposure. It was, however, recently reported that KRAS status cannot be readily predicted on the basis of smoking history alone. KRAS mutations are frequently found in adenocarcinomas with mucinous bronchioloalveolar carcinoma, occurring in 28–86% of cases. Mucinous BAC was reported to be more often associated with non-smoking status. Several meta-analyses revealed that KRAS mutations may be associated with shortened survival; however, some studies reported that KRAS mutations are not independently associated with prognosis in patients with lung adenocarcinoma. As noted above, clinicopathological findings of KRAS-mutated adenocarcinoma cases have not yet been fully clarified. We analyzed the relationship between the KRAS mutation and corresponding clinicopathological findings, focusing on non-mucinous and mucinous bronchioloalveolar elements.
Methods: EGFR and KRAS mutations were detected in DNA samples extracted from 182 surgically resected tissues of lung adenocarcinomas by Smart Amplification Process. The relationships between gene mutation status and clinicopathological features were analyzed. All adenocarcinoma cases were divided into bronchioloalveolar carcinoma (BAC), adenocarcinoma with bronchioloalveolar features (AWBF), and adenocarcinoma without BAC components (non-BAC). BAC/AWBF tumors were further assessed for the presence of mucinous features.
Results: EGFR and KRAS mutations were found in 76 (41.8%) and 30 (16.5%) cases, respectively. In the KRAS mutant group, BAC/AWBF was found in 22 cases, which included 10 non-mucinous and 12 mucinous tumors. Of 19 cases with mucinous BAC/AWBF, KRAS mutations were detected in 12 (63.2%), but no EGFR mutation was detected. In the KRAS mutant group, BAC/AWBF had significantly earlier pathological stages (p=0.032) and more favorable prognoses (P=0.004) than did non-BAC. Mucinous BAC/AWBF showed less smoking history (p=0.043, p=0.001) than did non-mucinous BAC/AWBF and non-BAC. Furthermore, transversion type KRAS mutations were more common in non-BAC (p=0.039).
Conclusion: KRAS-mutated adenocarcinomas can be divided into BAC/AWBF and non-BAC types. Non-BAC adenocarcinoma is related to smoking history and has a poor prognosis. BAC/AWBF adenocarcinoma, however, has a more favorable prognosis, and mucinous BAC/AWBF has little relationship to smoking history.
Keywords: Lung cancer, Adenocarcinoma, KRAS mutation, mucinous bronchioloalveolar carcinoma

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P2.098 THYMIDYLATE SYNTHETASE MRNA EXPRESSION IN LUNG CANCER PATIENTS TREATED WITH PEMETREXED

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Background: Pemetrexed (PMT), a multitargeted antifolate drug, inhibits thymidylate synthetase (TS) potently. PMT is effective in non-small-cell lung cancer (NSCLC) patients with non-squamous cell carcinoma. TS expression is lower in adenocarcinoma compared with squamous cell carcinoma. The relationship between clinical effectiveness of PMT and TS expression in lung

cancer cells is unknown. The purpose of this study is to determine whether TS expression affects therapeutic efficacy of PMT.
Methods: The subjects were NSCLC patients who treated with PMT. Samples were gotten by tumor biopsy before treatment. We dissected cancer cells from formalin-fixed paraffin-embedded tissue by using a laser microdissection. TS mRNA was analyzed by using real-time RT-PCR. TS protein expression was evaluated by using immunohistochemistry. We assessed the association between TS expression and therapeutic efficacy of PMT.
Results: Twenty-nine patients were enrolled. The median age was 67 years. Seventy-two percent of patients had a previous treatment with chemotherapy. Overall response rates were 27.6% for PMT. Median progression free survival (PFS) was 16.7weeks for PMT. TS mRNA expression could be evaluated in all samples. TS mRNA levels ranged from 0.001 to 33.590 (mean 2.451). TS mRNA expression was significantly lower in response group (CR+PR) compared with non-response group (SD+PD) (0.223±0.083 versus 3.195±1.752, $p<0.001$). TS protein expression was significantly lower in response group compared with non-response group ($p=0.030$). PFS was statistically superior for lower TS mRNA expression patients compared with higher TS mRNA expression patients (18.0 versus 15.0 weeks, $p=0.047$).
Conclusion: We could analyze TS mRNA expression in lung cancer cells specifically from biopsy specimens by using a laser microdissection. TS mRNA expression affected therapeutic efficacy of PMT. TS mRNA expression may be usefull predictive biomarker for NSCLC patients received PMT.
Keywords: Thymidylate synthetase, Pemetrexed, Laser microdissection

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P2.099 EXPRESSION OF HNRNP A1 BY NON-SMALL CELL LUNG CANCER CELLS REGULATES ANCHORAGE-INDEPENDENT GROWTH THROUGH THE ACTIVATION OF STAT3

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Background: hnRNP A1 is a member of the heterogeneous nuclear ribonucleoprotein (hnRNP) family, which binds pre-mRNA and plays multiple roles in the regulation of mRNA metabolism,such as mRNA alternative splicing, transport and stability. hnRNP A1 is also involved in the regulation of transcription, maintenance of telomeres, and microRNA processing. hnRNP A1 expression is deregulated in multiple types of cancer. In the present study we examined the expression and role of hnRNP A1 in human non-small cell lung cancer (NSCLC).
Methods: hnRNP A1 expression was evaluated by immunohistochemistry in 81 NSCLC tumors and their normal counterparts. We also analyzed the expression of hnRNP A1 in a panel of NSCLC cell lines. To study the role of this factor in lung cancer, hnRNP A1 expression was transiently down-regulated by siRNA in selected lung cancer cell lines. The effects of hnRNPA1 inhibition on proliferation and anchorage-independent growth were evaluated. The potential involvement of STAT3 in the hnRNPA1 mediated inhibition of anchorage-independent growth was analyzed through several technical approaches. Finally, STAT3 and phospho-STAT3 expression was analyzed in lung cancer samples by immunohistochemistry.
Results: In most of the tumors, as in normal lung tissue, the expression of hnRNP A1 was nuclear; however, some carcinomas also showed cytoplasmic localization of this protein. Transient downregulation of hnRNP A1 did not affect anchorage-dependent proliferation, but strongly enhanced anchorage-independent growth. We next investigated the molecular mechanisms by which hnRNP A1 exerted this effect. We analyzed the expression of STAT3, a transcription factor involved in anchorage-independent growth, resistance to anoikis, invasion, and metastasis. We found that down-regulation of hnRNP A1 increased the expression of STAT3 at both the mRNA and protein levels. In addition, higher levels of phospho-STAT3, the activated form of STAT3, were found when hnRNP A1 was down-regulated and cells were subjected to anchorage-independent conditions. Moreover, hnRNP A1 specifically bound and stabilized STAT3 mRNA. Finally, we found that in the series of lung tumors analyzed, low levels of hnRNP A1 tended to be

associated with high levels of phospho-STAT3.
Conclusion: Our data demonstrate that the expression of hnRNPA1 by lung cancer cells regulates anchorage-independent growth through a STAT3 dependent mechanism.
Keywords: hnRNPA1, STAT 3, Lung cancer

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P2.100 CD74, TGFB1 AND TGFB2 PROTEIN EXPRESSION ANALYSIS IN RESECTED NON-SMALL CELL LUNG CANCER AND ITS CORRELATION WITH CLINICAL OUTCOMES

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Background: Surgery remains the main curative option for non-small lung cancer (NSCLC) patients, but it is reserved to early stages. Adjuvant treatment, mainly chemotherapy, is offered to a high proportion of these patients. Even for patients with early stages NSCLC, the clinical behavior might be different after surgical resection. Recent studies have shown that aspects of the inflammatory process can influence the behavior of tumors. The CD74, TGFB1 and TGFB2 play a key role in regulating the inflammatory process. This aim of this study is to evaluate the expression of CD74, TGFB1 and TGFB2 in tumor and stroma, and correlate with clinicopathologic features and prognosis for overall and relapse free survival in patients with NSCLC who underwent curative resection.
Methods: From Jan 2003 to Dec 2007 we retrospectively review clinical and pathological data of patients with NSCLC who were submitted to complete surgical resection. One hundred twenty-nine patients with localized NSCLC operated without prior therapy and with availability of pathological material and clinical outcome were evaluated by immunohistochemical staining for CD74, TGFB1 and TGFB2 in tumor and stroma. Cases were analyzed according to the intensity and percentage of positive cells. Association between variables was performed according the method of chi-square or Fisher's exact test. Overall survival (OS) and relapse-free survival (RFS) were analyzed by the Kaplan-Meier method and comparison between them was done using the Log-rank test. Multivariate analysis for survival was calculated by proportional hazards model of Cox.
Results: CD 74 expression in more than 50% of the cells in tumor and stroma was observed in 14.1% and 56.1% respectively. The positivity of CD74 in more than 50% of the cells, when evaluated in the tumor, correlated with better relapse-free survival (RFS, 3 years: 93.3% vs. 67.8%, p = 0.018) and was associated significantly with female gender (p = 0.003), nonsmokers (p = 0.019), bronchioloalveolar and adenocarcinoma histologic types (p = 0.001) and stage I (p = 0.001), factors associated to good prognosis. Expression of TGFB1 in more than 50% of the cells in tumor and stroma was observed in 21.1% and 10.2% respectively. TGFB2 was positive in 52.8% in tumor and 30.7% in stroma. TGFB1 and TGFB2 did not correlate with OS and RFS. In multivariate analysis for RFS and OS, only pathological stage was identified as an independent determinant of prognosis.
Conclusion: In the present study, we observed that CD74 was determinant of better relapse free survival, but it is not an independent prognosticator. Expression of TGFB1 and TGFB2 was not correlated to prognosis in this group of patients.
Keywords: non-small cell llung cancer, Surgery, Prognosis, inflammatory

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P2.101 THE CONTRIBUTION OF BIOMARKERS TO ASSESS THE LEVEL OF INDIVIDUAL RISK IN THE SELECTION OF HIGH PREVALENCE SUBJECTS FOR CT SCAN LUNG CANCER SCREENING

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Background: Early detection of biological markers promise to complement the ability of low-dose CT to detect lung cancer. In previous study we shown the possibility of integrating the CT Scan screening and the result of biomarkers in the screening for lung cancer process. In this study we will present further data supporting this assessment as a tool to improve positive predictive models of individual breast cancer risk.
Methods: A randomised controlled screening trial for early lung cancer detection with low-dose CT is ongoing in Tuscany, Italy, in a cohort of 1406 high-risk (smokers and ex smokers (less than 8 years) active asymptomatic subjects. Several markers were analyzed on sputum and plasma samples at baseline, in particular genetic instability (LOH, MSI), and plasma DNA quantification. Evaluation of biomarkers was shown to be of special interest and a larger study has been carried out for several groups of subject. In this presentation data are presented for the group of subjects with 4 negative CT Scan screening tests who were assessed for biomarkers at baseline.
Results: 96.4% of subjects enrolled in the Italung trial accepted to donor peripheral blood and uninduced sputum. In a first analysis we published results on 98 subjects: cases of screen-detected lung cancer; controls negative at baseline CT screening, and subjects positive for non-calcified nodule (NCN ≥ 5mm and NCN≥3mm at repeated) at baseline but negative for cancer at the follow-up CT examination. Allelic imbalance showed good performance for screening of NCN ≥5mm. Results of the study including the lung cancer cases detected at repeated rounds (1,2,3) and in a larger sample of subjects which were classified as always negative for NCN in all the 4 screening rounds showed that subjects negative at all the 4 screening round were negative at escreate analysis in the 75% of subjects assuming a cut off of 23% (133 out of 175 subjects , with the 8% of inadequate sputum) . The average DNA plasma in this group (N=175) was 3.6 ng DNA/ml plasma (SD 2.7). Ever CT Scan negative subjects (i.e. any NCN duing the4 screening cycle) in the 81.4% were under the cutoff of 5 ng of plasma DNA.
Conclusion: In this confirmitory study based on large number of ever CT Scan negative subjects the value of molecular biomarkers in the assessment of the individual risk of lung cancer was important in the classification of subjects . A full evaluation of lung cancer cases at repeated screening test and of the groups in whom a NCN was detected at repeated screening test is on going. Results untill now confirm the hypothesis that biolmolecular marker might be a complementary source of informnation in the assessment of individual lung cancer risk. This results can be helpful in the design of an efficient strategy for lung cancer screening integrating individual risk assessment with biomarkers and CT Scan screening.
Keyword: CT SCan Screenng

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P2.102 BRAF AND PIK3CA GENE MUTATION STATUS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Specific mutations of the epidermal growth factor receptor (EGFR) gene are predictive for favorable response to tyrosine kinase inhibitors (TKIs) and are associated with a good prognosis. Nevertheless, tumor that initially responds to EGFR-TKIs almost inevitably becomes resistant later. Other mechanisms of resistance to EGFR inhibitors could involve activating mutations of the other main EGFR effector pathway, i.e., the phosphoinositide-3-kinase/phosphate pathway and BRAF-MEK-ERK pathway. The aim of this study was to investigate the mutation status of phosphoinositide-3-kinase catalytic alpha (PIK3CA) and BRAF gene in patients with non-small cell lung cancer (NSCLC).
Methods: A total of 242 patients with NSCLC from 2007 to 2009 with available archival tissue specimens were included. The hot-spot mutations of exon 11 and exon 15 of the BRAF oncogenes and the exon 9 and exon 20 in the PIK3CA gene were screened by high-resolution melting analysis (HRMA) method, and the mutation positive samples were confirmed by direct sequencing.
Results: Of thees 242 cases, 170 were

adenocarcinoma, 52 were squamous cell carcinoma, and 20 were the others. 6 were I stage, 14 were II stage, and 222 were III and IV stage; 166 were male, 76 were female; The mean age of these patients was 58 years, range from 23-88 years. The PI3KCA activation mutation rate was 2.48% (6/242), 1.66% (4/242) in exon 9 and 0.83% (2/242) in exon 20. The mutations in exon 9 included E545K(3 cases) and E545K and T544T(1 case). H1046R mutation was found in exon 20(2 cases). BRAF activation mutation rate was found in 2.48% cases (6/242), 1.66%(4/242) in exon 15 and 0.83%(2/242) in exon 11. The mutation in exon 15 was V600E (4 cases). Two activating mutations were found in exon 11, S446G and G460R. HRMA revealed abnormal melting profiles in 1 case harboring mutations in 2 different genes simultaneously.
Conclusion: Our study indicated that PIK3CA and B-RAF have a low frequency mutation in patients with NSCLC. This may have a potential significance for the target therapy.
Keywords: B-RAF, Lung cancer, PIK3CA

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P2.103 MIR-29B AND MIR-381 ARE DYSREGULATED IN LUNG ADENOCARCINOMA AND MODULATE RESISTANCE TO SRC INHIBITORS IN LUNG CANCER CELLS

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Background: The Src kinase regulates cancer cell invasion through ID1, both are frequently over-expressed in human lung adenocarcinoma. The current study aimed at identifying microRNAs (miRs) controlled by Src that target ID1, and to test if modulation of these miRs in lung cancer cells lead to resistance against Src inhibitors.
Methods: The study included the human lung cancer cell lines A549, H460 and H1299. Cells were incubated with the Src inhibitors saracatinib and dasatinib, and miRs were extracted. To assess miR expression profiles, we used TaqMan® Array MicroRNA Cards (Applied Biosystems). Western Blotting was performed using anti-Src, anti-phospho-Src, anti-ID1 and anti-Actin antibodies. miR transcript levels were confirmed by real-time quantitative RT-PCR. Lentiviral vectors were used to express pre-miR and anti-sense-miR. Migration and invasion were tested using wound healing and transwell assays, respectively. Formalin-fixed and paraffin-embedded adenocarcinoma samples and matched alveolar lung tissue from 23 patients were used for miR expression analysis. P-values < 0.05 were defined as statistically significant.
Results: Upon incubation of A549 lung cancer cells with the Src inhibitor saracatinib, miR-29b and miR-381 were the most highly upregulated miRs with a binding site in the ID1 3'UTR. miR-29b and/or miR-381 suppressed the level of ID1 and significantly reduced cell migration a hallmark of the Src-ID1 pathway. Inhibition of endogenous miR-29b or miR-381 markedly enhanced ID1 expression. miR-29b repression resulting in increased ID1 levels significantly increased lung cancer cell migration and invasion. In addition the effects of the Src inhibitors saracatinib and dasatinib on migration and invasion were significantly attenuated in these cells. In human lung adenocarcinoma samples, miR-29b and miR-381 were significantly downregulated compared with matched alveolar lung tissue ($p=0.031$ and $p=0.007$). Tumor miR-29b expression negatively correlated with the previously determined ID1 nuclear H-score ($p=0.0446$). Moreover, tumor miR-29b and miR-381 levels were significantly associated with event-free survival ($p=0.03$ and $p=0.003$) and overall survival ($p=0.04$ and $p=0.02$).
Conclusion: We identified ID1 as novel target of miR-29b and miR-381. Our results further indicate that miR-29b and miR-381 are dysregulated in human lung adenocarcinoma, are involved in lung cancer cell migration and invasion via the Src-ID1 signaling pathway and modulate the resistance to Src kinase inhibitors in lung cancer cells.
Keywords: Inhibitor of differentiation protein 1, SRC, Lung cancer, miR-29b and miR-381

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P2.104 ELEVATED SURVIVIN IS PROGNOSTIC SIGNIFICANCE FOR NON-RESPONSE TO CHEMOTHERAPY AND REDUCED SURVIVAL IN LUNG CANCER WITH MALIGNANT PLEURAL EFFUSIONS

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Background: It is still often difficult for clinicians to confirm malignant pleural effusions (MPE). Survivin has been shown to inhibit apoptosis, enhance proliferation and promote angiogenesis. This study aimed to evaluate the diagnostic accuracy, and prognostic role of survivin in lung cancer with MPE.
Methods: Pleural effusion samples were collected from 67 lung cancer patients (58 lung cancers; 9 extrathoracic tumors), and from 68 patients with various benign conditions (31 with pneumonia; 37 with tuberculosis). Concentrations of pleural fluid survivin, Cyfra 21-1, and carcinoembryonic antigen (CEA) were measured simultaneously by enzyme-linked immunosorbent assay (ELISA). The sensitivity, specificity, and accuracy were calculated by receiver operating characteristic (ROC) analysis. The expression profile of survivin in pleural fluid, and its association with survival, were investigated.
Results: Survivin levels were significantly elevated in patients with MPE, especially primary lung cancer than in those of benign origin. Survivin, Cyfra 21-1, and CEA varied in diagnostic accuracy for differentiating MPE from benign pleural effusion by 67.5%, 68.3%, and 93.4%, respectively. Lung cancer patients with MPE who were positive for survivin expression were more refractory to chemotherapy ($P = 0.003$). Elevation of Prx1 was correlated with a reduced overall survival in univariate ($P = 0.0001$) and multivariate ($P = 0.004$) analyses.
Conclusion: Using the appropriate cut-off points, CEA currently provides the best diagnostic accuracy for patients with MPE. Survivin may be a useful adjunct of the conventional algorithm for diagnosing lung cancer with MPE. These findings suggest that elevated survivin expression may predict a poor-response to chemotherapy and shorter survival in lung cancer patients with MPE.

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P2.105 NEW BIOMARKERS INVOLVED LUNG CANCER DEVELOPMENT IN COPD PATIENTS.

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Background: Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) are both smoking related illnesses. Approximately 65% of all LC patients present COPD, which suggests that COPD is a risk factor for the development of LC and that there must be common pathophysiological mechanisms to both diseases. Immune dysfunction, abnormal activation of NF-Ä¸B, epithelial-mesenchymal transition, alterations of the degradation of extracellular matrix, among others have been implicated in the development of both diseases by several studies. Nonetheless, the most important mechanism shared by LC and COPD is chronic inflammation that causes alterations in the bronchial epithelium. Previous studies highlight the role of cytokines (IL-8,IL-1,IL-6), chemokines (RANTES, MCP-1), matrix metalloproteinases (MMP-9, MMP-3) and growth factors (TGF, VEGF) in the inflammatory process that takes place in both diseases. However, the understanding of the inflammatory mechanisms involved in LC and COPD is still limited. With this study we aimed at analyzing 80 markers (cytokines and growth factors) in BAL samples from patients with LC, COPD, LC and COPD and without LC or COPD by ELISA arrays, in order to obtain a possible predictive biomarker profile of LC in patients with COPD.
Methods: In order to analyse the bronchoalveolar lavage fluid protein profiles from four different groups of patients (with COPD, with LC, with COPD and LC and without COPD or LC), samples were collected from 60 individuals (15 per group) from the Virgen del Rocío Hospital (Seville, Spain) who had required flexible bronchoscopy for diagnostic reasons. Approximately

4-8 ml of sample was available to our experiments. Due to its low protein content, BALF samples needed to be concentrated before use. In order to study the protein profiles of the four groups of patients, a cytokine and growth factor screening was performed. The protein array used in this study is a commercially available array kit that analyses the expression levels of 80 cytokines and growth factors (Quantibody® Human Cytokine Antibody Array 1000 – RayBiotech, Norcross, GA, USA). Validation of the cytokine arrays results was performed through western blot.
Results: The analysis of the 80 cytokines and growth factor arrays in BAL samples from 60 patients from each group was performed using the scanner GenePix and the BABILOMICS software to create heat maps (using the samples' Euclidian distance). This analysis revealed the differential expression of 17 markers (EGF, VEGF, IGFBP2, GDF15, TIMP1, TNFR I, TNFR II, IL-8, IL-1a, IL-1ra, IL6sR, ICAM-1, Eotaxin 2, MCP1, MIG, MIP1b and MIP1d). The most noticeable changes were observed between the control group and the remaining groups as well as differences between adenocarcinoma and squamous cell carcinoma, with the latter one resembling the expression that occurs in patients with only COPD. The array data was later on validated by western blot with specific antibodies, confirming the results of the previous technique.
Conclusion: The citokines have important paper in cronical inflamation process in both disease lung cance and COPd.
Keywords: citokines, grow factors, Lung cancer, COPD

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P2.106 SPECIFIC GENE MUTATIONS AND EXPRESSION STATUS IN NSCLC

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Background: In NSCLC, mutations and expression levels of specific genes in cancer cells have been shown to affect the response rates to related target –therapies or chemo-therapies. For instance, EGFR mutation and TKIs therapy, ERCC1 gene expression and platinum based-drugs, RRM1 gene expression and gemcitabine.
Methods: From Mar. 2010 to Feb. 2011, we performed real time PCR to detect the mutation status of EGFR (exons 18, 19 and 21) and KRAS (codons 12 and 13), as well as the expression level of ERCC1, RRM1, TYMS, TUBB3, VEGF and BRCA1 in 90 NSCLC patients
Results: 90 NSCLC patients were enrolled (median age 64, ranged 25~83; 58 males and 32 females; 42 adenocarcinomas, 15 squamous-cell carcinomas, and 33 other subtypes). Among the specimens, there were 68 fresh tissues, 16 FFPE samples, 4 whole blood samples and 2 pleural effusion samples. The results showed that the mutation rate of EGFR and KRAS was 18.5% (15/81) and 11.1% (9/81), respectively. EGFR and KRAS mutation were mutually exclusive. The high level expression rate of ERCC1, RRM1, TYMS, TUBB3, VEGF and BRCA1 was 18.8% (16/85), 14.1% (12/85), 7.1% (6/84), 30.6% (26/85), 21.1% (16/76) and 8.4% (7/83), respectively.
Conclusion: The data base has been set up successfully and the data were still increasing. We treated our patients according to their gene status. Further investigations are needed to study the relationship between gene status and patients' response and survival..
Keyword: gene mutation; gene expression; lung cancer; data base

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P2.107 A PROSPECTIVE STUDY EXPLORING SERUM TUMOR MARKER PREDICTING OBJECTIVE RESPONSE AND SURVIVAL IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER

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Background: The clinical relevance of serum tumor marker, including cytokeratin 19

fragment(CYFRA21-1), CA125, CA 19-9, and carcinoembryonic antigen (CEA) as surrogate biomarker in advanced non-small cell lung cancer is a matter of debate.
Methods: Serum levels of above four tumor markers during chemotherapy were studied prospectively with radioimmunoassay at baseline and after 2 courses in patients with advanced NSCLC. Data were correlated with radiologic objective response (OR) after 4 courses and survival.
Results: Ninety-two patients were evaluable for serologic response assessment after 2 chemotherapy courses, and radiologic response assessment after 4 courses. CA125 reduction was statistically different in patients with objective response and progressive disease (P=0.036). Receiver operating characteristic curves (ROC) analysis demonstrated declines of CA125 and CYFRA21-1 predicting an OR to chemotherapy, with the AUC of 0.764 (95%CI, 0.664- 0.846; P=0.0001), a sensitivity of 74.63%, and specificity of 84% for CA125, and the AUC of 0.646 (95%CI, 0.539 - 0.744; P=0.0175), a sensitivity of 77.27%, and specificity of 64% for CYFRA21-1, respectively. Survival analysis demonstrated median progression-free survival was 10 months for patients with CYFRA21-1 response compared with 7 months for patients without serologic response (P=0.003). The 1-year overall survival rate was 79.2% for patients with CYFRA21-1 response and 72.5% for patients with CA125 response compared with 38.6% and 70.8% for patients without response, respectively (P=0.012 and P=0.037, respectively). Multivariate COX analysis indicated CYFRA21-1 response as independent prognostic factors for PFS (HR=0.353, P=0.0005) and OS (HR=0.558, P=0.012).
Conclusion: CYFRA 21-1 appeared to be a reliable surrogate marker of chemotherapy efficacy and survival in patients with advanced NSCLC.
Keywords: tumor marker, Non-Small-Cell Lung Cancer

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P2.108 THE NUCLEAR FACTOR κB (NFκB) AND NOTCH SIGNALLING PATHWAYS AND BRCA1 MRNA EXPRESSION IN STAGE IV NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P)

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Background: Little is known about the potential effect of genetic alterations in the NFkB and Notch pathways on NSCLC p. Musashi 2 activates HES-1 in the Notch pathway, and HES-1 can abrogate CYLD. A20, AEG-1, EZH2 and TRAF6 are also involved in NFkB activation. BRCA1 and RAP80 are modulators of cisplatin-based chemotherapy. Mutations in NFKBIA and DUSP22, which prevent NFkB activation, were described in the sequencing exome of a single NSCLC p, together with K-ras mutations.
Methods: mRNA expression of Musashi 2, CYLD, HES-1, A20, EZH2, AEG-1, TRAF6, NFKBIA, RelA, BRCA1 and RAP80 was analyzed by quantitative RT-PCR in tumor samples from 60 advanced NSCLC p. Expression levels by terciles were correlated with clinical characteristics and outcome to chemotherapy. Mutations in NFKBIA and DUSP22 were sequenced in 28 and 21 patients, respectively, and in 12 cancer cell lines.
Results: p characteristics: 36 male; 39 adenocarcinomas; 22 smokers; 23 bone metastases; 9 EGFR mutations; 10 K-ras mutations. No NFKBIA or DUSP22 mutations were observed in any of the p or cell lines. PFS was 12.3 months (m) for p in the lowest tercile of AEG-1 expression vs 9.3 m for p in the intermediate tercile and 4.8 for p in the highest tercile (P=0.002). The multivariate analysis showed that only AEG-1 expression was associated with shorter PFS (HR, 1.43; P=0.006). Expression levels of the other genes did not correlate with outcome. However, we had previously generated a two-gene risk model based on AEG-1 and BRCA1 expression: p with high levels of both genes are considered high-risk, p with low levels of both genes are low-risk, and p with high levels of one and low levels of the other gene are intermediate-risk. In the present study, PFS was 13 m in the low-risk group, while it was 7.6

m for the intermediate-risk group and 5.3 m for the high-risk group (P=0.02).
Conclusion: NSCLCs have variegated gene expression. AEG-1 and BRCA1 mRNA expression is a genetic signature that can be used as a prognostic model for the management of NSCLC p.
Keywords: NFkB, Notch pathways, Non-Small-Cell Lung Cancer, BRCA1 mRNA expression

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P2.109 TUMOR HETEROGENEITY AND MOLECULAR DIAGNOSTICS: KRAS MUTATION DETECTION IN SITU USING PADLOCK PROBES AND ROLLING CIRCLE AMPLIFICATION

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Background: The impact of activating KRAS mutations on EGFR inhibitor therapy in non-small cell lung cancer (NSCLC) is debated. Also, little is known about the role of KRAS mutations during lung cancer tumorigenesis, and if tumor heterogeneity with regard to mutation status is important for treatment response and prognosis.
Methods: We have developed an RNA-based genotyping assay that targets KRAS-mutations in codon 12 and 13 in situ on tissue slides by the use of multiple mutation specific padlock probes and rolling-circle amplification.
Results: KRAS genotyping was performed on cytologic tumor imprints as well as on fresh-frozen and formalin-fixed paraffin-embedded tissue sections from NSCLC and colon cancer specimens. The results were concordant with pyrosequencing data from of corresponding crude tissue extracts. Moreover, the distribution of wild type (green rolling-circle products) and mutated (red rolling-circle products) KRAS alleles could be determined for single cancer cells in different parts of the tumors.
Conclusion: This in situ method offers single cell mutation detection for diagnostics and holds great promise as a tool to investigate the role of oncogenic mutations in complex tumor tissues without the use of microdissection.
Keywords: Kras, Mutation, padlock probe, EGFR therapy

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P2.110 BUILDING A COMPREHENSIVE DATABASE FOR THE LUNGSCAPE PROJECT: A WAY TO BRIDGE GENOMICS AND CLINICAL PRACTICE IN THE EUROPEAN THORACIC ONCOLOGY PLATFORM (ETOP).

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Background: Since the identification of activating EGFR mutations, a number of distinct oncogenic and transforming driver mutations have been described in non-small lung cancer (NSCLC), affecting a growing patient population, and helping to define therapeutic strategies. The Lungscape project aims at building a virtual biobank to facilitate an international high-quality analysis of large numbers of tumors for genetic alterations linked to clinical and biological characteristics. Lungscape is evolving in step-wise fashion, starting with a retrospective analysis of 1500 completely resected NSCLC in 10-15 European institutions and then moving to samples from advanced disease. Finally, prospective trials will be designed to test treatment of molecularly defined tumors.
Methods: While tumor samples will be banked locally, a central electronic database will store anonymized comprehensive molecular and clinical data. Participating centers will use a secure web-based application to enter data into the central database. The system will capture detailed pathological parameters like tumor stage,

grade, histological subtype (including diagnostic immunohistochemistry), precise surgical procedure as well as patient characteristics, including age, gender, ethnicity, smoking status, and complete oncologic history including at least 3 years of documented follow-up. Genetic alterations will be progressively recorded, with a basic query for EGFR mutations and overexpression/amplification as well as EML4-ALK translocation. Data on KRAS, BRAF and HER-2 mutations, MET mutations and overexpression/amplification will be recorded if already performed and gradually implemented for every sample. Additional gene abnormalities, e.g regarding PI3K/PIK3CA, LKB1, PTEN, b-catenin, TRAIL-R2 genes will be added to molecular pathology parameters, based on available functional data in the literature and potential therapeutic interventions. In accordance with prevailing knowledge, special attention will be paid to enriching the virtual biobank with rare mutation-harboring tumors coupled with complete clinical records.

Results: The database is based upon an extensible information module, enabling the quick accommodation of changing data capture analysis needs across different studies. Its capabilities include secure data collection from multiple sites, a central and unique data review and acceptance workflow, and integrated charting. The attribute definitions are linked directly to end-user query-building and data retrieval, without any reprogramming. These parameterized data sets are directly available for time-series and cross-sectional statistical analysis and visualization. All activities will be coordinated by the ETOP office

Conclusion: Lungscape will enable investigators to generate biological hypothesis for personalized treatment approaches and provide an adequate trial platform for hypothesis testing.

Keywords: virtual biobank, NSCLC rare genetic alterations, ETOP, clinical database

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P2.111 RRM-1 IS PREDICTIVE OF CLINICAL BENEFIT FROM FIRST LINE PLATINUM DOUBLET THERAPY IN NON-SMALL CELL LUNG CANCER

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Background: Standard first line therapy for NSCLC is platinum-based doublet with / without biologic agents but responses remain variable. Clearly, new approaches are needed to predict benefit from chemotherapy in NSCLC. Except for EGFR mutation, the clinical utility of tissue-based biomarkers such as ERCC1, RRM1, thymidylate synthetase (TS), and K-ras remains uncertain. We conducted a retrospective analysis of Stage IV NSCLC patients diagnosed and treated at our institute over a 2 year period to correlate five commercially available biomarkers with best overall response to first line platinum-based treatment and overall survival.

Methods: Approximately 550 patients with Stage IV NSCLC patients were treated at NYU Clinical Cancer Center during 2008 and 2009. Of these, 65 patients fulfilled the following eligibility criteria for this retrospective study: biopsy-proven, available cell blocks from Stage IV patients; measurable lesion/s by imaging studies; tumor specimen expression of ERCC-1, RRM-1, EGFR, TS and for EGFR and K-ras mutation analysis performed by Response Genetics Inc. Best overall response to first line treatment was classified as "clinical benefit" (CR, PR, SD) or Failure (PD). Survival was defined from start of treatment until death from any cause. Continuous variables such as age at diagnosis, and ratio of gene transcripts of: EGFR, ERCC1, RRM1, TS, were described by means, standard deviations, medians and ranges. Associations between gene expressions were assessed using Pearson's correlation coefficient (R). Categorical variables, such as EGFR and K-ras mutation status, gender, performance status, histology and response, were described by frequency distributions. Associations between histological types and gene expressions were assessed using Fisher's exact test. Multivariate logistic modeling was used to assess individual and combined effects of the gene expressions on clinical benefit to first line platinum-based chemotherapy. The Kaplan-Meier method was used to plot survival curves and to estimate the median survival with a 95% Confidence Interval. Cox proportional hazards model was used to assess individual and combined effects of the gene expressions on survival. All tests were done at a 5% significance level.

Results: EGFR and TS gene transcript ratios did not predict clinical benefit to platinum doublets or survival. In univariate model, RRM-1 expression levels were highly predictive of resistance to platinum-based therapy (platinum/pemetrexed being the most common regimen), odds ratio (OR) of 0.40 (95% CI: 0.19-0.86). Similarly, ERCC-1 expression levels were predictive of treatment resistance (OR=0.54, 95% CI: 0.29-1.02); however, not statistically significant (p=0.06). When tested in a multivariate model (including: EGFR, ERCC-1, TS), RRM-1 retained its predictive effect (OR=0.35, 95% CI: 0.14-0.86).Presence of EGFR mutation was also highly predictive of response to platinum doublet (p=0.03). ERCC-1 was positively correlated with RRM-1; R=0.36 (p=0.003), as well as with TS; R=0.27 (p=0.027) ERCC-1 expression levels (controlling for EGFR, ERCC-1, TS-2) were independently predictive of decreased survival; hazard ratio of 1.76 (95% CI: 1.12-2.77).
Conclusion: RRM1 levels predict responses to platinum doublet therapies in lung cancer, while ERCC-1 levels are prognostic for survival. Correlation of ERCC-1 with RRM-1 and TS suggests that these markers may co-operate in resistance to platinum based regimens.
Keywords: ERCC-1, RRM-1, TS, EGFR, K-ras, NSCLC, Biomarkers

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P2.112 MITOCHONDRIAL FREE CIRCULATING DNA CONCENTRATIONS AND THEIR RELATIONSHIP TO ERLOTINIB TREATMENT IN PATIENTS WITH ADENOCARCINOMA OF THE LUNGS

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Background: It has been found that change of circulating free mitochondrial DNA (mtDNA) concentrations are correlated with chemotherapeutic effects in solid tumors. Present study was to determine and compare changes of plasma mtDNA concentrations before and after erlotinib treatment, and the potential prognostic value of plasma mtDNA concentrations.
Methods: After informed consent, lung cancer patients who had adenocarcinoma and were going to receive erlotinib treatment were enrolled. Patients' plasma were collected immediately before starting erlotinib treatment, day 15 and day 29 after starting erlotinib treatment, when patients' disease were progressed.
Results: Of 53 enrolled patients, best erlotinib treatment response was partial response in 26, stable disease in 13, and progressive disease in 14. mtDNA concentrations are shown in Table 1. Plasma mtDNA concentrations was significantly decreased on day 15 comparing day 0 levels in patients with progressive disease (p=0.028). Plasma mtDNA concentrations were similar or elevated on day 15 comparing day 0 levels in patients with partial response (p=0.808). The concentration of plasma mtDNA did not correlated with time to disease progression.
Conclusion: Plasma mtDNA levels did not correlated with patient's time to disease progression when patients received erlotinib treatment. Its' level was decreased on day 15 of those patients who had disease progressed to erlotinib treatment later.
Table . Plasma free mitochondrial DNA levels in 53 erlotinib treatment patients

Concentrations (copies/mL)	Partial response	Stable disease	Progressive disease
Day patient No	26	3	4
mean, SEM*	297, 757	26, 874	3776, 3
range	54-75	228-644	63-2733
Day 5 patient No	23		3
mean, SEM*	39, 986	774, 22	568, 387
range	26-25	6-2395	54-4925
Day 29 patient No	24		8
mean, SEM*	277, 473	2935, 948	359, 667
range	56-7587	7-9383	39-4637
Day PD patient No	7	5	9
mean, SEM*	88, 446	694, 27	6387, 289
range	46-3287	57-45	73-6827

*SEM, standard error of mean; Day PD, day of disease progression.
Keywords: Adenocarcinoma, erlotinib, mitochondrial DNA

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P2.113 ALK GENE COPY NUMBER GAIN AND AMPLIFICATION IN NSCLC: ITS FREQUENCY AND HISTOLOGIC FEATURES

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Background: In non-small-cell lung carcinoma (NSCLC), ALK gene copy number gain and amplification have not been extensively investigated.
Methods: A total of 452 NSCLC samples were analyzed by fluorescence in situ hybridization (FISH) and chromogenic in situ hybridization (CISH) for ALK and EGFR gene status. ALK gene copy number gain/amplification and EGFR gene polysomy/amplification were evaluated. EGFR mutation was examined by direct sequencing method in the available cases.
Results: Ninety-six cases (21.2%) showed ALK gene copy number gain and 16 (3.5%) amplification. The cases with ALK gene copy number gain consisted of 47 adenocarcinomas (ADCs) (49.0%), 41 squamous cell carcinomas (SCCs) (42.7%), 5 adenosquamous carcinomas (5.2%), and 3 the others (3.0%). The ALK gene amplification showed 7 ADCs (43.7%), and 9 SCCs (56.3%). There was an association between ALK gene copy number gain and EGFR polysomy in ADC (p= 0.026) compared to SCC (p= 0.064). There was no association between ALK gene copy number gain/amplification and EGFR gene amplification/mutation in NSCLC.
Conclusion: ALK gene copy number gain was not infrequently found in NSCLCs and the incidence was similar between ADC and SCC. In addition, ALK gene copy number gain was associated with EGFR polysomy in ADC.
Keyword: Non-small-cell lung cancer, ALK, EGFR, gene copy number, amplification, polysomy

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P2.114 NHERF1 AS A POTENTIAL NEW MARKER FOR LUNG CANCER

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Background: Lung cancer is the principal cause of cancer-related mortality in industrialized countries, with over 250.000 new cases each year in Italy. NSCLC which includes adenocarcinoma (ADC), squamous cell carcinoma (SCC), large cell carcinoma (LCC), and bronchioloalveolar carcinoma, accounts for nearly 85% of all cases. In the last years, there has been a remarkable increase in the understanding of the biological mechanisms that underlie lung cancer development, which has led to the identification of novel markers and therapeutic targets. A major focus of research has been the development of molecularly targeted agents and the identification of biomarkers for patient selection. The Na+/H+ exchanger regulatory factor 1 (NHERF1) is an adaptor molecule that leads several cellular receptors and other proteins to the plasma membrane of different types of cells. Our previous studies showed that NHERF1 alterations correlate with the progression and invasiveness of primary breast (Mangia, Histopathology 2009) and metastatic colorectal cancers. Aim of this study was to evaluate the role of NHERF1 in primary and metastatic lung nodules as a potential new marker of tumor progression.
Methods: Differences of NHERF1 expression in the membrane, cytoplasmic and nuclear compartment were studied by immunohistochemistry. We evaluated 38 paraffin-embedded cell block FNA of lung nodules from 23 primary NSCLC (8 SCCs, 4 LCCs and 11 ADCs), and 15 lung metastases from different sites (3 breast, 5 colorectal, 2 kidney, 2 uterus, 1 prostate, 1uretelial,1 hypopharynx).
Results: In the 38 cell blocks we observed a different NHERF1 expression comparing membrane, cytoplasmic and nuclear compartments. The nuclear NHERF1 staining was increased compared to cytoplasmic and membrane expression; the difference was statistically significant (P=0.001) when nuclear versus membrane staining was considered. When we examined only the 23 primary NSCLC, there was no significant difference of NHERF1 expression in the three cell compartments. Moreover, in the 15 metastatic lung nodules, NHERF1 expression showed a trend similar to total lung nodules, and nuclear NHERF1 level expression

was higher than membrane expression (P =0.028).
Conclusion: Our findings demonstrated that paraffin-embedded cell block FNA of lung nodules provide useful material to detect NHERF1 status. Expression levels of NHERF1 in different cellular compartments suggest a dynamic role of this marker in lung cancer. The high nuclear NHERF1 expression appears to contribute to the malignant metastatic process, as previously demonstrated in metastatic colorectal cancer. Further studies focusing this approach are ongoing in our institution.
Keywords: Lung cancer, Nherf1, cell block FNA

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P2.115 PKM2 AS A BIOMARKER FOR CHEMOSENSITIVITY TO CISPLATIN-BASED CHEMOTHERAPY IN METASTATIC/ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Tumour cells have been shown to express exclusively the embryonic M2 isoform of pyruvate kinase (PKM2), which is a key enzyme that regulates aerobic glycolysis in tumor cells. Use of RNA interfering (RNAi) targeting PKM2 significantly inhibits tumor growth when combined with cisplatin in xenograft models. We evaluated the predictive significance of PKM2 in patients with stage IIIB (with pleural effusion) or IV NSCLC treated with cisplatin-based chemotherapy in the 1st line setting.
Methods: PKM2 mRNA expression was analysed by RT-qPCR in FFPE primary tumors from 148 NSCLC patients after microdissection for the selection of cancer cells. The analysis was performed with a set of primers and probes which amplify only the M2 isoform.
Results: The patients' characteristics were all typical for advanced/metastatic NSCLC (median age 60 years, 82% males, 58% adenocarcinomas and 30% squamous cell carcinomas, ECOG Performance status 0-1: 86%). PKM2 was successfully amplified in all specimens. Time to tumor progression (TTP) was significantly lower in patients with overexpression of PKM2 (4.9 vs. 6.4 months for high and low expression, respectively, p=0.028). Similarly, median overall survival (mOS) was significantly decreased in patients with upregulation of PKM2 (10.1 vs. 17.0 months for high and low expression, respectively, p=0.01). Multivariate analysis revealed that PKM2 high mRNA expression (HR: 1.6, p=0.02), stage IV disease (HR: 4.2, p=0.03) and ECOG PS 2 (HR: 5.9, p=0.022) as independent prognostic factors for decreased TTP. Similarly, PKM2 high mRNA expression (HR: 1.9, p=0.02), stage IV disease (HR: 4.5, p=0.03) and ECOG PS 2 (HR: 6.1, p=0.002) were revealed as independent prognostic factors for decreased mOS.
Conclusion: These results provide evidence that the PKM2 mRNA expression could be used as a predictive factor for sensitivity to cisplatin-based chemotherapy. The results should be validated prospectively in an independent patient cohort.
Keywords: chemosensitivity, PKM2, NSCLC, Cisplatin

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P2.116 ADVANCED NSCLC: PROGNOSTIC ROLE OF THE EXPRESSION OF MYELOID-DERIVED SUPPRESSOR CELLS RELATED MARKERS IN PERIPHERAL BLOOD SAMPLES.

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Background: Myeloid-derived suppressor cells (MDSC) are found in most patients with advanced cancers, and are potent inhibitors of innate and

adaptive immunity. Marker genes associated with the presence of MDSC are CD11b, CD18, CD115, GR1, IL-4Rα and IL-13. The aim of this study was to determine the expression level of these genes by qRT-PCR in patients with advanced non-small cell lung cancer (NSCLC) and to correlate them with clinico-pathological and prognostic variables.
Methods: RNA was isolated from peripheral blood collected from NSCLC patients (n=50) and controls (n=54). qRT-PCR was performed to analyze the expression of CD11b, CD18, CD115, GR1, IL-4Rα and IL-13. Relative expression was normalized by endogenous genes (GAPDH and β-actin) using the Pfaffl formulae. Statistical analyses were considered significant at $p<0.05$.
Results:
We found significant differences in the expression levels of 3 analyzed genes (CD115, GR1 and IL4a) and in other two differences were borderline (CD11b, p=0.061; and IL13, p=0.068) between patients and controls. Pair-matched samples comparing pre and post-treatment expression levels of CD18, GR1 and IL4Ra showed that they were significantly reduced after chemotherapy. Lower levels of expression of CD11b were related with progressive disease (p=0.005). The prognostic impact of the studied variables was assessed by Cox univariate analysis (see Table) and Kaplan-Meier plots. We found that those patients with baseline CD11b expression below the median had significant worse progression-free (p= 0.005) and overall survival (p=0.013). Table: Univariate Cox analysis for CD11b

Univariate Cox analysis

Variable	HR	95% CI		p
		TTP		
CD11b (≤med/ >med)	2,35	1,27	4,35	0.006
		OS		
CD11b (≤med/ >med)	2,15	1,16	3,99	0.015

Conclusion: This study shows that it is possible to detect and quantified MDSC-related markers in peripheral blood samples of advanced NSCLC patients. The expression of the analyzed genes, especially CD11b, could have prognostic value in advanced NSCLC. (This work was supported in part, by a grant [RD06/0020/1024] from Red Temática de Investigación Cooperativa en Cáncer, RTICC, Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Science and Innovation & European Regional Development Fund (ERDF) "Una manera de hacer Europa")
Keywords: Advanced NSCLC, prognostic, Myeloid-derived suppressor cells

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P2.117 EVALUATION OF HIGHLY SENSITIVE PNA-LNA PCR CLAMP METHOD FOR EGFR L858R MUTATION DETECTION IN LUNG ADENOCARCINOMA PATIENTS.

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Background: Direct sequencing is widely accepted method for EGFR mutation identification, but has limited sensitivity. It often requires additional procedures, like microdissection, to enrich the sample in cancer cells, when their content in tissue specimen is less than 50%. PNA-LNA PCR clamping represents allele-specific approach to gene analysis and demonstrates potent accuracy and ability to detect mutant alleles even if present in low fraction of cells.
Methods: 79 DNA samples isolated from fresh-frozen and FFPE tissues, which mutation status was formerly confirmed by sequencing, were analyzed by PNA-LNA PCR clamping for EGFR point mutation L858R in exon 21.
Results: L858R mutation was detected in 8/79 (10%) samples by direct sequencing, whereas in 12/79 (15%) samples by PNA-LNA PCR clamping. All mutant-positive samples by sequencing were correctly determined by PNA-LNA PCR clamp. The remaining 4 L858R mutant-positive samples were recognized as wild type by sequencing. Two of them contained only 5% and 20% of cancer cells, respectively. Surprisingly, in the other two samples PNA-LNA PCR clamping method detected only low levels of EGFR mutant allele, despite the cancer cell contents were high (100% and 80%).
Conclusion: PNA-LNA PCR clamp technique enables sensitive and reliable detection of EGFR mutant allele in specimens with cancer cell content insufficient for direct sequencing or genetically heterogenous. Regarding its extremely high

sensitivity, PNA-LNA PCR clamping should be validated thoroughly prior implementation into EGFR diagnostic routine to prevent overdiagnosis.
Keywords: EGFR, FFPE tissue, L858R mutation, PNA-LNA PCR clamp

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.118 ASSESSMENT OF THYMIDYLATE SYNTHASE (TS) MRNA AND PROTEIN EXPRESSION IN NON SMALL CELL LUNG CANCER PATIENTS TREATED WITH PEMETREXED-BASED THERAPIES.

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Background: In non-small cell lung cancer (NSCLC), higher TS levels have been reported in both squamous cell (SCC) and large cell carcinoma (LCC) compared to adenocarcinoma (ADC). Antifolates are part of the therapeutic armamentarium for NSCLC and pemetrexed has consistently showed a selective benefit in patients with non-squamous NSCLC. Aim of this study was to retrospectively assess TS expression, at both mRNA and protein levels, in a series of pemetrexed-treated patients, as a potential predictive factor of efficacy.
Methods: TS expression levels were analysed in two series of both histological and cytological formalin-fixed and paraffin embedded specimens (FFPE) from patients treated with pemetrexed-based regimens: the first series was collected at San Luigi Hospital (n=52) including 42 ADC, 6 SCC, 4 NSCLC-not otherwise specified, the second series was collected at Regina Elena National Cancer Institute (n=34) including 16 ADC, 8 SCC, 3 NSCLC-not otherwise specified, 5 LCC and 2 adenosquamous carcinoma. Due to the limited amounts of tissue (especially cytologic) specimens available, total RNA extraction was possible in 64 out of 87 cases and TS gene expression was assessed using RealTime PCR. TS protein expression was performed using immunohistochemistry in all cases and scored with 2 **Methods:** the first considering only the percentage of TS positive tumor cells in the tissue (TS%) and the second (TS H-SCORE), obtained multiplying the percentage of TS positive tumor cells and the staining intensity. Staining intensity was classified as 0 (no staining), +1 (weak), +2 (moderate), or +3 (strong). Statistical analyses were performed using the STATISTICA7.0 software.
Results: TS mRNA expression was assessed using the $2^{-\Delta\Delta Ct}$ method, using β-Actin to normalize data and a total RNA (Stratagene) as calibrator. Gene expression analysis (median 8.08) showed significantly higher TS mRNA levels in non-ADC compared to ADC (p=0.02), while no other correlation with clinico-pathological data (age, gender, stage) or with TS protein expression (TS H-SCORE and TS%) were found. Statistical analyses for TS protein expression were separately performed using TS% (median 30%) and TS H-SCORE (median 55) data, respectively. In both these two groups, no correlation between protein expression and both gender and age, respectively, was found. A statistically significant superior TS protein expression in non-ADC compared to ADC specimens was found only for TS H-SCORE (p=0.012), without any statistical significance with TS% (p=0.146). Similar results were observed when TS protein expression was correlated with disease extent: TS H-SCORE (p=0.028) but not TS% (p=0.186) was significantly higher in stage IIIB compared to stage IV patients. As expected response to therapy was associated with a better survival (log rank test P=0.00039). Overall survival analyses are ongoing.
Conclusion: This retrospectively study consistently confirmed the differential expression of TS among the different histotypes of NSCLC. Standardization of TS assessment techniques, at the mRNA or protein level, may help clinicians to select the most appropriate group of patients to be be trreated with pemetrexed-based therapies.
Keywords: immunohistochemistry, Thymidylate synthase, Pemetrexed, real-time PCR

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.119 THE PROTEOMIC CLASSIFIER VERISTRAT® IDENTIFIES ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS GAINING CLINICAL BENEFIT FROM TREATMENT WITH FIRST LINE SORAFENIB AND ERLOTINIB.

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Background: We recently reported the result of a phase II study of first line erlotinib and sorafenib in unselected patients with advanced NSCLC (Lind et al Clin. Cancer Res 16,3078,2010). In an attempt to find biomarkers predictive for overall survival we analyzed pretreatment derived serum samples for proteomic signatures in the previously described serum matrix-assisted laser desorption ionization proteomic classifier (VeriStrat). 50 patients were enrolled in the phase II study of which 49 pretreatment serum samples could be analyzed.
Methods: Overall survival (OS) data was analyzed using conventional survival analysis methods. Univariate analysis was performed using the Mantel-Haenszel method and log-rank p values (with PRISM) and the Cox proportional hazards method, with associated p values (SAS). Confidence intervals for median survival estimates were calculated using SAS.
Results: VeriStrat classification identified 33 (67%) as predicted to have "good" and 15 (31%) predicted to have "poor" outcomes; 1 sample was of indeterminate classification VeriStrat classification was not predictive of disease control rate nor of EGFR mutation (n=7) status in this cohort. VeriStrat good patients had statistically significantly improved OS compared with VeriStrat poor patients. The hazard ratio (HR) between groups was 0.30 (95% CI: 0.12-0.74), log-rank p = 0.009. The median OS was 13.7 months (95% CI: 12.0 months-undefined) for VeriStrat good patients and 5.6 months (95% CI: 1.6-7.6 months) for VeriStrat poor patients. In addition, center and histology (adenocarcinoma vs squamous and large cell carcinoma) were statistically significant in univariate analysis. For analysis by histology, the HR was 2.81 (95% CI: 1.05-7.51), with median OS of 12.4 months (95% CI: 6.3 months - undefined) for adenocarcinoma patients and 4.7 months (95% CI: 1.6-10.9 months) for squamous and large cell carcinoma patients. Stratifying by histology, only adenocarcinoma patients have sufficient numbers to attempt further analysis. For VeriStrat good vs poor the HR is 0.45 and log-rank p value = 0.21; however this result has limited value due to only 7 of the 34 adenocarcinoma patients being classified as VeriStrat poor
Conclusion: The proteomic classifier VeriStrat may identify a subset of patients that derives significant clinical benefit from upfront treatment of advanced NSCLC patients with EGFR/VEGF inhibitors. These findings should be confirmed in prospective studies.
Keywords: proteomics, VEGF EGFR inhibition

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P2.120 ESTROGEN UP-REGULATES OSTEOPONTIN EXPRESSION AND SYNERGY WITH EPIDERMAL GROWTH FACTOR PROMOTE LUNG CANCER CELL MIGRATION

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Background: Estrogen has been postulated to contribute to the development and progression of non-small cell lung cancer. It's also recognized that osteopontin (OPN) plays an important role in tumor progression and metastasis. We explored the characteristics of estrogen, and investigated the connections between estrogen and OPN in lung cancer cells migration, including the signaling pathway involved. The separate and combined effect of Tamoxifen - an estrogen receptor (ER) antagonist, and Gefitinib - an epidermal growth factor receptor (EGFR) antagonist, on the cancer cell migration

were also studied.
Methods: A549 and PE089 lung cancer cell lines were used for in vitro studies. Pleural effusions from patients with lung adenocarcinoma were collected for the measuring of the estrogen and OPN concentrations as well as their impact on lung cancer cell lines.
Results: ER- β is the predominant receptor type in lung cancer cell lines. Estrogen promoted cancer cell proliferation, migration, and matrix metalloproteinase 2 activity. Confocal microscopy and Western blotting revealed ER-β translocation out of mitochondria and mitochondrial swelling on the stimulation of estrogen. The mitochondrial respiratory complexes were attenuated. Estrogen induced OPN expression. Osteopontin promoted cancer cell migration through αvβ3 integrin binding. Estrogen and OPN concentrations were both elevated and positively correlated in the malignant pleural effusion from patients with lung adenocarcinoma. Estrogen and OPN affected cell migration through activation of MEK-ERK pathway, which is a common downstream pathway of EGFR activation. Synergistic effect of ER antagonist and EGFR antagonist on the inhibition of lung cancer cells migration was noted.
Conclusion: Estrogen up-regulates OPN expression and synergy with epidermal growth factor which promote lung cancer cell migration. Estrogen, with its receptor and OPN, has the potential to be a prognosticator and a new therapeutic target in lung cancer. Understanding the receptors status of patients and tumor characteristics could help better direct the selection of targeted treatment.
Keywords: Epidermal growth factor receptor (EGFR), Estrogen, Lung cancer, osteopontin

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.121 VALUE OF CEA, NSE, CA211, SCC AND CYFRA21-1 IN THE DIAGNOSIS OF LUNG CANCER

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Background: To investigate the clinical value of combined detection of the tumor makers carcinoembryonic antigen (CEA), neuro-specific enolase (NSE), carbohydrate antigen 211 (CA211) squamous cell carcinoma associated antigen (SCC) and cytokeratin fragment 19(CYFRA21-1) of the serum and the pleural effusion in patients with lung cancer,and to find some clues in the diagnosis of lung cancer.
Methods: Using electrochemiluminescence immunoassay and immunoradiometric assay, the five tumor makers in the serum and the pleural effusion were measured in 65 lung cancer patients, 52 benign pulmonary diseases patients and 50 normal controls.
Results: In lung cancer group ,the levels of five tumor makers in the serum and the pleural effusion were significantly higher than those in benign pulmonary diseases group and normal control group (P<0. 05), but there was no significant difference in benign pulmonary diseases group and normal control group (P>0. 05). For different pathology of lung cancer, there was significant difference in five tumor makers in the serum and the pleural effusion(P<0. 05), the level of CEA was significantly higher in adenocarcinoma (P<0. 05) and SCC in lung squamous cell carcinoma(P<0. 05), while NSE in the small cell lung cancer(P<0. 05). Combined detection of these tumor markers has more sensitivity than single detection. In the pleural effusion, sensitivity, specificity and positive predictive value of five tumor markers in lung cancer group were 99.28%, 91.17% and 98·23% and were 92.71%, 62.52% and 88.20% in the serum.
Conclusion: Combined detection of five tumor makers in the serum and the pleural effusion has a high sensitivity and positive predictive value for the diagnosis of lung cancer, and different tumor maker will provide a scientific and reliable evidence for differentiation the pathology of lung cancer.
Keyword: Lung cancer; Tumor marker; CEA; NSE; SCC; CYFRA 21- 1; CA211;Combined detection.

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P2.122 ARRAY CGH ANALYSIS OF SMALL-SIZED ADENOCARCINOMA OF THE LUNG

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Background: It is well known that lung cancer is closely associated with gene abnormality. Recently, comprehensive studies of advanced lung carcinoma have demonstrated that many oncogenes have an impact on its prognosis. However, there have been no detailed studies of genetic abnormalities in early small-sized adenocarcinoma of the lung. In order to clarify the early genetic abnormalities present in this type of cancer, we examined the whole genome of surgically resected lung cancer specimens using array-based comparative genomic hybridization (array-CGH), and found a region in early but advanced adenocarcinoma that was significantly amplified in comparison with in situ adenocarcinoma.
Methods: Six in situ adenocarcinomas (types A and B, Noguchi classification: Noguchi M. et al., Cancer 1995), and 9 small but advanced adenocarcinomas (types D and E, Noguchi classification) were evaluated using array-CGH (CancerArray-800: Inazawa J. et al. Cancer Science 2004). The tumors were methanol-fixed and paraffin-embedded, and the tumor cells were selected by laser-capture microdissection (LM200, Olympus). The genomic DNA of the tumor cells and corresponding normal cells was then extracted and evaluated by array-CGH. The results were compared with the outcomes of individual cases, and the significance of any correlations was analyzed by t test and C-clustering.
Results: Array-CGH analysis revealed that types A and B in situ adenocarcinoma and types D and E adenocarcinoma exhibited a novel type of copy number profile, with significant differences in the copy number of 33 genes on various chromosomes. These abnormalities were observed at 1q.32.1, 3q, 4q.35.2, 5q, 8p11.21, 11p15.5, and 15q21.1. In particular, types D and E adenocarcinoma showed significantly higher copy numbers at 3q21-tel than types A and B adenocarcinoma.
Conclusion: Previous reports have indicated that chromosome 3 is frequently rearranged in various carcinomas, and that this region is likely involved in the tumorigenesis of lung adenocarcinoma. Our results also demonstrated DNA gains on the long arm of chromosome 3 more frequently in types D and E adenocarcinoma than in types A and B in situ adenocarcinoma. Types D and E adenocarcinoma were small but advanced, and showed a less favorable outcome than types A and B in situ adenocarcinoma. These results indicate that amplification of 3q21-tel might be related to malignant transformation of lung adenocarcinoma. Further studies will be required to elucidate the target oncogenes involved in the transformation of in situ adenocarcinoma to invasive adenocarcinoma.
Keywords: small-sized adenocarcinoma, Array CGH

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P2.123 NON-SMALL CELL LUNG CANCER (NSCLC) GENOTYPING IN A BRAZILIAN COHORT

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide and NSCLC represents 85% of lung tumors. The major recurrent molecular alterations found among NSCLC tumor samples are either mutation, amplification or inversion/fusion detected in genes such as EGFR, KRAS, BRAF, MET and ALK. Cell signaling elicited by these altered pathways interferes with normal cell function and is thought to play a fundamental role in the carcinogenesis and progression of lung cancer. As molecular diagnosis will determine the therapy of choice and might differ utterly in each case, detection of such alterations is crucial for proper NSCLC management. Differences in the frequency of those targets have been observed among different populations, particularly EGFR mutation between Asian and Caucasian. Brazilian population is genetically heterogeneous and highly mixed, and a report of NSCLC genotyping in such population is missing.
Methods: 162 paraffin-embedded cases of NSCLC radically resected from 2003 to 2007 were retrospectively collected at two different cancer centers in Brazil and were analyzed for EGFR (exons 18 to 21), KRAS (exon 2) and BRAF (exons 11 and 15) mutational status by direct bidirectional gene sequencing and for MET amplification and

ALK rearrangement status by FISH in tissue microarray sections.
Results: Evaluation of valid information has shown that median patient age was 62.8 years; 52.9% were male. At diagnosis, 13.8% were never smokers, 46.9% current and 39.3% former smokers. Histology analysis has shown that 55.6% of tumors were adenocarcinoma, 7.2% bronchioloalveolar and 32.7% squamous cell carcinoma. EGFR analysis was successful in 150 cases and mutations were identified in 25.3% (n=38) of the patients (6, 19, 13 and 5 mutations in exons 18, 19, 20 and 21 respectively; 5 cases encompassing mutations in 2 different exons); 52.8% of mutated cases for EGFR were adenocarcinoma, 8.3% bronchioloalveolar and 36.1% squamous cell carcinoma. Remarkably, the percentage of mutation detected in exon 21 was lower than that described on literature, contrasting with the higher incidence of exon 18 and 20 mutations. KRAS mutations were observed in 30 out of 148 analyzed cases (20.3%), in which 76.7% were adenocarcinomas. 13 out of 145 patients harbored BRAF mutations (9.0%), predominantly in squamous histology (61.5%), 8 were found in exon 11, 5 in exon 15. Finally, MET gene increased copy number (mean ≥5 copies/cell) was observed in 21 out of 152 evaluated cases (13.8%), where 73.7% represented adenocarcinomas. ALK rearrangement was present in 4 out of 161 cases (2.5%), 3 of them exhibiting adenocarcinoma and 1 bronchioloalveolar histology.
Conclusion: The prevalence of molecular defined patient subsets in our cohort was only slightly different to American, European and Asiatic published series. The histological subdivision of NSCLC into distinct molecular groups based on specific mutations or gene amplification/ abnormal fusion is a promising strategy for patient stratification, leading to potentially sensitive patient selection and informed drug choice. To our knowledge, this study represents the first comprehensive analysis known NSCLC genotyping in a large cohort of Brazilian patients.
Keywords: Non-small cell lung cancer, genotyping

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P2.124 EFFECTS OF CHEMO-IMMUNOTHERAPY ON CD4+CD25+ REGULATORY T CELLS IN NON SMALL CELL LUNG CANCER (NSCLC).

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Background: The combination of chemotherapy and anti-EGFR monoclonal antibodies has proven clinical efficacy in non small cell lung cancer (NSCLC). However, the mechanism of its clinical activity remains elusive so far. Direct effects on the tumor cells as well as immuno-mediated effects might both be involved. $CD4^{+}CD25^{high}FoxP3^{+}$ regulatory T cells (Treg) play a key role for maintenance of tolerance in rodents and men. Recent reports emphasized the important role of increased Treg levels in patients with epithelial malignancies for tumor immune escape. The aim of the current study is to determine i) the role of Treg levels on therapeutic response and ii) the impact of the neoadjuvant chemo-immunotherapy on the Treg compartment.
Methods: 30 patients suffering from NSCLC (stage IB – IIIA) were included in a neoadjuvant clinical study protocol (INN06 study) and received up to two cycles of chemo-immunotherapy (Cetuximab + Docetaxel + Cisplatin) prior to surgery. Treg were measured in peripheral blood (PB) in a fixed schedule which included quantitative and functional assessment prior to initiation of therapy and prior to every cycle thereafter as well as at the end of neoadjuvant therapy. Relative and absolute quantification using TruCount beads of Treg was assessed by flow cytometry. In parallel, the proliferative capacity of Treg was measured by EZ4U assay of magnetically isolated $CD4^{+}CD25^{+}$ and the respective control $CD4^{+}CD25^{-}$ T cell populations.
Results: In comparison to baseline, Treg levels significantly decreased during chemo-immunotherapy (227/μl prior to treatment initiation and 120/μl at the end of neoadjuvant treatment), whereas the total $CD4^{+}$ T cell compartment remained constant (1238/μl and 1398/μl, respectively). Of

note, FoxP3 expression was unaffected in the $CD4^+CD25^{high}$ Treg compartment. Ex vivo cultures of purified Treg from PB confirmed the anergy phenotype of the $CD4^+CD25^+$ population, thus excluding that these cells are activated T cells. Correlative data with clinical endpoints are currently under investigation and will be presented at the meeting.

Conclusion: The observed decrease of Treg but not of total $CD4^+$ T cells throughout chemo-immunotherapy suggests that Treg are predominantly affected by the neoadjuvant treatment. As an alternative, reduction of the tumor load might also contribute to reduced Treg burden. Future studies will clarify whether the observed Treg frequencies prior to and during chemo-immunotherapy are correlated with clinical response to therapy via modulation of mAb-induced anti-cancer effects (e.g. antibody dependent cell-mediated cytotoxicity ADCC).

Keywords: Regulatory T Cells (Treg), Chemo-immunotherapy, Neoadjuvant Therapy

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.125 PROGNOSTIC SIGNIFICANCE OF EGFR GENE COPY NUMBER GAIN IN NSCLC: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have become an established treatment modality for advanced non-small-cell lung cancer (NSCLC). Although benefits with TKIs appear most prominent in patients with somatic EGFR mutations, EGFR gene gain has also regarded as a predictive marker. In order to understand the predictive nature of any biomarker an understanding of the prognostic significance is also necessary

Methods: We performed a systematic computerized search of MEDLINE (PubMed; from inception to 16th January, 2011) to identify all published articles reporting on EGFR gene copy number analysis in NSCLC. Outcomes included overall survival (OS), progression-free survival (PFS), and time-to-progression (TPP) in untreated populations. Summary hazard ratios (HR) for time-to-event outcomes and corresponding confidence intervals were estimated using fixed and random effects meta-analysis.

Results: From 68 potential articles, 12 eligible studies comprising 540/1245 (43.4%) total patients with EGFR gene gain provided data on OS. By random effects, the summary HR for OS was 1.14 (0.94-1.38) for patients with EGFR gene gain versus wild-type patients. There was no sign of study heterogeneity, and no differences between random and fixed effects modeling. Effects were consistent between subgroups based on ethnicity (HR=1.01 [0.79-1.30] versus 1.36 [0.96-1.92], Whites versus Asians) method of gene gain analysis (HR=1.08 [0.87-1.34] versus 1.5 [0.83-2.7] CCS versus other) and stage (HR=1.15 [0.91-1.46] to 1.09 [0.71-1.67] stages I-III versus I-IV).

Conclusion: It does not appear that EGFR copy number gain in NSCLC is associated with survival. The histological and molecular complexity of NSCLC does however introduce some limitations into the analysis of gene gain. Prospective studies that allow for interaction to be determined according to specific biomarkers will provide additional real-time data regarding the prognostic significance of EGFR gene gain and its implications in personalized medicine.

Keywords: Gene Gain, Epidermal growth factor receptor, Prognosis

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P2.126 ROLE OF HORMONE RECEPTOR EXPRESSION IN PATIENTS WITH ADVANCED STAGE LUNG CANCER TREATED WITH CHEMOTHERAPY.

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Background: In lung cancer epidemiologic evidence supporting a role for hormonal status has been inconsistently reported and the mechanism modulating the expression and function of hormonal receptors in this disease remains still unclear. We aimed to retrospectively assess potential correlations between sex-linked hormone receptor expression and the clinical outcome of patients with advanced stage lung cancer treated with chemotherapy and sufficient amounts of tumour tissue available for immunohistochemical analyses, in a single institution.
Methods: One hundered and thirty consecutive cases (100 men) diagnosed at San Luigi Hospital in the period of time from January, including 2008 to June 2010 were considered including 57 adenocarcinomas (AC), 34 squamous cell carcinomas (SCC), 5 large cell carcinomas (LCC) and 24 small cell lung cancer (SCLC); the remaining ten cases were "NSCLC-NOS" (non small cell lung cancer-not otherwise specified). The immunodetection of estrogen receptors (ERa and ERβ), progesterone receptor (PR), EGFR and ERCC1 was scored assessing both staining intensity and extension; aromatase reactivity (AR) was scored as 0 (totally negative) or 1 (presence of cytoplasmic staining).
Results: ERβ nuclear expression was higher than ERa and PR, which had a weak or null expression, mainly in women. According to median expression levels, no significant correlation was found between ERβ and AR with age, sex, stage of disease, response to chemotherapy and histology. EGFR expression was significantly higher in SCC (p=0.002) as well as ERCC1 (p=0.01). In males AR positive tumours (23%) had a worse outcome (p=0.03) as well as those NSCLC with high ERb expression. In NSCLC group, males with tumours AR negative and low ERCC1 expression had a better outcome than those patients with high levels of both proteins (p=0.026). Furthermore, the association of low levels of both ERCC1 and ERb in NSCLC patients resulted in better outcome compared to those NSCLC expressing at least high levels of either ERCC1 or ERb (p=0.02).
Conclusion: Contradictive data are reported about the role of hormonal status in lung cancer. In this retrospective study we detected a mild association between hormonal receptor status and prognosis in males more than in females, that should be validated in prospective trials. Preclinical data indicate the efficacy of aromatase inhibitors in lung cancer and this study confirmed a potential role of aromatase in lung cancer patients.
Keywords: hormonal status, immunohistochemistry, Lung cancer, advanced stage

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P2.127 MITOCHONDRIAL VDAC2 IS TRANSCRIPTIONALLY REGULATED BY P63 AND CONFERS SHORTER SURVIVAL IN NON-SMALL CELL LUNG CANCER

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Background: Resistance to apoptosis is a hallmark of cancer and a major problem limiting the effectiveness of treatment in non-small cell lung cancer (NSCLC). The mitochondrial dependant anion channel isoform 2 (VDAC2) gene is amplified in cancers, and inhibits apoptosis by binding to, and preventing activation of BAK(1). VDAC2 is required for cancer cell cytotoxicity of a new class of drugs called erastin(2) however the variability of VDAC2 expression in NSCLC is unknown. Here we show that VDAC2 is prognostic in NSCLC, and using gene expression meta-analysis, identify p63 as a critical transcriptional regulator and potential biomarker for classifying erastin sensitive NSCLC.
Methods: Using gene expression meta-analysis of 601 tumours from 7 public gene expression datasets in NCBI GEO a meta-signature was generated, corresponding VDAC2 overexpression in NSCLC. The transcription factor, p63 was included in the meta-signature and so we set to investigate any link further. P63 is an already established biomarker in squamous lung tumours and so VDAC2 expression was determined using regression analysis to establish any correlation between the two. We identified a potential p63 binding site in VDAC2 implicating potential transcriptional regulation. This was verified by chromatin immunoprecipitation sequencing (ChIPseq).
Results: We identified VDAC2 as an independent prognostic factor in both univariate and multivariate

analyses (versus histology, gender, age, and stage). A conserved 6 gene-metasignature was identified comprising ANKRD27, BICD2, IL6ST, MEF2C, PCYT1A, and p63. Most of these genes were shown by promoter sequence interrogation, ChIPseq, and qPCR validation to be p63 targets. Silencing p63 by siRNA in squamous NSCLC cells led to VDAC2 down-regulation. Silencing either VDAC2 or p63 caused resistance to erastin, a potent inducer of cell death. We then validated the correlation between VDAC2 and p63 expression in vivo. Using qRTPCR in 20 tumour samples, 10 squamous and 10 non-squamous it was found that VDAC2 was elevated significantly in the high p63 expressing squamous subset only.
Conclusion: In summary, using meta-signature analysis of large scale gene expression data, we have discovered a therapeutically relevant biological connection between p63 and VDAC2. Since p63 expression is found selectively in the squamous tumours, we propose that this group of cancers might be selectively targeted by erastins, facilitating personalized therapy with this agent.
Keywords: VDAC2, p63

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P2.128 DEVELOPMENT OF A MULTIVARIATE MODEL USING FLUORESCENCE IN SITU HYBRIDIZATION AND CLINICAL FEATURES TO PREDICT THE LIKELIHOOD OF CARCINOMA IN PATIENTS WITH INDETERMINATE PERIPHERAL LUNG NODULES

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Background: Previous studies have demonstrated the utility of routine cytology with reflex fluorescence in situ hybridization (FISH) on bronchial brushing specimens of indeterminate peripheral lung nodules for the diagnosis of lung cancer. The goal of this study was to determine whether FISH abnormalities and other clinical features could predict likelihood of carcinoma in patients with indeterminate peripheral lung lesions after a negative initial bronchoscopic evaluation.
Methods: A retrospective review of medical records was performed to identify patients who had a negative bronchoscopic evaluation for an indeterminate peripheral nodule that included a bronchial brushing for routine cytology and FISH testing. Only patients with clinical follow-up after bronchoscopy were included in this study (N=149 specimens from 147 patients; median time to last follow-up=65 days). Reflex FISH testing using probes directed to 5p15, 7p12 (EGFR), 8q24 (MYC), and centromere 6 (Abbott Molecular Inc. Des Plaines, IL) was performed on residual cytology specimens diagnosed as negative (n=130), atypical (n=10) or suspicious (n=9). FISH testing results included negative (n=127) and polysomy (n=22). A polysomy result was rendered when a minimum of five cells were identified having three or more copies in at least two of the four loci evaluated by FISH, with at least one locus having five or more copies. The primary outcome was time to malignancy. Pathology confirmation and/or clinical indication of disease progression/metastasis during clinical follow-up were considered evidence of malignancy (50/147 patients, 34%). Hazard ratios (HR) for test results and clinical features were calculated using Cox proportional hazards regression model analyses using SAS version 9 (Cary, NC). The robust sandwich variance estimates were used to account for the two patients with an additional specimen. P values < 0.05 were considered statistically significant.
Results: The mean age of the 147 patients was 67.6 years (SD: 11.2, range 35-91) and 86 (59%) were males. Most patients (78%) had a smoking history having 33.9 mean pack years (SD: 35.0, range 0-200). Peripheral nodule CT measurements were available in 135/149 of nodules with a mean lesion size of 2.8 cm (SD: 1.6, range 0.5-10.5) and 33 (22%) nodules showed spiculation. On univariate analysis, a polysomy FISH result (HR=4.04, P<0.001), pack years (HR=1.01 per year, P<0.001), spiculation (HR=2.55, P=0.003), age (HR=1.03 per year, P=0.019) and a suspicious cytology result (HR=2.29, P=0.034) were significant predictors of malignancy over time. Polysomy FISH (HR=3.87, CI=2.03-7.40, P<0.001), pack years (per pack year up to 50: HR=1.03, CI=1.01-1.04, P<0.001), and spiculation (HR=2.11, CI=1.14-3.90, P=0.018) were

the most significant predictors of malignancy over time after multivariate analysis and were used to create a prediction model (c-statistic=0.78).
Conclusion: We developed a multivariate prediction model using FISH, nodule spiculation and smoking pack years which may stratify the risk of a patient having lung cancer subsequent to a negative bronchoscopic workup. This model may be especially useful in predicting a patient's risk of malignancy over time in certain situations when these variables are known. Further studies are needed to validate this prediction model.
Keywords: peripheral lung nodule, FISH, cytology, bronchial brushing

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P2.129 GENETIC VARIANTS ASSOCIATED WITH THE RISK OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: Published studies show that variations of genes participating in glutathione metabolism, DNA repair, and inflammatory response pathways may alter susceptibility to Chronic Obstructive Pulmonary Disease (COPD), but results are controversial and inconclusive.
Methods: We evaluated 470 single nucleotide polymorphisms (SNPs) from 56 genes in the 3 above pathways in 620 cases and 893 controls to identify susceptibility markers for COPD risk. Logistic regression models were used to assess SNP effects on COPD risk adjusting for sex, age, and smoking status. Stratified analyses assessed differential genetic effects on COPD risk with and without lung cancer. Fisher's combination test assessed the gene-based effects. COPD cumulative risk model was calculated using the most significant SNPs.
Results: Twenty SNPs from 12 genes were found to be significantly associated with COPD risk (P<0.01); gene-based analyses confirmed 2 genes (GCLC and GSS) and identified additional 3 (GSTO2, ERCC1, and RRM1). Carrying 12 high-risk alleles may increase COPD risk by 2.7-fold; 8 SNPs altered the risk of COPD with lung cancer 3.1-fold, and 4 SNPs altered the risks of COPD without lung cancer 2.3-fold.
Conclusion: Our findings indicate that multiple genetic variations in 3 selected pathways contribute to COPD risk; GCLC, GSS, GSTO2, ERCC1, and RRM1 may be susceptibility genes to COPD. Functional studies are needed to elucidate the mechanisms of these genes in COPD development.
Keywords: inflammation response pathway, chronic obstructive pulmonary disease, glutathione metabolism pathway, DNA repair pathway

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P2.130 PEMETREXED EXHIBITS THE ANTI-METASTASIS ACTIVITY IN NON-SMALL CELL LUNG CANCERS

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Background: Pemetrexed has been approved for second and first-line treatment in non-small cell lung cancer (NSCLC) patients. Recently, there are some clinical biomarkers for predicting the therapeutic response. But, little report was discussed the inhibition of tumor cells metastasis by pemetrexed. The aim of this study is to establish the correlation between the changing of new biomarker levels and the anti-metastasis.
Methods: Human NSCLC cell lines, with variable expression of the known molecular determinants of pemetrexed sensitivity, were exposed to pemetrexed. Antitumor effect was measured by growth inhibition by MTT assay. Using Superarray cancer pathway

gene array, a total of 482 genes was screened in A549 cell after pemetrexed treatment. Migration and invasion ability were determined by Boyden chamber and wound healing. Gelatin zymography, RT-PCR and western blot were used to analysis nm23, lipocalin 2 and E-cadherin expression.
Results: A549 is sensitive to Pemetrexed, but H1355 is a resistant to Pemetrexed. Pemetrexed inhibited A549 migration and invasion ability, increased E-cadherin expression and decreased EMT (endothelial- mesenchymal transition) in A549. Pemetrexed decreased MMP-2 activity and increased TIMP-1 and TIMP-2 expression in A549. nm23-H1 and Lipocalin2 were up-regulated expression in following exposure to Pemetrexed in A549 cells. Further, RNA interference (RNAi)-targeted Lipocalin2 generated anti-metastasis to Pemetrexed in A549 cells. In contrast, inhibition of Nm23-H1 expression would induce the migration in A549.
Conclusion: From the results in this study, nm23-H1, and Lipocalin2 could play a role as genetic determinants of therapeutic response and inhibition of tumor cells metastasis of Pemetrexed in lung cancer.
Keywords: Lipocalin 2, nm23-H1, Pemetrexed, Lung cancer

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P2.131 JANUS-FACED FUNCTION OF β-CATENIN ON TUMOR METASTASIS IN NON-SMALL CELL LUNG CANCER

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Background: β-catenin plays a dual role in cells as a major structural component of cell-cell adherence junctions (EMT pathway) and as a pivotal signaling molecule in the Wnt pathway. However, few studies have analyzed the functions of β-catenin on tumor metastasis regarding Epithelial-Mesenchymal Transition (EMT) and Wnt pathways.
Methods: To address the dual role of β-catenin on tumor metastasis, we compared the expression of Wnt1, β-catenin and E-cadherin by immunohistochemistry in 35 primary tumors and the corresponding metastatic lesions.
Results: The alterations of β-catenin from primary to metastatic tumors appeared in 34.3% (12/35, 9 ADCs and 3 SCCs), and it was significantly correlated with poor overall survival ($p<0.05$). Among them, 66.7% (6/9) ADCs showed simultaneous loss of E-cadherin, while all of the SCCs accompanied Wnt1 overexpression. According to the expression pattern, the altered expressions of β-catenin were observed in 28.6% (4/14) from membranous type to decreased membranous expression and in 38.1% (8/21) from intact membranous to cytoplasmic or nuclear transitions. In decreased membranous type, 3 tumors were β-catenin+/E-cadherin loss/Wnt1- phenotype, and significantly correlated with loss of E-cadherin ($p<0.05$). In the cytoplasmic or nuclear transition type, there was significant association between β-catenin alteration and Wnt1 overexpression ($p<0.05$).
Conclusion: These findings show that β-catenin plays a crucial role on tumor metastasis and overall survival. In addition, the alteration of β-catenin might be regulated by EMT pathway (cadherin-catenin system) in ADCs with decreased membranous type, but mediated by Wnt pathway in SCCs with cytoplasmic or nuclear transition types.
Keywords: β-catenin, Wnt1, E-cadherin, Non-small cell lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.132 SEQUENCE COMPLEXITY OF EML4-ALK FUSION VARIANTS IDENTIFIED IN NON-SMALL CELL LUNG CANCER

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Background: EML4-ALK mutant lung cancer patients have been defined as a specific subgroup that may benefit greatly from ALK inhibitor. Yet the algorithm to screen patients with ALK fusion need to be optimized in clinic and the exact common variants of EML4-ALK fusion need further investigation.
Methods: Clinical samples were routinely tested for EML4-ALK fusion by both specific RT-PCR and RACE-PCR-Sequencing technologies. All electrophoresis bands of PCR products and sequencing chromatographs were manually analyzed.
Results: In a total of 313 cases of NSCLC, we detected 14 cases of EML4-ALK fusion variant 1 (V1), 7 cases of variant 3 (V3), 5 cases of EML4-ALK fusion 2, 2 cases of EML4-ALK variant 6 (V6), and 1 case of EML4-ALK variant 9 (V9). Overall EML4-ALK fusion rate is 9.27%, concordant to the data reported previously. Notably, in one case harboring V6, the genotypes of multiple sequencing showed actually a novel V6 of E13;ins90A20 (termed as V6b by our group) co-existing with one other novel variant of E17ins27;ins125A20, termed as V10 by us. In one other case harboring V3, the EML4-AK variant was actually a novel variant of E6ins36;del33A20, termed as V3c by us.
Conclusion: In routine clinical testing setting, novel EML-ALK fusion variants have been identified and the most common variant of EML4-ALK fusion is V1, suggesting the sequence complexity of ALK fusion with EML4 gene.
Keywords: EML4-ALK, gene fusion, Non-small cell lung cancer

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P2.133 GDP-MANNOSE-4,6-DEHYDRATASE (GMD) AND GDP-FUCOSE TRANSPORTER IN NON-SMALL CELL LUNG CANCERS (NSCLCS) : THEIR DECREASED EXPRESSION IN SQUAMOUS CELL CARCINOMAS BY IMMUNOHISTOCHEMISTRY

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Background: We have previously reported that low expression of α1,6-fucosyltransferase (FT) , an enzyme for the core fucosylation of N-glycans, is significantly more prevalent in squamous cell carcinomas compared with non-squamous cell carcinomas of the lung. GMD generates GDP-fucose from GDP-mannose, and is imperative for the synthesis of all fucosylated oligosaccharides. GDP-fucose is transported into the Golgi apparatus by GDP-fucose transporter to serve as a substrate of FTs.
Methods: In the present study, we examined expression of GMD and GDP-fucose transporter by immunohistochemistry in 156 surgically resected NSCLCs.
Results: High, moderate and low expression of GMD was found in 32 (20.5%), 32 (20.5%) and 92 (59.0%) NSCLCs, respectively. High/moderate, low and no expression of GDP-fucose transporter was found in 7 (4.5%), 23 (14.7%) and 126 (80.8%) NSCLCs, respectively. Low GMD expression was significantly more prevalent in tumors from men than in those from women ($p = 0.02$), in tumors from smorkers compared with nonsmokers ($p = 0.047$), and in squamous cell carcinomas compared with non-squamous cell carcinomas ($p = 0.0003$) by the χ^2 test. Multivariate logistic regression analysis for the correlation between GMD expression and various characteristics revealed a significant association between low GMD expression and squamous cell carcinomas, as compared with non-squamous cell carcinomas (low vs. moderate, $p = 0.005$; low vs. high, $p = 0.02$). Among biological characteristics of tumors studied previously in this cohort of NSCLCs, Ki-67 labeling index was significantly higher in tumors with low GMD expression than in those with high GMD expression (low vs. high, $p = 0.003$). Low expression of α1,6-FT was more prevalent in tumors with low GMD expression than in those with moderate or high GMD expression ($p = 0.002$). Low GDP-fucose transporter expression was significantly more prevalent in squamous cell carcinomas compared with non-squamous cell carcinomas ($p = 0.003$) by the χ^2 test. GMD and GDP-fucose

transporter expressions were not associated with survival.
Conclusion: These results indicate that GMD and GDP-fucose transporter may be new markers of NSCLCs with specificity for histology.
Keywords: GMD, GDP-fucose transporter

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P2.134 SECRETOME PROTEOMICS TO IDENTIFY INDICATORS FOR LUNG CANCER TREATMENT RESPONSE PREDICTION AND MONITORING

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Background: Lung cancer is currently the number one cause of cancer-related deaths worldwide. Five-year survival rates for both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are still less than twenty percent due to late stage of presentation, treatment failure and lack of biomarkers for personalized therapy. Aim of this study is to identify protein biomarkers that can be used for treatment response prediction and therapy monitoring.
Methods: Rather than following a broad strategy by analyzing the proteome of whole cell or tissue lysates, we chose to use a more specific approach based on the assumption that the best tumor markers are shed or secreted by the tumor and can be detected in blood. Secretome (i.e. all proteins shed from or secreted by a cell or tissue) proteomics[1] was performed on a set of tumors from conditional mouse models for SCLC and NSCLC[2,3], a set of human and mouse SCLC and NSCLC cell lines and a series of human NSCLC cell lines with a range of IC50-values for cisplatin (1.5 – 15 μM). Secretomes were obtained by collecting serum-free media from the cell lines or collecting PBS in which a tumor tissue piece had been incubated. [1] Workflow comparison for label-free, quantitative secretome proteomics for cancer biomarker discovery: method evaluation, differential analysis, and verification in serum. Piersma SR et al.. J Proteome Res. 2010 Apr 5;9(4):1913-22. [2] Mouse model for lung tumorigenesis through Cre/lox controlled sporadic activation of the K-Ras oncogene. Meuwissen R et al.. Oncogene. 2001 Oct 4;20(45):6551-8. [3] Induction of small cell lung cancer by somatic inactivation of both Trp53 and Rb1 in a conditional mouse model. Meuwissen R et al.. Cancer Cell. 2003 Sep;4(3):181-9.
Results: In the secretome samples, up to 2,000 proteins can be identified with 80% reproducibility by label-free, shotgun nanoLC tandem mass spectrometry and quantified by spectral counting. The beta-binomial test[4] is used to find significant differences in protein expression between the different secretomes and network analysis is performed to provide insight into the underlying cellular mechanisms. The secretomes from the mouse models are used to find proteins specifically secreted by either NSCLC or SCLC, while the comparison between the secretomes of the several human and mouse cell lines allows extrapolation of the results from the mouse models to the human situation. Furthermore, the analysis of the cell lines with various cisplatin IC50-values permits selection of the protein markers that are indicative of sensitivity or resistance. The results of the different proteomics analyses will be presented along with the most promising biomarker candidates and an overview of the functional network analysis. [4] Pham TV et al.. Bioinformatics. 2010 Feb 1;26(3):363-9.
Conclusion: To our knowledge, this is the first secretome proteomics study to discover protein biomarkers for lung cancer treatment response prediction and monitoring. Our proteomics approach has identified numerous known and novel potential protein biomarkers for personalized therapy and provided new insights in treatment resistance.
Keywords: treatment response prediction, protein biomarkers, secretome proteomics

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P2.135 IGF1R AND SRC ARE FUNCTIONALLY ACTIVATED IN NON SMALL CELL LUNG CANCER (NSCLC) AND TARGETED BY SPECIFIC INHIBITORS

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Background: The insulin-like growth factor type I receptor (IGF1R) is a tyrosin-kinase receptor highly expressed in various solid tumors which regulates cell growth, differentiation, survival, transformation and metastasis. Its over-expression and gene amplification have been demonstrated in non-small cell lung cancer (NSCLC) with special reference to the squamous histology. Tyrosine kinase inhibitors and monoclonal antibodies showed promising blocking effects of IGF1R in pre-clinical studies. The tyrosine kinase c-SRC is a signaling transducer of different TK receptors and is highly expressed in lung cancer tissues and cell lines. We tested in four NSCLC cells the effect of figitumumab, a monoclonal antibody against IGF1R in association with a potent c-Src inhibitor, dasatinib (BMS-354825), and to analyse the presence of a putative IGF1R-SRC activated pathway in NSCLC tumor tissues.
Methods: MTT proliferation assay was performed in cell lines (adenocarcinoma A549, squamous cell carcinoma Calu-1 and H520, large cell carcinoma H1299) both at 48 and 72 hours. FACS analysis was performed at 72 hours to detect apoptotic events following both single agents and combination drug administration. Furthermore IGF1R and SRC mRNA tissue expression was analysed using RealTime PCR in a series of 92 surgical NSCLC specimens (including 50 adenocarcinomas, 9 BACs, 32 squamous cell and one large cell carcinoma) and matched normal tissue samples. In 56 of these cases, immunohistochemical assessment of the activated form of both p-IGF1R and p-SRC, was also performed.
Results: At 72 although not at 48 hours, both Figitumumab and Dasatinib alone showed a moderate activity in biological triplicates of all cell lines, the former with a mild superior effect in H1299 and Calu-1, compared to A549 and H520 cell lines. At the same time, the simultaneous administration of the 2 agents resulted in a synergistic increase of cell proliferation blockage in three out four cell lines, H1299, Calu-1 and A549 cells, as compared to single agents efficacy, with a combination index (CI) < 1. Conversely a strong antagonistic effect was observed in H520 cell line. The effect of the concomitant administration of figitumumab and dasatinib at 72 hours was also evaluated by means of cell apoptosis assay. Although both dasatinib and figitumumab showed modest pro-apoptotic effects when administered as a single agent (except in H520 cell line, in which Figitumumab alone slightly increased the apoptotic rate), a higher rate of apoptotic cells was found with the dasatinib/figitumumab combination in both H1299 and Calu-1 cells. IGF1R and SRC mRNA tissue expression analyses showed higher IGF1R tumor expression and modulation (normal/tumor expression) in squamous cell carcinoma as compared to non-squamous histotypes.. A strong linear correlation between IGF1R and SRC mRNA expression levels was detected, confirmed by protein expression analysis which demonstrated a linear correlation between the phosphorylated forms of IGF1R and SRC proteins.
Conclusion: Our in vitro and tumor tissue data preliminarly support the combined inhibition of IGF1R and SRC as a novel therapeutic strategy for a subset of NSCLC patients with a functionally activated status of the IGF1R-SRC pathway.
Keywords: IGF1R, SRC, Figitumumab, squamous cell carcinoma

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P2.136 PROGNOSTIC SIGNIFICANCE OF SYSTEMIC INFLAMMATORY RESPONSE AND EPIDERMAL GROWTH FACTOR RECEPTOR GENE STATUS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The somatic activating mutation of the epidermal growth factor receptor (EGFR) gene (EGFR mutation) with EGFR-tyrosine kinase inhibitor (EGFR-TKI) treatment has been regarded as a prognostic factor for survival in patients with non-small cell lung cancer (NSCLC). Elevated level of C-reactive protein (CRP), a systemic marker of inflammation, has been also regarded as a prognostic factor. No study, however, has been reported about the asssociation between systemic inflammatory response and EGFR status.
Methods: We retrospectively analyzed the association between systemic inflammatory response and EGFR status in Japanese patients with advanced

NSCLC and investigated if they were independent prognostic factors for survival. A total of 240 Japanese patients with advanced NSCLC whose EGFR statuses were analyzed participated in this study. To assess the systemic inflammatory response, we used Glasgow Prognostic Score (GPS). That is, hypoalbuminemia (<35 g/L =1) and a raised CRP (>10 mg/L =1) were combined to form a prognostic score (0, 1, and 2).
Results: EGFR mutations were found in 107 patients (44.6%). The CRP levels were significantly higher and the albumin levels were significantly lower in patients with wild type EGFR than in patients with EGFR mutations (19.3 ± 3.6 mg/L vs 4.6 ± 10.6 mg/L, P <0.0001, and 40.1 ± 4.6 g/L vs 41.3 ± 3.8 g/L, P =0.034, respectively). GPS of 0 was significantly found in patients with EGFR mutations (P <0.0001). Based on a multivariable analysis, EGFR mutations were significantly associated with GPS of 0 (odds ratio [OR]; 2.93, 95% confidence interval [CI]; 1.51 - 5.90, P =0.0014). Median overall survival (OS) of patients with EGFR mutations was significantly longer than that of patients with wild type EGFR (29.7 months vs 12.0 months, P <0.0001). There were also significant differences in median OS among patients with GPS of 0, GPS of 1, and GPS of 2 (25.5 months vs 14.2 months vs 4.1 months, P <0.0001). Based on a multivariate analysis, ECOG PS of 0 or 1 (hazard ratio [HR], 0.26; 95% CI, 0.15 - 0.46; P <0.0001), EGFR mutations (HR, 0.44; 95% CI, 0.28 - 0.68; P = 0.0003), and GPS of 0 (HR, 0.44; 95% CI, 0.29 - 0.69; P =0.0003) were significantly associated with longer OS.
Conclusion: This study showed the association between systemic inflammatory response and EGFR status in patients with advanced NSCLC and both were independent prognostic factors for survival.
Keywords: Non-small cell lung cancer, epidermal growth factor receptor gene mutation, C-reactive protein, systemic inflammatory response

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.137 ANALYSIS OF THE PROGNOSTIC ROLE OF REGULATORY T-LYMPHOCYTE-ASSOCIATED MARKER EXPRESSION IN RESECTABLE NSCLC

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Background: Regulatory T-lymphocytes (Tregs) play a critical role in immune tolerance to tumor cells. Several molecules, including CD4, CD8A, CD25, CD127, CTLA-4, IL-10 and TGFβ-1 have been reported markers of Tregs. Another highly specific marker for Tregs is FoxP3, a transcription factor which appears to be a master control gene for their development and function. The aim of this study was to determine the expression of these genes by RT-PCR and to correlate them with clinico-pathological and prognostic variables in NSCLC.
Methods: RNA was isolated from frozen lung specimens (tumor and normal lung) from resectable NSCLC patients (n=150). RT-PCR was performed to analyze the expression of: CD4, CD8A, CTLA-4, FoxP3, IL-10, CD25, CD127 and TGFβ-1. Relative expression was normalized by an endogenous gene (GUSB) using the Pfaffl formulae. Statistical analyses were considered significant at p<0.05.
Results: Tumor samples had significantly higher expression of CD25 (x2.1) and lower expression of CD127 (x0.42) than normal lung tissues, reflecting a Treg phenotype infiltrating the tumor. Survival analyses revealed that patients with high FoxP3 expression had reduced TTP (median 22.1 vs 66.6 months, p= 0.017) and OS (median 26.8 vs 49.7 months, p= 0.036) whereas those with high CD4 or CD8A expression had improved OS (median 26.8 vs 48.1 and 27.9 vs 48.1, respectively). A multivariable Cox regression model for TTP and OS was built using variables that were found significant in the univariate analysis (FoxP3, CD4, and CD8A, nodal involvement, tumor size and PS). Regarding TTP

and OS, this analysis revealed that FoxP3 and PS were independent prognostic markers (see table).
Table: Multivariate Cox regression analysis for time to progression (TTP) and overall survival (OS).

	TTP			OS		
	HR	95% IC	P	HR	95% IC	P
PS FoxP3	2.08 2.20	1.04-4.15 1.17-4.13	0.036* 0.014*	2.13 2.47	1.10-4.12 1.32-4.62	0.024* 0.004*

HR, hazard ratio; CI, confidence interval; *p<0.05, statistically significant.
Conclusion: FoxP3 is a transcription factor necessary and sufficient for induction of the immunosuppressive functions in Tregs. In concordance, our results indicate that high expression of FoxP3 in tumor samples is a poor prognostic marker for TTP and OS. Furthermore the multivariable COX regression analysis showed that FoxP3 is an independent prognostic marker. Therefore, FoxP3 expression could be used as a new biomarker of prognosis in resectable NSCLC. Supported by grants PS09-01149 and RD06/0020/1024 from ISCIII.
Keywords: prognostic, Tregs, NSCLC

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P2.138 PROGNOSTIC VALUE OF CD133 EXPRESSION AND IT'S COMBINATION WITH EXPRESSIONS OF ERCC1, RRM1 AND BRCA1 IN LUNG CANCER

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Background: CD133 is one of the most representative cancer stem cell markers. This study was to investigate the potential prognostic value of CD133 expression in lung cancer and it's relationship with the DNA repair genes ERCC1, RRM1 and BRCA1.
Methods: Tumor samples from 73 patients (46 males and 27 females) were immunohistochemically examined for the expressions of CD133, ERCC1, RRM1 and BRCA1, and their associations with overall survival were analyzed. The significances of the expressions of CD133 and DNA repair genes in clinical and pathological characteristic were evaluated.
Results: Stages of the tumors were IA (n = 20), IIB (n = 13), IIA (n = 6), IIB (n = 4), IIIA (n = 10), IIIB (n = 8) and IV (n = 12). Histology revealed adenocarcinoma (n = 36), squamous carcinoma (n = 24), combined adenocarcinoma and squamous carcinoma (n = 8), combined small cell lung cancer and squamous carcinoma (n = 3), other type (n = 2). Of the 73 tumors, 36 (49.3%) were positively stained for CD133, and 19 (52.7%) of the CD133-positive tumors were adenocarcinoma. CD133-negative expressers showed a significantly longer overall survival than CD133-positive expressers (62.9 vs. 45.8 months, p=0.047). CD133-negative/ ERCC1-positive expressers showed a prolonged overall survival than CD133-positive/ERCC1-negative expressers (67.9 vs. 54 months, p=0.013). CD133-negative/ RRM1-positive expressers showed a prolonged overall survival than CD133-positive/ RRM1- negative expressers (60.3 vs. 43.5 months, p=0.047). Cox-regression analysis showed that TNM, ERCC1 and CD133 were the independent prognostic factors.
Conclusion: CD133 expression is an independent prognostic marker and the combination of CD133 with ERCC1 and/or RRM1 may provide better prognostic value in predicting the overall survival of the patients with lung cancer.
Keywords: CD133, DNA repair genes, Lung cancer, immunohistochemistry

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P2.139 HYPONATREMIA IS A PROGNOSTIC MARKER OF SURVIVAL FOR LUNG CARCINOMA

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Background: Lung carcinoma is the most prevalent and most deadly solid tumor worldwide. Hyponatremia is frequently observed on the basis of SIADH in patients suffering from small cell lung carcinoma (SCLC) but also from non small cell lung carcinoma (NSCLC). This electrolyte imbalance is associated with higher mortality and morbidity. If hyponatremia influences median survival of lung

tumors remains controversial. In the current study we retrospectively analysed if median survival is directly impacted by hyponatremia and evaluate if hyponatremia is a prognostic marker for lung carcinoma.
Methods: Between 2006 and 2009 we analysed 2048 lung carcinoma without and 97 (4.7%) with hyponatremia in a single center study (Berlin/Tumor-Centre-Buch, Germany).
Results: While 14.2% of the SCLC (296 SCLC without and 49 SCLC with hyponatremia) developed hyponatremia, only 2.7% of the NSCLC patients (1752 NSCLC without and 48 NSCLC with hyponatremia) where affected. 63 males and 34 females developed hyponatremia. Overall survival (OS) after 2 years was 9.9% ± 6,6 for females and 35.1% ± 7,6 for males (p=0,08). Hyponatremia was mostly observed in stage of advanced disease. 75.5% of SCLC and 73.3% of NSCLC with hyponatremia had distant metastases correponding to tumor stage IV. Median survival in lung carcinoma with hyponatremia was reduced compared to normonatremic average survival (0.84 ± 0.14 vs. 1.01 ± 0.04 years, p=0,08). Sodium levels below 125mmol/l where associated with reduced survival (OS (2 years) 11,8% ± 6,9 vs. 34,3% ± 8,5, p=0,12). Survival curves were similar in hyponatremic patients regardless of the lung tumor histogy (OS (2 years) 25.2% ± 7,6 for NSCLC vs 23.5% ± 8,5 for SCLC, p=0,8). Overall survival (2 years) of normonatremic patients was 30.8% ± 1,3 (p=0,08). Correction of serum sodium above 138mmol/l was correlated to extended median survival (1.11 ± 0,12 years, p=0,007) for both NSCLC and SCLC patients while medium survival was only 0.43 years if serum sodium could not be elevated above 138mmol/l (0.55 ± 0,22 years, p=0,017 for NSCLC and 0.42 ± 0,1 years for SCLC, p=0,14).
Conclusion: These data suggest that hyponatremia can influence survival of patients with lung carcinoma. The degree of hyponatremia (lowest serum sodium) and its normalisation (maximal serum sodium) can modify median survival. Serum sodium below 125mmol/l is correlated with increased mortality. In addition we observed a positive correlation between serum sodium and tumor stage. This suggests that hyponatremia on the basis of SIADH corresponds to tumor mass. Women suffering from hyponatremia displayed shorter survival, but were overall less frequently affected than man (63 men in comparison to 34 women, ratio 2:1). In summary these data indicate that serum sodium is a relevant prognostic marker of survival for small cell and non small cell lung carcinoma.
Keywords: survival, Hyponatremia, lung carcinoma, prognostic marker

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P2.140 DECREASED EXPRESSION OF LKB1 IS CORRELATE WITH LOSS EXPRESSION OF P16 AND OVER EXPRESSION OF P53 AND ADVANCED TUMOR STAGE IN NON-SMALL CELL LUNG CARCINOMA

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Background: It is well known that about 36% of stage I non-small cell lung carcinoma (NSCLC) patients will eventually experience recurrent disease, even when it is detected at an early stage and potentially curative surgery is performed. However, the mechanism of tumor progression and potential development of drug resistance is still not well understood. LKB1, (liver kinase B1), a serine/thronine kinase, is encoded by LKB1/STK11 gene on the chromosome 19p and a primary upstream kinase of adenine monophosphate-activated protein kinase (AMPK) involved in the regulation of both cellular polarity and energy metabolism. Germline mutations of LKB1 gene are the leading cause of Peutz-Jeghers syndrome and found in 90% of this patient population. Somatic mutation of LKB1 is associated with a variety of solid tumors and 30-40% of NSCLC. Recent studies have shown that endogenous LKB1 knockdown accelerates cell cycle progression through G1/S checkpoint in human kidney cell line, and Lkb1-deficient enhances tumor metastasis in mouse model. The tumor-suppressor activity of LKB1 has been suggested to function through regulation of p53 and/or the Ink4a/Arf pathways. However, the relationship of LKB1, p53 and p16 has not been well understood. In this study, we have investigated the expression and potential relationships among LKB1, p16 and p53 in NSCLC.
Methods: TMAs of NSCLC were constructed. A

total of 194 cases were included. Mouse monoclonal antibodies against LKB1 protein (1:200 dilution), p16 protein (1:250 dilution), and p53 protein (1:100 dilution) were used, and immunoreactivity was scored in both nuclei and cytoplasm using a scale from 0 (undetectable) to 2+ (strongly positive).
Results: Among 194 cases, 166 cases were early stage of tumors (pT stage 1 and 2) and 28 cases were late stage of tumors (pT stage 3 and 4). The expressions of LKB1, p16 and p53 in different stage of tumors were summarized in Table 1. In addition, the loss of LKB1 expression in squamous cell carcinoma and adenocarcinome is 31.3% and 22.5%, respectively (P>0.05). Table 1

	Loss of LKB1	Loss of p16	Over expression of p53
Low tumor stage (1/2)	26.1% (30/115)	53.2% (66/124)	54.8% (23/42)
High tumor stage (3/4)	40 % (8/20)	73.7% (14/19)	75% (6/8)
All cases	28.1% (38/135)	55.9% (80/143)	58% (29/50)

Conclusion: The decreased expression of LKB1and p16, and over expression of p53 are common in NSCLC. Although there is no significant difference of loss LKB1 expression between squamons cell carcinoma and adenocarcinoma, the decreased expression of LKB1 and p16, and over expression of p53, were correlated with advanced tumor stage. Our date suggests that loss of LKB1 expression in NSCLC may related to disease aggressiveness and dysfunction of p16/INK4A cell cycle-dependent signaling pathways.
Keywords: LKB1 expression, p16/INK4A signaling pathway, p53 expression, Non-small Cell Lung Carcinoma

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P2.141 EGFR MUTATIONAL STATUS IN FALSE-NEGATIVE COMPUTED TOMOGRAPHY-GUIDED LUNG NEEDLE BIOPSY SPECIMENS OF NON-SMALL-CELL LUNG CANCERS

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Background: Computed tomography-guided lung needle biopsy (CTNB) is an accurate and useful technique for diagnosing lung tumors. However, false-negative cases occasionally become apparent after lung tumor resection. Epidermal growth factor receptor (EGFR) gene mutations are a characteristic of non–small-cell lung cancer (NSCLC). Here we determined the EGFR mutational status of lung tumors misdiagnosed from CTNB specimens but correctly diagnosed after surgery.
Methods: Between 2000 and 2008, 1109 CTNBs were performed at our hospital; 12 of these tumors were diagnosed as non-malignant at CTNB and were only correctly diagnosed after surgery. We reviewed the pathological findings of these CTNB sections to identify those that did not contain malignant components. DNA was extracted from formalin-fixed paraffin-embedded tissues of both CTNB and surgically resected specimens of these cases. The EGFR mutational status was subsequently determined using a mutant-enriched PCR assay.
Results: EGFR mutations were detected in CTNB specimens (1/12, 8.3 %) and in the corresponding surgically resected tumors (3/12, 25%). Two mutant cases from surgically resected tumors showed the wild-type EGFR gene in CTNB specimens. One case harbored the same EGFR mutation in both CNTB and surgically resected specimens.
Conclusion: Our results indicate that the detection of EGFR mutations aids the diagnosis of NSCLC in pathologically negative CTNB specimens.
Keywords: CT guided biopsy, EGFR mutation

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P2.142 SYSTEMIC INFLAMMATORY STATUS AT BASELINE AFFECTS SURVIVAL AND BEVACIZUMAB ACTIVITY IN NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: The introduction of Bevacizumab (Bev) in the first-line treatment of NSCLC patients, has brought a great benefit in term of progression-free-survival(PFS) and survival (OS). However, the toxicity and costs related to these treatments, highlight the need of biomarkers capable of predicting Bev activity. We investigate the prognostic value of several clinical and biologic variables in 62 inoperable NSCLC patients who had received frontline chemotherapy in combination with bevacizumab. Forty-five patients had received treatment according to the mPEBev regimen (phase II study, EUDRACT#2008-00-6051-40) and 17 with standard platinum-based chemotherapy between December 2008 and February 2010
Methods: Clinical and biologic variables from sixty-two metastatic NSCLC patients undergone frontline-ciplatinum-based chemotherapy and Bev were evaluated for their capability to predict longer PFS and OS. The Student-t test, the Pearson Ki-square test, Kaplan Meier survival curves and Cox regression analysis were performed to evaluate the correlation among variables and outcome.
Results: Patients showed a 76.6% response rate, a median PFS of 8.00 (95% CI 6.64-9.36) months and a median OS of 15 (95% CI 10.66-19.34) months. In the univariate analysis, baseline neutrophils count >7500 cells/ml and neutrophil/lymphocyte ratio (NLR) >4 were strongly associated with worse PFS and OS ($p<0.01$) while baseline monocytes count > 600 cells/ml was correlated only with worse OS ($p<0.01$). NLR variable was not entered into the Cox's model due to the strong correlation with neutrophils count (Pearson Ki square < 0.05). Multivariate analysis showed that neutrophils count >7500 cells/ml was associated with worse PFS (HR 2.076; p=0.013) and OS (HR 3.465; p=0.004), while monocytes count >600 cells/ml was associated only with worse OS (HR 2.218; p=0.048). We then created a predictive model based on these three prognostic factor in which patients with no adverse factor (41% of the group) had a median OS of 20.00 (95% CI 16.81-23.18) months, while patients with at least one adverse factor had a median OS of 7.00 (95% CI 1.91-12.09) months ($p<0.001$).
Conclusion: These results suggest that the systemic inflammatory status at baseline in NSCLC patients may play an intriguing role in determining Bev activity and patients' survival. Furthermore they provided us three potentials and easy-to-do biomarkers able to predict the outcome of NSCLC patients receiving Bev which warrant prospective evaluation.
Keywords: bevacizumab, NSCLC, prognostic factors

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P2.143 SCREENING FOR EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS ASSOCIATED TO TYROSINE-KINASE INHIBITORS IN LUNG ADENOCARCINOMA PATIENTS FROM ARGENTINA

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Background: Epidermal growth factor receptor (EGFR) activating mutations in the EGFR gene confer sensitivity to the tyrosine kinase inhibitors in patients with lung cancer. No previous studies of characterization of EGFR mutations have been performed in patients from Argentina. We evaluated the feasibility of large-scale screening for EGFR mutations in such patients and analyzed the association between the mutations and some clinical covariables.
Methods: From March 2010 through December 2010, lung adenocarcinomas from 166 patients from different centers in Argentina were screened for EGFR mutations in exons 18, 19, 20, and 21, in a central laboratory. All specimens were reviewed to ascertain at least 70% neoplastic cells/ nucleated cells. Genomic DNA was extracted from macro dissected tumor cells of formalin-fixed paraffin-embedded tissue sections and smears. Amplifications of exons 18 through 21 of EGFR gene was performed using nested primers as published. PCR fragments were sequenced and analyzed in both forward and reverse directions; mutations were verified by three independent amplifications. Patient

age, gender and smoking status were documented. **Results:** Among the first 166 patients with lung adenocarcinoma included for somatic EGFR kinase domain sequencing, the median age was 62 years (SD 11, 020) and 54% were female. Smokers or former smokers accounted for 62% of patients, 38% of the patients were never smokers. 92% of specimens submitted were paraffin embedded. Eighteen samples were inadequate so excluded from the study. 124 samples of 147 specimens included in the study were successfully amplified (84%). Among the 124 patients with interpretable results, 31 (24%) were found to have at least 1 mutation in the EGFR kinase domain. The majority of the mutations associated with TKI sensitivity were located in exon 19 (18/31): Del E746–A750 in 12 cases, Del L747–T751 in 2 cases, L747 – E749 del P ins in 2 cases, and E746– T751 del I ins and p. A743S in 1 case each one. Three patients carried L858R mutation in exon 21, and non-classic mutations L861Q and R831H in exon 21 were observed in 6 patients. In 4 patients, mutations related to TKI resistance were observed (T790M, p.A767_V769dupASV and R776H in exon 20). In one patient T790M was combined with L858R sensitizatizing mutation in exon 21. One patient carried S768I mutation in exon 20 with controversial association to TKI sensitivity. Non-smokers had more frequently TKI sensitivity mutations than smokers and former smokers (p=0.002, Fisher test), but we found no association between sex and mutation status. **Conclusion:** EGFR mutations related to TKI response were characterized from tumor samples in a serie of Argentinean patients with lung adenocarcinoma. EGFR TKI resistance mutations were observed in 4 patients that have no previously received TKI treatments. One of the strengths of sequencing is that it detects unknown mutations as well as known ones. The results showed that large-scale screening of patients for EGFR mutations, are feasible to perform using DNA sequencing with the aim of selecting lung cancer patients who benefits from EGFR TKIs treatment.

Keywords: EGFR, tirosine kinase inhibitors, Adenocarcinoma

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P2.144 ASSESSMENT OF EGFR, VEGFR, AND SELECTED DOWNSTREAM SIGNALING MOLECULES IN NON-SMALL CELL LUNG CANCER

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Background: Epidermal growth factor receptors (EGFR) and vascular endothelial growth factor receptors (VEGFR) are thought to be related to cancer cell proliferation and survival. Whether they are associated with cancer patient's clinical outcome is not clear. We analyzed EGFR, VEGFR and selected downstream signaling molecules in non-small cell lung cancer (NSCLC) with pathological and clinical correlation. **Methods:** 88 cases of surgically treated NSCLC were included in the study. Tissue microarray (TMA) of the tumors was prepared. Immunohistochemical staining (IHC) for EGFR, VEGFR, Akt, BAD and PTEN (phosphatase and tensin homolog deleted on chromosome 10) and fluorescence in situ hybridization (FISH) for EGFR were performed on TMA sections. The results were correlated with pathological characteristics and clinical outcome. **Results:** EGFR overexpression was detected by FISH and IHC (66.7% vs. 31.8 %). EGFR assessed by FISH was mainly in the form of polysomy rather than amplification, with a tendancy to higher rate in high grade tumors ($p = 0.08$) and positive nodal spread ($p = 0.07$). Squamous cell carcinoma showed higher VEGFR expression ($p < 0.05$). BAD expression was associated with later pathologic stage ($p < 0.05$) and weakly with adenocarcinoma. Weaker associations were also noticed between PTEN and adenocarcinoma (earlier pathologic stage and more well-differentiated morphology). Overexpression of these factors was not associated with patient's survival including follow-up to 3 years post-surgery. **Conclusion:** EGFR, VEGFR, BAD and PTEN are associated with certain pathological and clinical features in NSCLC.

Keywords: EGFR, VEGFR, BAD, Non-small cell lung cancer

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P2.145 ASSOCIATION OF GENETIC POLYMORPHISMS WITH IMMUNOHISTOCHEMICAL EXPRESSION OF THYROID TRANSCRIPTION FACTOR 1 (TTF1) IN ASIAN NSCLC ADENOCARCINOMA PATIENTS.

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Background: Thyroid transcription factor-1 (TTF1) is a lineage-dependent proto-oncogene highly expressed in patients with adenocarcinoma. We evaluated the association of single nucleotide polymorphisms (SNPs) and immunohistochemical expression level of TTF1 in Asian lung adenocarcinoma.

Methods: Sixty-four SNPs were identified from healthy Asian cohorts of three ethnicities: Chinese, Malay and Indian. This was compared with 71 patients with adenocarcinoma. The majority of the patients were of Chinese descent. The median age was 60 years (range: 34-85 years). Genomic DNA was isolated from the peripheral blood sample of the patients. The qualitative assessment of immunohistochemical expression of TTF1 was classified as nuclear expression positive and negative. Contingency analysis was applied to identify the association of TTF1 genotypes and IHC categories and Fisher exact test P value was calculated. Kaplan-Meier analysis was used to estimate survivorship-type functions. Parametric log-rank test was adopted to evaluate the possible difference in survival across the IHC categories.

Results: TTF1 was highly expressed in 84% (N=60) of the patient samples. Among the 64 SNPs, three SNPs [-702G>A, IVS2+470G>A and 813_814insGGCGGGGGC] were significantly associated with the immunohistochemical expression level of TTF1 (P=0.04, 0.01 and 0.04 respectively, Table 1). The variant alleles (-702A, IVS2+470A and 813_814ins) across three SNPs were correlated with absence of TTF1 expression. Median overall survival of the patients in the present study was 18.6 months. Although our analysis did not observe significant survival association with TTF1 expression categories based on IHC scoring system, there was modest trend to better survival associated with positive TTF1 expression (positive TTF1 vs negative TTF1: 20.37 vs 15.27 months; P>0.05). **Table 1.** Association betweenTTF1 pharmacogenetics and Immunohistochemical expression in Asian NSCLC adenocarcinoma patients.

#	SNP	Genotypes	TTF1 expression, n		p-value
			Negative	Positive	
1	-702G>A	GG	8	57	0.04
		GA	2	3	
		AA	1	0	
2	*IVS2+470G>A*	GG	8	44	0.01
		GA	0	12	
		AA	3	2	
3	*813_814insGGCGGGGGC*	wt/wt	8	56	0.04
		wt/ins	0	0	
		ins/ins	3	3	

Conclusion: This exploratory study showed that polymorphisms in the TTF-1 proto-oncogene (-702G>A, IVS2+470G>A and 813_814insGGCGGGGGC) have significant association with its expression level. Further investigations are needed to assess the utility of the identified SNPs as a biomarker for the clinical management of lung adenocarcinoma patients.

Keywords: Asian NSCLC adenocarcinoma, Polymorphisms, IHC, TTF1

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P2.146 DNA HYPERMETHYLATION IN PROGRESSIVE ADVANCED NON SMALL CELL LUNG CANCER

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Background: DNA hypermethylation of tumour-supressor genes results in decrease of their functions and subsequent facilitation of tumour development. Epigenetic changes can play the role in cellular systems responsible for (i) cell cycle control, (ii)

tumour cell proliferation and differentiation, (iii) cell adhesion,invasion and metastasis, (iv) regulation of apoptosis, as well as (v) DNA repair gene transcription and detoxification of DNA adducts, induced by cancer chemotherapy.
Methods: Epigenetic hypermethylations were detected by Multiplex ligation-dependent probe amplification (MLPA) technique. We investigated 30 genes from the above mentioned cellular systems. Tissue samples from patients with clinically confirmed NSCLC having progressed on chemotherapy and targeted therapy were examined. Relations between methylations of genes and sex, cancer type and stage, smoking status and response to therapy were studied in detail. Statistical analysis was performed using contingency tables, chi-square test, Wilcoxon test and Kruskal Wallis analysis. In addition, we have evaluated effect of hypermethylations in EGFR and KRAS mutated tumours.
Results: The study comprised 123 patients, 75 males, 48 females,most frequent cancer types were adenocarcinoms (72),squamous cancers (32),anaplastic (9) and non specified NSCLC(10). All of patiens suffered from tumour stages III and IV., more frequent were tumours of stage IV (76). Hypermethylation of at least one gene was found in 11 patients (90.2%).Most frequently methylated genes were CDH 13 in 48%,WT 1-in 38.2% , APC in 30.1%., RASSF1A in 30.1%, ESR 1 in 23.6%,CDKN2B -22.8%,PAX5- 19.5%,PAX6-13.8%,IGSF4-11.4% and GATA5 -10.6%. Hypermethylations were found more frequently in adenocarcinomas. Most common combinations of methylated genes were : CDH 13 and WT1, APC and WT1,CDH 13 and PAX6 and APC and CDH13. All combinations were significantly increased in adenocarcinomas as well as in EGFR mutated tumours. None of epigenetic ganges is related to chemotherapy and targeted treatment effectiveness, detailed analysis of time to progression and overall survival is presented.
Conclusion: Conclusion :Epigenetic hypermethylations of tumour related genes in NSCLC are frequent and may be found in several different groups of genes simultaneously, particularly in adenocarcinomas and in EGFR mutated tumours. Epigenetic changes should be understood as evidence of diversity of lung cancer lesions and potentially serve as prognostic and/or predictive factors. This work was supported by Czech Ministry of Health grant IGA NS9718.

Keywords: Chemotherapy, targeted therapy, DNA hypermethylation, epigenetics

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.147 LUNG CANCER BIOMARKER CANDIDATE DISCOVERY BY PROTEOMIC PROFILING OF TUMOR-NORMAL HUMAN LUNG TISSUE PAIRS

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Background: Lung cancer is the main cause of cancer-related deaths with a worldwide mortality of more than one million per year. More than 2/3rds of the patients present with advanced and thus incurable disease. The introduction of biomarkers could be useful for every stage of the disease including diagnosis, prognosis, response to treatment, and recurrence. Modern "omics" techniques, including mass spectrometry-based proteomics, have shown tremendous utility in identifying large numbers of proteins as candidate biomarkers.
The wide dynamic range of concentration and number of proteins found in plasma make it a challenging matrix to perform biomarker discovery experiments. An alternative strategy is to perform biomarker discovery experiments directly in tissue, where mass spectrometry-based proteomics can

sample a larger range and number of proteins emanating. The aim of this study is to build a biomarker candidate database for lung cancer prognosis using proteomics profiling on both lung cancer tumors and their adjacent tissues.
Methods: Data from proteins elevated in tumors will be combined with genomic and transcriptomic data to prioritize candidates for development of quantitative assays to be used in clinical validation studies. 19 paired tissue specimens (tumor vs. adjacent normal lung tissue) were collected following a standard operating procedure. 10 pairs were collected from the Centre Hospitalier de Luxembourg, and the Cooperative Human Tissue Network (CHTN) procured 9 pairs. All tissues were shipped and stored at temperatures below -75 °C before sample preparation. The tissues were lysed and proteins were digested with trypsin using previously published methods. The tissue digests were subjected to 2-D reverse-phase HPLC separation (nanoACQUITY UPLC System, Waters Corp, Milford, MA) followed by fragmentation on an LTQ Orbitrap Velos mass spectrometer (Thermo Scientific, San Jose, CA). Data analysis was performed using X!Tandem and OMMSA search engines, as well as Xpress for label free quantitative analysis.
Results: Initial experiments have identified more than 4,000 proteins in tumor and normal tissues. Approximately 30% more proteins were identified in tumor tissues compared to adjacent "normal" tissues, with more than 1,000 proteins found exclusively in tumors. Quantitative analysis demonstrated high MS1 peak intensity correlations across all patients for both tumor and normal sample types. Further statistical analysis on the discovery data established a list of 140 proteins whose abundance was significantly elevated in tumors. In addition, proteomic analysis will be conducted on other types of samples from lung cancer patients including plasma and pleural effusion fluid, as well as plasma from mice xenografted with human lung tumor tissues. Candidate biomarkers will be verified using immunoaffinity enrichment of peptides coupled to stable isotope dilution and selected reaction monitoring mass spectrometry.
Conclusion: Using this state of the art mass spectrometry based proteomic discovery strategy we establish extensive lists of potentially new plasma biomarkers for use in diagnosis and management of lung cancer patients. These biomarkers will then be verified using a set of several hundred of lung cancer and normal patient plasmas using also a mass spectrometry multiplexed assay. The selected potentially useful markers will then be validated in specific clinical situations.
Keywords: proteomics, Biomarkers, Mass spectrometry, Lung cancer

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P2.148 LOW STROMAL CD99 EXPRESSION IS INDEPENDENTLY ASSOCIATED WITH SHORTER SURVIVAL IN NSCLC

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Background: The importance of the tumor stroma has become evident since the introduction of anti-angiogenic therapy. The delicate interactions of cancer cells with stromal fibroblasts, inflammatory cells and cells of the vasculature play an essential role at all stages of tumorigenesis. However, beside angiogenic factors the mechanisms of tumor-stroma interactions are pooly understood. The aim of our study was to identify stromal proteins with clinical relevance in NSCLC.
Methods: We compiled a list encompassing 200 potential stromal candidate genes based on available literature and gene expression array data generated from lung cancer stroma after microdissection. The immunohistochemical protein expression of these genes in lung cancer was screened in the Human Protein Atlas (www.proteinatlas.org). Finally, 15 proteins were selected that showed a differential staining pattern, i.e. variation in stromal staining intensity between different lung cancer samples. The corresponding antibodies were then applied on a tissue microarray (TMA) including 190 NSCLC samples and the stromal staining was graded with regard to intensity and fraction of stained cells.
Results: Univariate and multivariate analysis

revealed that strong stromal CD99 expression correlated with good prognosis (OR = 2.0 CI: 1.0-3.8). This association was independent of the relative amount of tumor stroma, the amount of inflammatory cells and clinical and pathological parameters such as stage and performance status. The relevant prognostic impact of stromal CD99 expression was further confirmed in an independent TMA cohort of 240 lung cancer cases (p= 0.017). Furthermore, utilizing double staining fluorescence microscopy, we showed that CD99 is differentially expressed in stromal lymphocytes as well as in cancer associated fibroblasts.

Conclusion: We identified the membrane protein CD99 (also known as MIC2) as a novel stromal factor with prognostic relevance in NSCLC. Further studies are warranted to elucidate the functional role of CD99 expression in tumorigenesis.

Keywords: tumor stroma, CD99, Prognosis, tissue microarray

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P2.149 EXPRESSION OF ANGIOGENIC AND LYMPHANGIOGENIC GENES AS BIOMARKERS OF PROGNOSIS IN EARLY-STAGE NSCLC

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Background: Angiogenesis, the formation of new blood vessels from pre-existing vasculature, begins in early stages of the disease and is a key step in tumor growth and metastasis. Tumor cells dissemination from the primary tumor may also occur through the lymphatic system. The process of angiogenesis and lymphangiogenesis are mainly regulated by VEGF family members. The aim of the present study was to analyze the expression of angiogenic/lymphangiogenic genes in a cohort of resectable NSCLC patients and to correlate them with clinico-pathological variables and prognosis.

Methods: RNA was obtained from tumor and normal lung specimens from 150 resectable NSCLC patients. RT-PCR was performed to assess the expression of PIGF, VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2, VEGFR-3, NRP1 and NRP2. Relative expression was normalized by an endogenous gene (GUS) using the Pfaffl formulae. Differences were considered statistically significant at $p<0.05$.

Results: We found that tumor samples had a significant higher expression of PIGF and lower expression of VEGF-D compared to normal tissue (2.55X and 0.030X, respectively). The survival analysis revealed that the group of patients with high expression of VEGF-A had a significantly reduced TTP (p=0.028) and OS (p=0.008) whereas those with values of VEGF-D or VEGF-B below the median had reduced OS rate (p=0.004 and p=0.063, respectively). Moreover, a subgroup of patients characterized by a combination of high expression of VEGF-A and low VEGF-D had the worst prognosis in terms of TTP (p=0.029) and OS (p<0.0001) when compared with other possible combinations of both markers. A multivariable Cox regression model was built using variables found significant in the univariate analysis. The Cox analysis revealed that tumor size, histology and the combined variable (VEGF-A and VEGF-D) were independent prognostic markers for TTP; whereas nodal status, histology and the combined variable (VEGF-A and VEGF-D) were independent prognostic markers for OS (see table). Table: Multivariate Cox regression analysis for TTP and OS

Variables	TTP			OS		
	HR	95% CI	p	HR	95% CI	p
Tumor size	2.017	1.05-3.87	0.035*	-	-	-
Histology	1.865	1.20-2.89	0.005*	1.473	1.01-2.16	0.047*
High VEGF-A & Low VEGF-D	2.733	1.42-5.28	0.003*	2.759	1.49-5.12	0.001*
Nodal status	-	-	-	1.922	1.05-3.51	0.034*

HR, hazard ratio; CI, confidence interval; *p<0.05, statistically significant.

Conclusion: VEGF family members are master control genes of the angiogenic and lymphangiogenic processes and may have a crucial role in the prognostic of the disease. We found a markedly lower expression of VEGF-D in tumor samples compared with normal lung tissue that needs to be further investigated. Moreover, the combination

of high expression of VEGF-A and low expression of VEGF-D identified a NSCLC subgroup with a poorer prognosis in our cohort of early-stage NSCLC. Supported by grants PS09-01149 and RD06/0020/1024 from ISCIII.
Keywords: Prognosis, NSCLC, angiogenesis, lymphangiogenesis

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.150 5'-NUCLEOTIDASE (CN-II) EMERGES AS A NEW PREDICTIVE BIOMARKER OF RESPONSE IN THE GEMCITABINE-CISPLATIN TREATMENT OF NON-SMALL CELL LUNG CANCER

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Background: Pharmacogenetics/genomics studies aimed at identify predictive biomarkers have given contradictory results in patients with non-small cell lung cancer (NSCLC). A possible explanation might reside in studies focussed on single candidate biomarkers, explored in small size series, without standardized unbiased methods, as well as in different settings for tumor type, stage and evaluation of treatment outcome.
Therefore we evaluated whether the expression levels of all the pivotal genes involved in chemosensitivity/resistance to platinum and gemcitabine, studied by validated real-time PCR methods in laser-microdissected specimens, influenced tumor response in patients with NSCLC uniformly treated with gemcitabine-platinum-based regimens.
Methods: Response rate was evaluated, according to the Response Evaluation Criteria in Solid Tumors (RECIST), in 58 chemonaive patients affected stage III (50) and IV (8) NSCLC who received a platinum and gemcitabine regimen. Excision repair cross-complementing 1 (ERCC1), human equilibrative nucleoside transporter-1 (hENT1), deoxycytidine-kinase (dCK), 5'-nucleotidase (5'-NT), cytidine-deaminase (CDA), and ribonucleotide-reductase subunits (RR1 and RR2) were analyzed by quantitative-RT-PCR in fresh microdissected tumor specimens collected before treatment. Frequency distribution of responses above and below the median level of biomarkers expression were compared using a two-sided Fisher's exact test
Results: Patients were treated for at least 2 cycles. The best overall responses observed were a complete remission in one case (1.7%), 28 (48.8%) partial responses and 18 (31.1%) stable diseases, while 11 patients experienced disease progression. By adopting cut-off values according to median expression levels, among all the studied genes, 5'-NT was the only gene differently expressed in the responders (complete and partial response) and no responders (stable and progressive disease) patients ($p=0.016$). Indeed, the overexpression of this catabolic enzyme was significantly associated to a poor response to treatment.
Conclusion: This is the first study to demonstrate the role of 5'-NT expression on the efficacy of gemcitabine-cisplatin treatment. The validation of this role in future prospective multicenter trials will offer new tools for treatment optimization of currently available treatments in selected NSCLC patients.
Keywords: 5-NT, Resistance, platinum/gemcitabine

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P2.151 EML4-ALK FUSION GENE IN LUNG ADENOCARCINOMA IN THAILAND

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Background: The EML4-ALK fusion gene represents the most recent Molecular Targets in NSCLC. Attempts have been made to utilize this fusion gene as the prognostic and predictive indicator for the treatment of Non-Small-Cell-lung-Cancer. In the past, we have learned the significance of EGFR, VEGF and KRAS mutations to success and failure of NSCLC treated by TKI such as Irressa or Tarceva. With the arrival of EML4-ALK fusion gene detection, we ask "Should we examine EML4-ALK fusion gene in all NSCLC prior to starting the

targeted therapy ?"
Methods: Materials and Methods : 66 lung Adenocarcinoma patients' cancer tissue (36 male , 30 female) were screened for EGFR protein Overexpression and EML4-ALK expression using Immunohistochemical (IHC) technique. EML4-ALK positivity was further confirmed by DNA sequencing. EGFR and KRAS mutations were identified by DNA sequencing. Targets selection for the treatment was done according to genotype.
Results: Of 66 cancer tissues of NSCLC screened, 5 cases (7.5%) habored EML4-ALK fusion gene, 5 cases (7.5%) habored KRAS mutation and 42 (63%) habored EGFR mutations. 14 cases (21%) had no EGFR mutations but had cKIT and HER2 protein Overexpression and gene mutations. Interestingly enough, 5 cases who carried EML4-ALK fusion gene did not have any EGFR and KRAS mutations. Those with EGFR mutations responded to the treatment by TKI very well at the rate of 83% (35/42), while those with KRAS mutation failed the treatment. 5 cases of EML4-ALK fusion gene were excluded from the targeted therapy and used chemotheray instead with relatively good response 40% (2/5).
Conclusion: Discussion and Conclusion: NSCLC with EML4-ALK fusion gene represented a subset of lung Adenocarcinoma with unique gene feature and clinical feature. This entity should be be identified and if found must be treated differently in order to acheive success. Identification of EML4-ALK and KRAS in NSCLC along with EGFR mutations should be done routinely prior to TKI or targeted therapy to obtain the best possible results. Yes EML4-ALK fusion gene should be use as Prognostic and Predictive indicators in NSCLC treatment. Details of the study will be given in the presentation.
Keywords: EML4-ALK fusion gene, lung cancer with EML4-ALK gene

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P2.152 CIRCULATING ENDOTHELIAL PROGENITOR CELLS IN RESECTABLE NON-SMALL CELL LUNG CANCER DURING ADJUVANT CHEMOTHERAPY COMBINED WITH ENDOSTAR

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Background: Antiangiogenic molecules can inhibit neovascularization in lung cancer, but their effect on circulating endothelial progenitor cells(cEPCs) is still unclear. Several hypotheses have been proposed that antiangiogenic drugs enhance the treatment efficacy of cytotoxic chemotherapy, including impairing the ability of tumors to regrow after therapy. Therefore, our study aims to examine the level of cEPCs (VEGFR2+ /CD133+) in the peripheral blood of resectable non-small cell lung cancer patients(NSCLC) treated by either chemotherapy combined with endostar(recombinant human endostatin) or chemotherapy alone as adjuvant therapy.
Methods: Thirty three patients with resectable NSCLC were enrolled. Ten healthy individuals were as control. The blood samples of the patients were from a clinical trial(NCT01124253). Among them,18 patients treated by chemotherapy alone and 15 patients treated by chemotherapy combined with endostar. Peripheral blood was taken from the patients before surgery and after postoperative adjuvant therapy. Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll density gradient centrifugation. cEPCs labeled with VEGFR2, CD133 were counted by flow cytometry. Furthermore, we measured VEGFR2, CD133, CD34, and VE-cadherin mRNA in blood samples by means of a quantitative reverse transcription-PCR approach.
Results: The percentage of cEPCs in the total PBMCs was 0.26%±0.14% in NSCLC patients without treatment intervention versus 0.045±0.032% in healthy controls($p = 0.00$). There was a significant difference of cEPCs numbers in stage I—II compared with III ($p = 0.027$) in the preoperative blood samples. The cEPCs numbers were significant lower in the combination therapy group than in chemotherapy alone group in the postoperative blood samples ($p=0.014$). Time to disease progression(TTP) in the patients with low cEPCs number (less than 0.35%) was longer than in those with high cEPCs number after adjuvant treatment ($p =0.00$, log rank). The preoperative VEGFR2 mRNA level was significantly correlated to disease progression ($p = 0.00$, log rank test).
Conclusion: This study showed that NSCLC patients had high cEPCs numbers. An early antiangiogenic therapy in combination with chemotherapy may be beneficial for the success of resectable NSCLC adjuvant therapy, and cEPCs may be a novel biomarker in those patients with no measurable targets.

Keywords: circulating endothelial progenitor cells, Lung cancer, Chemotherapy, neovascularization

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P2.153 MUTATION ANALYSIS OF EGFR GENE OF LUNG CANCER PATIENTS IN THE NORTHERN THAILAND

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Background: Mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) is mandatory for dramatic responses to EGFR tyrosine kinase inhibitors either gefitinib or erlotinib. Lung cancer patients who have mutant EGFR also have better responses to systemic chemotherapy and longer survival than those who do not have mutation. This study aims to investigate the incidence of EGFR mutation at tyrosine kinase domain among the northern Thai lung cancer patients.
Methods: Tumor tissues were obtained retrospectively from paraffin blocks of 68 non-small cell lung cancer patients who received surgical resection at Maharaj Nakorn Chiangmai Hospital, Faculty of Medicine, Chiang Mai University between January 2007 and December 2009. Tissues were subjected to DNA extraction, DNA amplification by polymerase chain reaction and followed by direct sequencing. Clinical parameters, including age, sex, smoking, histology and TMN stage, were analyzed to identify the correlation between these parameters and EGFR mutations.
Results: Ten EGFR mutations were found in 18 out of 68 patients (26.47%). Six of which, delE746 – A750, delL747 – S752insQ, A839T, V851I, E868G and L858, were previously reported mutations. The other four, L688F, A722T, G724D and P848S, were novel mutations. EGFR mutation status was statistic significant associated with female (P=0.0038) or adenocarcinoma histology (P=0.0343). Correlation between clinical parameters and EGFR mutations and prognosis are being analyzed.
Conclusion: The incidence of EGFR mutation among the northern Thai lung cancer patients is similar to the incidence of EGFR mutation worldwide. EGFR mutation status is statistically associated with female or adenocarcinoma histology.
Keywords: Lung cancer, EGFR, Northern Thailand, Clinical parameters

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.154 ESTROGEN RECEPTOR BETA IN NON-SMALL CELL LUNG CANCER AS A MOLECULAR TARGET FOR ANTIESTROGEN THERAPY – EXPRESSION AND GENDER DIFFERENCES

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Background: Recent investigations demonstrate important role of estrogens in occurrence and progression of non-small cell lung cancer (NSCLC) as well as expression in the lung tumor tissue of estrogen receptor beta (ERbeta) that are a good prognostic markers of NSCLC. Thus, ERbeta seems to be important pathogenetic factor of NSCLC and target for antiestrogen therapy. But the data about ERbeta in the NSCLC are not numerous till now and results differ significantly because of using semiquantitative methods for estimation only. That is why we have developed a new immunofluorescence flowcytometry methodology for quantitative evaluation of ERbeta expression and used it for

study ERbeta expression in the NSCLC patients – totally and separately in female and male because of well known gender differences in NSCLC disease progress.
Methods: NSCLC surgical biopsy specimens of 32 patients (16 women and 16 men) were analyzed by flowcytometry. Single-cell suspensions were incubated with primary and isotype antibodies (anti-ERbeta 14C8 and IgG2a, Abcam) overnight and with secondary FITC-conjugated antibody (F2772,Sigma) for 1.5h. Mean cell fluorescence and number of stained cells were analyzed with WinMDI software and Kolmogorov-Smirnov statistical approach respectively. ERbeta expression was estimated as ratio of the specific parameter (level or intensity) to the same isotype one. MCF-7 cell culture was characterized and used as a reference for the antibody activity control. Three levels of ERbeta expression rate were used for the comparison: high – more than in 50% of the cells; moderate – in 30-49%; low – less than in 30% of the cells.
Results: Generally in all the NSCLC patients investigated ERbeta was revealed in about 80% of cases with significant differences in intensity of ERbeta expression in various tumors – from 8% to 77%. Low ERbeta expression was shown in 44%, high – in 18% and moderate ERbeta expression – in 38% of patients. 2. In women mean ERbeta expression level was in about 1,4 times higher as compared to men (37% and 27% of patients respectively). 3. High ERbeta rate was revealed more frequently in women than in men – in 31% and 6% of patients respectively. Moderate ERbeta expression rate was also often in women than in men – in 50% and 31% of patients respectively. Antipodal, low ERbeta expression rate was revealed more frequently in women than in men – in 19% and 63% of patients respectively. 4. The same gender differences were shown for high, moderate and low intensity of ERbeta expression.
Conclusion: 1. NSCLC is characterized by ERbeta expression in most of the patients with high and moderate level in about half of cases. 2. Higher ERbeta expression in women than in men could be one of the reasons of the gender differences in NSCLC disease progress. 3. We believe that at least half of the NSCLC patients (especially women) with ERbeta expression could benefit from adjuvant antiestrogen treatment. Thereby of ERbeta have to be obligate index among the other tumor markers studying in NSCLC patients. Supported by Russian Foundation for Basic Research (Grants N 10-04-00551 and N 11-04-00542).
Keywords: Non-small cell lung cancer, estrogen receptor beta, immunofluorescence, flow cytometry

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P2.155 L861Q HETEROZYGOUS MUTATION IN EXON 21 MAYBE PROMINENT IN PULMONARY MUCOEPIDERMOID CARCINOMA

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Background: The incidence of pulmonary mucoepidermoid carcinoma PMECï is extremely rare. Little is known about its molecule events . Although it usually has an indolent behavior, some PMEC show more aggressive, with 5-year survival as low as 30% for the high-grade or nodes metastasis patients. Epidermal growth factor receptor(EGFR) mutation status is common in East Asia non-small cell lung cancer, but it is unknown for EGFR mutation status in PMEC, which has the same histological origin from pulmonary epithelium .The aim of this study is to detect the EGFR mutation status in PMEC so as to discuss the feasibility of targeted treatment in this disease.
Methods: From January 2001 through December 2009, 20 PMEC patients (11 male and 9 female) were treated in our center. All of the patients were treated with surgery and diagnosed by pathology. Sequencing analysis was used to exam exons18-21 of the EGFR gene mutation.
Results: The exon21 L861Q heterozygous deletion mutation was found in five patients. The most homonymy mutation type was in exon20, an SNPc.2607GA (p.Q787Q) was detected in nine out of 20 tumor samples . None case was with a heterozygous exon19 deletion mutation. One case was with a homonymy exon18 mutation (I760I). Six cases had no mutation among the 20 patients.
Conclusion: As a meaningful rare EGFR mutation type, L861Q heterozygous mutation in exon21 may be a potential target of EGFR-directed treatment in pulmonary mucoepidermoid carcinoma. The further studies are needed in the future.

Keywords: mucoepidermoid carcinoma, EGFR mutation, Pulmonary

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.156 TRANSCRIPTOME COMPARISONS OF LASER MICRODISSECTED VS. MACROSCOPIC LUNG SAMPLES.

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Background: Determining cell-specific expression patterns in transcriptome discovery endeavors may be important for the precision of cancer cell signatures. Here we describe the use of an expression microarray study on non-small cell lung cancer (NSCLC) samples and surrounding tissue, comparing macroscopic lung tumor and tissue samples ("grind and bind"), versus tumor and alveolar compartment cells laser capture microdissected (LCM) from the same macroscopic lung samples.
Methods: An initial set of 32 pairs of macroscopic tumor and non-tumor samples (18 pairs adenocarcinoma, 14 pairs squamous-cell carcinoma,) was selected for bulk/macro sampling. Of these, all were reanalyzed using laser capture microdissection (LCM) for sampling the tumor (T) and nontumor (NT) cells. For macroscopic samples, 50 to 80 μg of tissue was used to isolate total RNA. Gene expression profile was determined using Affymetrix Human Genome Gene 1.0 ST genechip. For the LCM samples, from representative slides histologically confirmed and mapped by a pathologist, approximately 1000 tumor or nontumor alveolar cells/sample were collected by LCM; too few bronchial cells were available to analyze by microarray in this first sampleset. cDNA was amplified using Nugen Pico amplification system. QA at each step was rigorous, replicates performed, and individual samples or batches discarded if sub-optimal.
Results: Genes that were differentially expressed at least x with an adjusted p-value <. were selected as candidate genes. From our macroscopic sample set, in the adenocarcinoma group genes were up-regulated in tumor tissue and genes were down-regulated.Compared to our macroscopic samples, in our LCM sampleset for the adenocarcinoma carcinoma, only a minority (-%) of genes appeared up- or down-regulated in both conventional macroscopic, and laser microdissected samples. The squamous cell carcinoma results are being analyzed. The top (based on LCM fold-change) up and down-regulated candidates for adenocarcinoma carcinoma are listed here in Column , and compared to macroscopic tissues in Column . [FC=fold change tumor versus nontumor].

Gene.Symbol	FC LCM	adj.P.Val LCM	FC Macro
SPINK	. 33.9	. 0.012	. 7.8
OCIAD	. 5.9	. 0.000	. 2.6
---	. 5.4	. 0.018	. 1.1
SNORAA	. 4.6	. 0.026	. 1.7
---	. 3.6	. 0.006	. 1.5
BAIAPL	. 3.4	. 0.036	. 1.7
GOLM	. 3.4	.0.049	. 2.5
MUC	. 3.2	. 0.006	. 1.5
EHF	. 3.1	. 0.041	. 1.7
DEPDC	. 3.1	. 0.013	. 1.6
WIF	-. -6.5	. 0.006	-. -4.5
GMFG	-. -6.6	. 0.048	-. -1.5
ABIBP	-. -6.6	. 0.003	-. -2.6
MRC	-. -7.8	. 0.034	-. -1.7
PECAM	-. -8.5	. 0.014	-. -2.1
HBB	-. -8.6	. 0.038	-. -2.9
FMO	-. -9.1	. 0.003	-. -3.0
CAV	-. -9.6	. 0.003	-. -2.9
FABP	-. -12.5	. 0.007	-. -8.6
SFTPC	-. -22.6	. 0.008	-. -3.2

Conclusion: LCM-coupled microarray expression profiling identifies a large number of differentially expressed transcripts that are distinctly different from macroscopic lung tissue samples, suggesting that admixture from stromal cells in tumors likely is a significant confounder for expression signatures of lung cancer. This implies requisite caution when looking at conventional discovery datasets for cancer signatures. A microdissected bronchial epithelium dataset is currently being accrued to refine these results. Layering with epigenome-wide data is ongoing.
Keywords: Microarray, transcriptome, Laser microdissection, Lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.157 SIGNIFICANCE OF DELTA-LIKE LIGAND 4 (DLL4) ON THE ANGIOGENESIS IN NON-SMALL CELL LUNG CANCER

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Background: Delta-like ligand 4 (Dll4) is a Notch ligand that is upregulated by vascular endothelial growth factor (VEGF) and hypoxia, and is reported to have a role in normal embryonic vascular development and in tumor angiogenesis. However, few studies have investigated the role of Dll4 in non-small-cell lung cancer (NSCLC). The aim of this study was to characterize the expression of Dll4 in NSCLC and to assess whether it is associated with other angiogenesis, or hypoxic markers.
Methods: Paraffin-embedded samples of 35 patients (21 male, 14 female; median age 71 years) undergoing complete surgical resection for pathological IA-IIIA NSCLC were studied retrospectively. Immunohistochemistry was used to evaluate the expression of the angiogenesis markers, including Dll4, VEGF, CD34, platelet-derived growth factor receptor (PDFGR)-beta, and hypoxia-inducible factor (HIF)-1alpha.
Results: The Dll4 expression was observed preferentially in the cytoplasm in 57.1% (20 out of 35) of NSCLC. The expression was not significantly associated with any clinicopathological factors, including age, sex, smoking history, histology, differentiation, vascular invasion, lymphatic permeation, and pathological stage. The Dll4 expression showed a significant correlation with the VEGF expression (P=0.0024), but did not have any correlations with other angiogenesis and hypoxic markers. In the cases which expressed VEGF, the Dll4 expression was significantly associated with PDGFR-beta expression (P=0.014).
Conclusion: Dll4 is expressed with more than half of NSCLC samples, and the expression is associated with VEGF. Under VEGF signaling, Dll4 may have an important role to induce PDGFR-beta, which increase endothelium in NSCLC.
Keywords: DLL4, NSCLC, angiogenesis

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.158 METHYLATION EVENTS IN LUNG CANCER: WHOLE GENOME EXPLORATIONS OF PAIRED TUMOR AND NON-TUMOR CLINICAL SAMPLES

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Background: In lung cancer, hypermethylation of specific gene promoters is found during the early histological stages. Thus far, surveys of methylation have focused on specific gene panels (e.g., 5–20 genes) while some large-scale studies have examined longer gene lists or larger sets of CpG islands. To explore common methylation events on a genome-wide scale, we analyzed the methylation profiles of paired tumor and non-tumor samples using the HELP assay, which yields information on 1.2 million fragments throughout the genome.
Methods: The HELP (HpaII tiny fragment Enriched by Ligation mediated PCR) assay is based on restriction enzyme libraries generated by methylation sensitive (HpaII) and methylation insensitive (MspI) isoschizomers and allows robust assessment of methylation status by comparing ratios of HpaII to MspI-generated fragments co-hybridized to a Nimbelgen custom high-density microarray. A wet-lab platform and a bioinformatic and statistical pipeline exist at our institution for this purpose. Because of template requirements, (3ug total DNA), only macroscopic tumor and non-tumor samples were rexamined.
Results: Preliminary analyses of 9 paired Adenocarcinoma samples separated tumor and non-tumor samples into clades based on their HpaII fragment profiles, although some exceptions were observed. We identified 1921 fragments (corresponding to 2 CpG sites each) that were highly significant ($p=5e^{-4}$). Of these, 1781 (93%) were hypermethylated in tumor, with the vast majority occurring within the gene body or promoter (1234 loci and 199 loci, respectively). In the opposite direction, 140 fragments were significantly hypomethylated in tumor. Of these, 44 were located within gene bodies, 3 within non-CGI promoters, and 93 within repetitive regions. We could identify both

known (e.g: HIC1, TYMS) and as yet unreported genes (e.g: (DICER1, HIST1H2AB, HIST1H3C) hypermethylated in their promoter regions in tumor versus non-tumor.
Conclusion: We show that individual methylation events are common in the adenocarcinoma genome, and can help differentiate adenocarcinoma from surrounding parenchyma. We are currently expanding our sample set, including squamous cell carcinoma, working on bisulfite sequencing validation of methylation at select loci, functionally evaluating those high-resolution loci, as well as embarking on integration with other genome-wide epigenetic and expression data. Supported by NIH-5RC1-CA14542

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P2.159 THE RELEVANCE BETWEEN EGFR GENE MUTATION AND AMPLIFICATION IN CLINICOPATHOLOGICAL CHARACTERISTICS IN CHINESE WITH NSCLC

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Background: Epidermal growth factor receptor (EGFR)-targeted therapy takes an important role in the treatment of patients with non-small cell lung cancer (NSCLC).. The EGFR mutation and amplification are predictive of response to different races with EGFR-targeted therapy. This study purposed to investigate the relevance between gene mutation and gene amplification regarding on clinical profiles and pathological characteristics in Chinese NSCLC patients.
Methods: Tumors from 205 operated patients of NSCLC from Nov, 2009 to Jan, 2011 were selected to determine EGFR gene mutations and amplifications. All these subjects had detailed demographic and clinical information available from Sun Yat-sen University Cancer Center Surveillance System. All the tissues were detected either by Real-time PCR for gene mutations in exon 19 and exon 21 or by Fluorescence in situ hybridization (FISH) for gene amplification. Chi-square ($\chi 2$) test was performed to analysis the relevance between EGFR mutation and gene amplification in different variables.
Results: The median age was 59 yrs (range: 29-80). There were 138 males (67%) and 67 (33%) females. Fifty-eight percent (119) of patients were smokers and 42% (86) were non-smokers. All the surgical specimens were identified with adenocarcinoma in 147, squamous-cell carcinoma in 52, adenosquamous carcinoma in 3, sarcomatoid carcinoma in 2, and lymphoepithelioma-like carcinoma in 1. Eleven percent (23) of patients pathologically presented in stage IA , 30% (62) in stage IB , 3% (5) in stage IIA , 12% (25) in stage IIB , 25% (51) in stage IIIA , 9% (19) in stage IIIB and 10% (20) in stage IV. The mutation frequency in EGFR was 32% (66 of 205 patients), including deletions in exon 19 (16%) and point mutations in exon 21 (16%). EGFR mutations occured in 60% of females versus 19% of males (P=0.000), 57% of non-smokers versus 14% of smokers (P=0.000), and 43% of patients with adenocarinoma versus 5% of non-adenocarcinoma (P=0.000). EGFR gene amplification was detected in 62128 of 205) of patients. The amplification frequency was not associated with age (P=0.624), gender (P=0.112), pathological subtype (P=0.190), smoking status (P=0.209) and stage (P=0.127). No relevance was observed between either EGFR gene mutation or amplification and tumor markers including CEA, SCC, NSE, CyFra21-1, and TSGF. There was a significant relevance between EGFR gene mutation and gene amplification (P=0.000). In patients with positive mutations, 86% (57 of 66) of patients involved in gene amplification. Instead, 45% (57 of 128) of patients with positive amplification involved gene mutations.
Conclusion: EGFR mutations are more common in Chinese patients with adenocarcinomas, nonsmokers and females.. EGFR gene amplifications harbor a high frequency in Chinese patients but no relevance is observed between amplification and clinicopathological characteristics.. There is significant relevance between gene mutations and amplifications. The EGFR mutation should be used as a clinical decision parameter to predict response to EGFR-tyrosine kinase inhibitors.
Keyword: NSCLC, EGFR gene mutation,amplification,

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P2.160 MICRORNA EXPRESSION PROFILES IN LUNG ADENOCARCINOMA TISSUES VERSUS ADJACENT LUNG TISSUES USING NEXT-GEN SEQUENCING

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Background: MicroRNAs (miRNAs) are small noncoding RNAs about 22 nucleotides in length and regulate mRNA expression by binding to 3'UTR of mRNAs and causing translation repression or degradation of mRNAs. Recent studies have revealed that microRNAs play important regulatory roles in carcinogenesis. However, how miRNAs regulate lung carcinogenesis is generally unknown. We used high-throughput sequencing technology to investigate miRNA expression profiles in a pilot study of paired lung adenocarcinoma amd noncancerous lung tissues.
Methods: Total RNA was isolated by Trizol from 7 pairs of lung adenocarcinoma tissues and noncancerous lung tissues, from the same patients. Small RNA library of each total RNA was constructed with Illumina's Small RNA Sample Prep Kit, followed by high-throughput sequencing. Statistical differences in microRNA expression between groups were analyzed by GenePattern software.
Results: More than 400 miRNAs were detected in the small RNA libraries. We compared the same 346 miRNAs between the two macroscopic sample sets (tumor vs. nontumor). There were 28 miRNAs with p value≤3.05E-04 and FDR≤0.049. Among the 28 miRNAs, four miRNAs (miR-195, miR-204, miR-551b and miR-598) were downregulated in cancer, and the other 24 miRNAs were upregulated in cancer, including miR-877, miR-9, miR-212, miR301b, miR-708, miR-642, miR-147b, miR210, miR-625, miR-21 and others. Comparing our top 28 miRNAs with the top 43 miRNAs from Yanaihara/Harris Cancer Cell 2006 using spotted microarrays, we found five miRNAs in common; the direction of T-NT differences of three of these common miRNAs (miR-21, miR-210 and miR-212) were the same.
Conclusion: MicroRNA expression profiling was performed by high-throughput sequencing, revealing 28 miRNAs with obvious statistical differences in expression between lung tumors and non-tumor tissues. Our microRNA expression signature was quite different from that of Yanaihara/Harris Cancer (Cell 2006) perhaps in part the platform (next gen sequencing) differs from Yanaihara's data (microarray), and in part because our data are from lung adenocarcinoma tumor tissues only (versus all histologies of NSCLC). Studies are ongoing to construct small RNA libraries from additional T-NT pairs, to validate the results with realtime PCR, and to generate microRNA:mRNA inverse correlations to test experimentally, using affinity binding assays and exogenous expression approaches we are developing.
Keywords: next-gen sequencing, gene regulation, microRNA

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P2.161 SERAL ESTRADIOL LEVELS IN SQUAMOUS AND ADENOMOUS LUNG CANCER AND EXPRESSION AND CLINICAL PATHOLOGICAL CORELATIONS OF ESTROGEN RECEPTORS AND CYP19

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Background: To Detect the seral estradiol(E2) levels in squamous and adenomous lung cancer and expression and clinical pathological corelations of estrogen receptors and CYP19.
Methods: Seral estradiol levels were dectected by RIA in female or postmenopausal women, with 76 cases of squamous adenomous and 58 cases of

squamous lung cancer patients. IHC was applied to detect the expression of ERÎ±,ERÎ²and CYP19 and analyze the clinical correlations with adenomous and squamous lung cancer.
Results: E2 levels were significantly higher in adenomous lung cancer patients than those in squamous lung cancer patients(P<0.001). The expressions of ERα,ERβin adenomous lung cancer patients were higher than those in squamous lung cancer patients(P<0.001). The expression of ERαin female than those in male(P<0.05). The expressions of ERβwere higher in highly differentiated adenomous lung cancer patients than those in poorly differentiated adenomous lung cancer patients. The expressions of CYP19 and ERβ were correlated with seral E2 expression P<0.01 r =0.561.
Conclusion: The carcinogenesis and development of adenomous lung cancer is correlated with E2 function. The expression of CYP19 and ERβ could be a target for anti-endocrine therapy for adenomous lung cancer.
Keywords: Lung cancer, estrogen receptor, CYP19

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P2.162 PGP AS A PATHOGENETIC FACTOR OF NON-SMALL CELL LUNG CANCER

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Background: Pgp is an ATP-dependent drug efflux pump for compounds with broad substrate specificity. It is responsible for decreased environmental carcinogen accumulation in normal tissues as well for drug accumulation in tumor cells mediating the development of multidrug-resistance to anticancer drugs. To answer the question if Pgp is a substantial factor taking part in lung carcinogenesis we have compared frequency and intensity of Pgp expression in normal and tumor tissues of non-small cell lung cancer (NSCLC) patients as well as the parameters in both of these groups with normal tissue of lung metastasis patients. We believe because in the latter case lung tissue is the only niche for metastatic cells it could be considered as the most appropriate "normal" control for the comparison with NSCLC and adjacent lung tissue.
Methods: Cell suspensions prepared from surgical biopsy specimens of NSCLC (37 samples), adjacent normal lung tissue (36 samples) and normal lung tissue of patients with lung metastasis (33 samples) were analyzed by flow cytometry. Staining procedure was performed with FITC-conjugated monoclonal antibody to external epitope of Pgp, clone 17F9, Becton Dickinson. FITC-conjugated mouse IgG2b, k in equivalent concentrations were used as isotypic control antibodies. Mean cell fluorescence as well as number of stained cells were analyzed with WinMDI software and Kolmogorov-Smirnov statistical approach respectively. Pgp expression was estimated by two parameters: ratio the mean cell fluorescence of the cells stained with anti-Pgp antibody to the mean cell fluorescence of the cells stained with isotypic antibody ratio as well as the number of specifically stained cells.
Results: 1. It was revealed increase Pgp expression in NSCLC compared to adjacent normal lung tissue. Median of Pgp expression frequency was 48% vs. 32% (p=0,015) and intensity of Pgp expression in about 1,4 times higher (p=0,038). 2. It was not shown any difference in Pgp expression frequency (p=0,497) and intensity (p=0,265) between NCSLC and normal tissue of lung with different cancer metastasis. 3. The parameters of Pgp expression were significantly decreased in normal lung tissue of NSCLC patients compared to normal lung tissue of the patients with lung metastasis (p=0,049 for intensity and p=0,031 for frequency of Pgp expression).
Conclusion: Increase Pgp frequency and intensity in NSCLC as compared to adjacent normal lung tissue, the close values to these indexes of NCSLC and normal tissue of lung with different cancer metastasis as well as decrease of Pgp expression in normal lung tissue of NSCLC patients compared to normal lung tissue of the patients with lung metastasis shows that ratio of Pgp in normal lung tissue is an important pathogenetic factor of NSCLC. We believe also that the decrease of Pgp expression in normal lung tissue could be substantial factor promoting the process of lung carcinogenesis. Supported by Russian Foundation for Basic Research (Grants N 10-04-00551 and N 11-04-00542).
Keywords: Non-small cell lung cancer, Pgp, pathogenetic factor, flow cytometry

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P2.163 INCREASED LEVEL OF SPD-L1 IN SERUM AND PLEURAL EFFUSION IN PATIENTS WITH LUNG CANCER AND ITS CLINICAL SIGNIFICANCE

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Background: Costimulatory signals play important roles in the regulation of immune response. PD-1/PD-L1 pathway delivers a potent co-inhibitory signal to T cells, resulting in T cell exhaustion and dysfunction. In addition to membrane-bound costimulatory molecules, soluble forms of costimulatory molecules have been found to exert important effect in immune regulation in cases with tumor, autoimmune diseases, transplantation and chronic viral infection. In this study, we investigated the existence of sPD-L1 in serum and malignant effusion of patients with lung cancer and to evaluate its clinical significance.
Methods: sPD-L1 in serum from 87 healthy volunteers, 68 cases of pneumonia, 90 cases of treatment naïve lung cancer between 2008-2010 were analyzed using ELISA method with our previously developed anti-human PD-L1 antibody. Effusion sPD-L1 concentration was also determined in 16 cases with malignant pleural effusion using the same method. Serum tumor marker of CEA, NSE and CYFRA211 and cytological study were used to confirm the diagnosis of malignant effusion. The results together with the clinical data in demography, phenotype of lung cancer as well as its response to treatment over time were analyzed.
Results: A higher level of sPD-L1 level in patients with lung cancer group (1.94±1.35ng/ml) was found compared with pneumonia group (1.57±0.83ng/ml, $P<0.05$) and control group (0.93±0.26ng/ml, $P<0.01$). No statistical correlation of sPD-L1 with age, sex, smoking status, primary size of tumor was found in lung cancer group. In subgroup analysis, we found sPD-L1 in NSCLC group (2.04±1.34 ng/ml) was higher than that in SCLC group (1.29±0.44ng/ml) ($P<0.05$). Among NSCLC patients, sPD-L1 of adenocarcinoma group (2.17±1.43ng/ml) was relatively higher than squamous carcinoma group (1.97±1.32ng/ml) but without significant statistical difference ($P>0.05$). sPD-L1 level increased progressively with progression of lung cancer, which was 1.08±0.20ng/ml in stage I-II group,1.93±1.56ng/ml in stage III group and 2.01±1.32ng/ml in stage IV group(compared with stage I-II, $P<0.05$). Patients with N3 metastasis was also found to have a higher sPD-L1 expression than N2 and N1 metastasis group, which were 2.23±1.77ng/ml, 1.91±1.27ng/ml and 1.71±0.94ng/ml respectively, but no significant statistical difference was found among the three groups ($P>0.05$). In patients with malignant pleural effusion, sPD-L1 level in effusion (7.21±5.64ng/ml) was found nearly six fold increased compared with corresponding serum oncentration($P<0.01$). In addition, the dynamic changes of sPD-L1 seemed to be correlated with serum tumor markers and could reflect tumor response to chemotherapy according to RECIST criteria to some extent. The relationship of sPD-L1 with overall survival remained to be investigated.
Conclusion: The existence of circulating sPD-L1 in human serum and pleural effusion is closely correlated with progression of lung cancer and might play a potentially important role in local and systemic tumor immune tolerate and escape.
Keywords: soluble programmed death ligand 1 (sPD-L1), Lung cancer, costimulatory molecule

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P2.164 ROUND ROBIN TEST TO EVALUATE THE REPRODUCIBILITY OF AN IMMUNOHISTOCHEMICAL SCORE WITH THERAPEUTIC RELEVANCE THAT DICHOTOMIZES NON-SMALL CELL LUNG CANCER INTO TUMORS WITH HIGH AND LOW EPIDERMAL GROWTH FACTOR RECEPTOR EXPRESSION

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Background: The randomized phase III FLEX study demonstrated that the addition of cetuximab to chemotherapy significantly improved overall survival compared with chemotherapy alone in the first-line treatment of advanced non-small cell lung cancer (NSCLC). A positive association between high tumor epidermal growth factor receptor (EGFR) expression (score ≥200 as measured by immunohistochemistry [IHC] on a continuous scale of 0–300) and clinical outcome in patients receiving chemotherapy plus cetuximab has been reported. This international round robin test (RRT) evaluated the inter-observer reproducibility of the EGFR IHC score.
Methods: After a feasibility study had been completed, a RRT was performed. Serial sections of a tissue microarray (TMA) comprising NSCLC tumor cores were stained using the DAKO EGFR pharmDX™ kit and DAKO autostainer. Staining was initially evaluated in a central reference laboratory. Ten international expert lung cancer pathologists then evaluated EGFR expression for 30 selected TMA cores. The selected cores, which included tumors of different histologies, were categorized after reference evaluation, as clearly high (n=10), clearly low (n=11) or equivocal (n=9), relative to the threshold EGFR IHC score of 200. The EGFR IHC score was calculated as the sum of the products of tumor cell membrane staining intensity (graded 0–3+) and the percentage of cells demonstrating each staining intensity, according to the following formula: EGFR IHC score = 1 x (% cells staining weakly [1+]) + 2 x (% cells staining moderately [2+]) + 3 x (% cells staining strongly [3+]). Analysis of between-rater agreement was based on the allocation of the EGFR IHC score into low (<200) and high (≥200) EGFR expression groups. The overall concordance rate with respect to the reference evaluation was defined as the mean of the per-rater concordance rates with respect to the reference evaluation. Kappa coefficients were calculated for the comparison of each rater with the reference evaluation.
Results: The RRT showed a high inter-observer agreement in EGFR IHC scoring among study participants, with an overall concordance rate of 91% and a mean kappa coefficient of 0.81. Tumors with a reference EGFR IHC score clearly below or above the cut-off (<150 or ≥250) were each categorized with an almost perfect mean concordance rate of 98%. Samples with a reference EGFR IHC score around the cut-off (≥150–<250) showed a high mean concordance rate of 74%.
Conclusion: The RRT demonstrated that assessing EGFR expression by this IHC scoring method allowed a highly reproducible allocation of NSCLCs into high or low EGFR expression groups, based on a cut-off score of 200. The study thereby indicates that this evaluation of the EGFR IHC score may be a clinically reliable method to facilitate the selection of patients with NSCLC expressing high levels of EGFR for first-line chemotherapy plus cetuximab who are those most likely to derive a substantial treatment benefit.
Keywords: EGFR, immunohistochemistry, Round robin test

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P2.165 DIFFERENTIAL EXPRESSION OF LONG INTERGENIC NON-CODING RNA IN LUNG ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA

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Background: Recent studies have identified a novel family of long intergenic non-coding RNAs (lincRNAs). At the present time, the function and mechanism of action of the vast majority of lincRNAs is unknown. However, there is emerging evidence that lincRNAs including HOTAIR, Kcnq1ot1, AIR, XIST and lincRNA-p21 are involved in widespread repression of gene expression through their interaction with chromatin-remodelling complexes. Furthermore, the expression of a number of lincRNAs including HOTAIR and MALAT-1 has been linked to the development of cancer.
Methods: Samples used in this study were the tumours and matching control tissue from six patients with lung adenocarcinoma and six patients with squamous cell carcinoma. Total RNA was extracted using the mirVana miRNA isolation kit (Ambion) according to the manufacturer's instructions. RNA was eluted in 100 l RNase-free water (Promega) and stored at -80°C. lincRNA expression profiling was carried out on total RNA extracts by Two-Color Microarray-Based Gene Expression Analysis (Agilent Technologies), which examined the expression of 27,958 Entrez Gene

RNA and 7,419 lincRNAs. qRT-PCR was used to confirm the expression of lincRNAs using the two-step TaqMan® reverse transcription polymerase chain reaction protocol (RT-PCR) and normalized to 18S. The 2-(Î”Î”CT) method (Livak & Schmittgen, 2001) was used to determine relative-quantitative levels of individual lincRNAs and were expressed as the fold-difference to the control.
Results: Microarray examination revealed differential expression of >1200 genes in both adeno- and squamous carcinomas, with some of the genes exhibiting up to 70-fold change. Of the 7419 lincRNAs examined, there were 123 up- and 97 down-regulated in both sample groups with > 2 fold-change. Further analysis to identify lincRNAs with the greatest change in expression (>1000 fluorescence units) demonstrated differential expression between the adeno- and squamous samples; only a small number of lincRNAs in adenocarcinomas were identified (5 up-regulated, 7 down-regulated). In contrast, there were 61 down-regulated and 12 up-regulated lincRNAs in squamous carcinomas. The microarray data also revealed there was no correlation between the changes in individual lincRNA levels and the expression levels of the mRNAs flanking them. Among the characterised lincRNAs, the expression levels of HOTAIR were shown to be reduced in both squamous and adenocarcinomas, whilst MALAT-1 expression was reduced in squamous but not adenocarcinoma samples, a result confirmed by qRT-PCR analysis. This finding contradicts other studies that have presented an increase in HOTAIR and MALAT-1 expression levels in cancer cells.
Conclusion: Development of adeno- and squamous cell lung cancer is associated with changes in expression of distinct groups of lincRNAs including HOTAIR and MALAT-1 that was independent of the expression of surrounding genes.
Keywords: intergenic, non-coding RNA, Lung cancer

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P2.166 IMPACT OF KRAS MUTATIONS (KRASMUT) ON CLINICAL OUTCOME IN STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) AND THEIR RELATIONSHIP WITH OTHER BIOMARKERS.

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Background: Kras accounts for 90% of RAS mutations in lung adenocarcinoma and approximately 97% of Krasmut in NSCLC involve codons 12 or 13. Kras tumour status cannot be easily predicted on the basis of smoking history alone. Krasmut status might help in the prediction of clinical outcome for pts receiving different treatments. The role of Krasmut as a predictor of response for pts with stage IV NSCLC treated with chemotherapy alone is poorly understood. Emerging data suggest that Krasmut are negative predictors of benefit from both adjuvant chemotherapy and anti-EGFR–directed therapies.
Methods: From August 2009 to January 2011 we analyzed Krasmut in samples from 114 stage IV NSCLC pts. We analyzed different types of Kras point mutations in codons 12 and 13 by direct DNA sequencing from paraffin-embedded tumor tissue (PETT). We also used DNA sequencing from PETT to analyze other mutations (EGFR) and mRNA gene expression to evaluate BRCA1and RAP80 levels. We evaluated the presence of Krasmut according to histological subtype.
Results: Krasmut were found in 21.9% (25 /114) Out of pts harboring Krasmut the median age was 59 y, 64% were male. According to smoking status 8% were never smokers, 32% former smokers and 60% current smokers. According to histology 72% were adenocarcinoma, 12% squamous cell carcinoma and 8% bronchioloalveolar carcinoma. According to PS ECOG 44% were PS0, 32% PS1 and 24% PS2. The distribution of metastatic sites was 37.8% lung, 11.8% lymph nodes ,11.8% CNS and 9.9% bone. The frequency of Krasmut subtypes were: G12C 44%, G12V 20%, G12A 16%, G12D 12%, G13D 4%, G13V 4%. EGFR mutation was present in 1

patient (4%). BRCA expression levels were 36% low, 4% intermediate, 0% high and 32% insufficient sample. RAP80 expression levels were 4% low, 24% intermediate, 12% high and 32% insufficient sample. For pts treated in first line with platinum based chemotherapy (21/25) the response rate (RR) was as follows Complete response 4%, Partial Response 12%, Stable Disease 9.5% and Progressive Disease 47.5%. Time to progression (TTP) was 6.6m and Overall Survival (OS) was 12.5m. TTP and OS according to Krasmut were: G12C 10.1m/15.4m, G12V 5m/14.1m, G12A 2.3m/8.5m, G12D 9.1m/9.6m ,G13D 3m/8.3m, G13V 3.2m/6.9m. Pts received a median of 2 lines of treatment (range 1-5). Seven pts (33.3%) were included in specific targeted studies for Krasmut pts beyond the second line. No differences were found in RR or TTP according to PS, gender smoking history, Krasmut subtype and BRCA1 or RAP80 levels. No differences were found in OS according to gender, smoking history, Krasmut subtype and BRCA1 or RAP80 levels except for PS (p=0.0033)

Conclusion: Krasmut were more frequent in male, smokers and former smokers and pts with adenocarcinoma. PS was associated with differences in OS. No other variables were associated with differences in RR, TTP or OS. The small sample size could explain the lack of differences.

Keywords: Kras mutations, Non-Small-Cell Lung Cancer, stage IV, biomarkers assesment

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P2.167 BLIND PREDICTION OF RESPONSE TO NEOADJUVANT TREATMENT WITH ERLOTINIB IN EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC) USING KINASE ACTIVITY PROFILES.

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Background: It has been well established that subcategories of NSCLC patients may benefit from epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI's), notably those with cancers that harbor mutated EGFR and wild type kRAS. However, certain patients lacking EGFR mutations might also benefit from TKI treatment. Previously (Hilhorst et al, J. Clin. Oncol. 28:7s, 2010 (suppl abstr 10566), we have shown that a classifier based on kinase activity profiles generated in the presence and absence of a kinase inhibitor can predict erlotinib response of NSCLC patients in a neoadjuvant setting. The aim of the current study was to evaluate this classifier using a blinded test set of patient tumor samples

Methods: Frozen tumor tissue was obtained from NSCLC patients (stage IA-IIIA) who were given 21 days of neo-adjuvant treatment with erlotinib prior to complete surgical resection. All specimens were analyzed for EGFR and kRAS mutation status. Tissue cryosections were lysed in M-PER buffer supplemented with phosphatase and protease inhibitors. Kinase activity profiles of the lysates were generated in the presence and absence of erlotinib on PamChip® microarrays comprising 144 tyrosine containing peptides derived from known human protein phosphorylation sites. Clinical response evaluation to erlotinib was based on histopathological examination of the tumor tissues and metabolic changes. A classifier for response prediction was established for this training set and subsequently applied to a blinded test set of 13 patients.

Results: Phosphorylation profiles were ATP dependent and differed between the patient samples. Addition of erlotinib to the samples resulted in inhibition of signals. Based on these on-chip inhibition profiles, a PLS-DA (partial least square discriminant analysis) classifier was obtained that distinguished responders and non-responders in the training set of 14 samples. Leave-one-out cross validation resulted in correct classification of 11 samples (79%). Application to the blinded test set of 13 samples resulted in correct prediction of outcome for 11 of 13 samples (85%). The training set contained one sample with an EGFR exon 19 mutation, one with an exon 20 in frame deletion and 2 samples with kRAS mutations. The test set contained two samples with exon 19 mutations and two samples with kRAS mutations. These results suggest that more patients might be eligible for erlotinb treatment.

Conclusion: This blinded study validates the use of a classifier based on kinase activity profiles of

patients' own tumor tissue to predict the response to treatment. This test that measures drug effects at the molecular level, may be an important step towards personalized medicine

Keywords: erlotinib, NSCLC, response prediction

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P2.168 CIRCULATING MIRNA AS MINIMALLY-INVASIVE BIOMARKERS FOR ADENOCARCINOMA OF THE LUNG

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Background: Early diagnosis and the ability to predict the most relevant treatment option for individuals is essential to increase survival time for non-small cell lung cancer (NSCLC) patients. Adenocarcinoma (ADC) NSCLCs are the single biggest cancer killer and so there is an urgent need to identify minimally-invasive biomarkers to enable its early diagnosis. Recent studies, by ourselves and others, analysing circulating miRNAs on a one-at-a-time basis, suggest that such miRNAs may have potential as biomarkers. Our aim here was to apply global profiling approaches to explore if miRNAs exist in the peripheral circulation of patients and with adenocarcinoma (ADC) and, if so, do they have potential as diagnostic biomarkers.

Methods: This study involved total RNA isolation from 80 sera specimens including those from patients with ADC of the lung (n=40; equal numbers of Stages I, II, III and IV) and age- and gender-matched controls (n=40 each). 667 miRNAs were co-analysed in these specimens using TaqMan low density arrays. Individual miRNAs were selected for qPCR validation.

Results: Successful isolation of RNA was achieved from all sera specimens. The quantities of RNA in ADC and control sera did not differ significantly. A panel of eight miRNAs, however, was found to be present at significantly higher levels in ADC compared to control sera. These include miR-30c-1*, miR-140, miR-345, miR-616*, miR-146b-3p, miR-566, miR-550 and miR-939. The trend observed using subsequent qPCR analysis reflected our global screening ($p<0.05$). Furthermore, a positive correlation was noted between miRNA expression and early tumour stage (i.e. Stages I & II); although the numbers of specimens included was too limited to derive a meaningful outcome on this and this trend was not observed at Stages III & IV.

Conclusion: Differences in miRNA profile identified here suggest that circulating miRNAs may have potential as diagnostic biomarkers for ADC. Of particular interest, this Panel of 8 miRNAs never previously associated with serum or with ADC. More extensive studies including larger cohorts of serum/specimens from ADC, as well as other lung cancer and controls, are warranted to further explore this initial discovery.

Keywords: Circulating miRNA, Adenocarcinoma, Early Tumour Stage

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P2.169 THE EXPRESSION PROFILE AND ROLE OF THROMBOXANE SYNTHASE IN NON-SMALL CELL LUNG CANCER: CORRELATION WITH PATIENT SURVIVAL

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Background: Thromboxane synthase metabolizes PGH2 into thromboxanes, which are biologically active on cancer cells. TXS over-expression has been frequently reported in cancers, and has been associated a poor prognosis. TXS blockade inhibits angiogenesis and induces tumor cell death, providing a rationale for intervention. This study aimed to determine the expression profile of TXS, its link to tumor angiogenesis, and if it is prognostic and/or a survival factor in NSCLC.

Methods: TXS expression was examined in human NSCLC samples (protein and tissue) and matched controls by western analysis and IHC. TXS metabolite levels were measured in human NSCLC plasma samples and age-matched controls by EIA. A 200-patient NSCLC TMA was stained

for TXS and CD-31. Staining was correlated with clinical parameters, including 5-year patient survival. TXS expression pattern was correlated CD-31 (microvessel density). Stable TXS over-expressing clones were generated and their effect on tumor growth/survival was examined both in-vitro (BrdU) and in-vivo (xenograft mouse model).
Results: TXS was over-expressed in human NSCLC samples, relative to matched controls. Significantly increased TXS protein and TXB_2 metabolite levels were observed in protein and plasma samples respectively. TXS tissue expression were also significantly higher in adenocarcinoma ($p<0.001$) and female patients ($p<0.05$). While no significant correlation with patient survival was observed, TXS expression was significantly associated with microvessel density in the same patients. Stable TXS over-expression significantly increased tumor cell growth in-vitro and also increased tumor growth (and reduced survival) in-vivo.
Conclusion: TXS is over-expressed in NSCLC, particularly in the adenocarcinoma subtype and female patients. While it was not found to be prognostic, TXS over-expression significantly increased tumor growth both *in-vivo* and *in-vitro*, suggesting that TXS promotes tumor survival in NSCLC. Our study also noted a significant correlation of TXS with microvessel density, suggesting that the pro-tumor effects of TXS expression are at least partly mediated via tumor angiogenesis. Further studies using our *in-vivo* models will confirm preliminary observations.
Keywords: thromboxane B2, thromboxane synthase, angiogenesis, in-vivo models

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P2.170 ULTRASOUND MYOCARDIAL TISSUE CHARACTERIZATION BY INTEGRATED BACKSCATTER DETECTS PRECLINICAL MYOCARDIAL DAMAGE IN UNRESECTABLE LOCAL ADVANCED NON-SMALL CELL LUNG CANCERS TREATED BY RADIOTHERAPY

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Background: Radiotherapy plays an important role in the multimodality management of patients with lung cancer. However, patients who received radiotherapy had an increased risk of cardiovascular mortality and there has been so far no ideal tool for the early noninvasive real-time detection of radiation induced myocardial damage. The purpose of this study is to determine whether ultrasonic integrated backscatter (IBS) can be used as a noninvasive device to detect early myocardial damage in unresectable locally advanced non-small cell lung cancers treated by radiotherapy.
Methods: Forty six left unresectable locally advanced non-small cell lung cancer patients (stage IIB-IIIB) treated with Vinorelbine :40 mg/m2, IV, day 1 and day 8; Cisplatin: 40 mg/m2, IV, days 1-3 and radiotherapy: 66 Gy in 33 fractions were entered into this study. Calibrated myocardial IBS (CMIBS, assessed by comparison of the anterior wall (AW), inferior wall (IW), anteroseptum (AS) and posterior wall (PW) with pericardial IBS intensity), cyclic variation of IBS (CVIBS) and conventional echocardiography parameters (LVIDd: the left ventricular internal diameter at end-diastole; IVSTd: the intraventricular septal thickness at end-diastole; PWTd: the posterior wall thickness at end-diastole; LVDs: the left ventricular end-systolic dimension; EF: the left ventricular ejection fraction; FS: the left ventricular fractional shortening. The peak velocity of early (E) and late ventricular filling (A) were also determined for calculating the ratio E/A) were investigated before (group A), during (group B, 3 weeks, the cumulative dose was about 30Gy) and after radiotherapy (group C, 6 weeks, the cumulative dose was about 60Gy).
Results: CMIBS of AW and AS were significantly increased after radiotherapy both during (group B, $p<0.05$) and at the end of treatment (group C, $p<0.05$) and meanwhile CVIBS and E/A were decreased significantly throughout the treatment period (group B, $p<0.05$ for both; group C, $p<0.01$ for both) compared with the beginning (group A).
Conclusion: Myocardial IBS offers a promising approach for early noninvasive real-time detection and characterization of evolution of cardiomyopathy induced by radiotherapy in lung cancer patients.
Keywords: Lung cancer, Radiotherapy, Myocardial damage, Ultrasonic integrated backscatter

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.171 ACTIVITY-BASED PROTEOMICS: BIOMARKER IDENTIFICATION IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Lung cancer is the leading cause of all cancer related deaths and treatment is still suboptimal. Novel biomarkers with a reliable predictive significance which may additionally represent therapeutic targets are therefore of utmost importance. In biomarker discovery studies transcript or protein abundances are typically compared in normal versus disease states. However, crucial changes in enzymatic activities remain undetected. Based on the work of Prof. Cravatt and others, activity-based proteomics has become a promising option to circumvent this limitation. This study aims to establish a robust and high throughput activity-based proteomics platform and to investigate the role of serine hydrolase activity profiles as prognostic biomarkers in lung cancer.
Methods: A fluorophosphate derivate (CAS-Number: 353754-93-5) was used to covalently target serine hydrolases in proteomes derived from human lung adenocarcinoma biopsies and corresponding normal lung tissues (tumor cell content: >50%, TNM-stage: I-IV). Tagged proteins were subsequently affinity purified and analyzed using a directed mass spectrometry based approach (LTQ-FTMS, Thermo Finnigan). Data were qualitatively analyzed using the Mascot 2.2 search engine and Progenesis LC-MS version 2.5 (Nonlinear Dynamics) was employed for relative quantification.
Results: The strategy described above results in the simultaneous qualitative and quantitative analysis of serine hydrolase activities in complex proteomes, thereby representing a valid alternative to activity-based proteomics approaches described so far. The analysis of 40 pairs of fresh frozen malignant and corresponding normal lung tissues in combination with clinical follow-up data led to the identification of two biomarker candidates that have previously not been associated with lung cancer.
Conclusion: Based on the results obtained in this study we conclude that activity-based proteomics represents a powerful strategy in the seek for novel biomarker candidates in human lung adenocarcinoma. Liu, Y., Patricelli, M.P. & Cravatt, B.F. Activity-based protein profiling: the serine hydrolases. Proceedings of the National Academy of Sciences of the United States of America 96, 14694-14699 (1999). Jessani, N., et al. A streamlined platform for high-content functional proteomics of primary human specimens. Nature methods 2, 691-697 (2005).
Keywords: Biomaker, NSCLC, Activity-based proteomics

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.172 EXAMINATION OF 12-LIPOXYGENASE AS A THERAPEUTIC TARGET IN NON-SMALL CELL LUNG CANCER: MECHANISMS CONTROLLING SURVIVAL AND INDUCTION OF APOPTOSIS FOLLOWING SELECTIVE INHIBITION

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Background: Platelet-type 12-LOX is an arachidonic acid metabolising enzyme resulting in the formation of 12(S)-HETE, which stimulates tumour cell adhesion, invasion and metastasis. The aim of this study was to examine the expression profile and role of this enzyme in NSCLC, and to determine if it is a potential target for intervention in-vitro and in-vivo.
Methods: A panel of retrospective resected lung

tumours was stained for 12-LOX expression by immunohistochemistry. A panel of NSCLC cell lines (A-549, SKMES-1, H-460) were treated with baicalein (100 nM, 1 μM, 10 μM), a selective inhibitor of 12-LOX, or 12(S)-HETE (100 ng/ml) and cell survival/proliferation examined by BrdU. Apoptosis following 12-LOX inhibition was examined (in all three cell lines) by High Content Screening and validated by FACS and DNA laddering. The effect of 12-LOX inhibition on NSCLC tumour growth and survival was examined in-vivo using an athymic nude mouse model (H-460 cell line). Gene alterations following 12-LOX inhibition (A-549, SKMES-1 and H-460 cell lines) were assessed by quantitative PCR arrays (Cancer PathwayFinder arrays to examine expression of a panel of 84 genes involved in tumourigenesis), and validated by RT-PCR.

Results: 12-LOX expression was observed to a varying degree in a range of human lung cancers with different histological subtypes. Baicalein significantly reduced proliferation/survival in all lung cancer cell lines, while 12(S)-HETE significantly increased proliferation. 12-LOX inhibition with baicalein also resulted in a significant increase in apoptosis, demonstrated by High Content Screeing (reduced f-actin content and mitochondrial mass potential) and confirmed by FACS and DNA laddering. Treatment with baicalein significantly reduced the growth of NSCLC tumours and increased overall survival in athymic nude mice. qPCR array data implicated a number of apoptosis/angiogenesis genes regulating these effects, including bcl-2, VEGF, angiopoietin 2, IGF-1, integrin A2 and A4.

Conclusion: 12-lipoxygenase is a survival factor and potential target in NSCLC, which is correlated with apoptosis and angiogenic factor expression. Selective targeting of this enzyme may have clinical benefit for the future treatment.

Keywords: apoptosis, in-vivo models, 12-lipoxygenase, 12-(S)-HETE

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P2.173 ANALYSIS OF MTOR SIGNALING PATHWAY BIOMARKERS IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH EVEROLIMUS AND DOCETAXEL IN A PHASE II CLINICAL TRIAL.

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Background: mTOR pathway activation is a critical oncogenic event in non-small cell lung cancer (NSCLC). Based on preclinical evidence of enhanced anti-cancer activity of docetaxel in combination with everolimus (RAD001) we conducted a translational phase II trial in advanced NSCLC. We also analyzed tissue-based markers of mTOR pathway activation.

Methods: Advanced stage NSCLC patients previously treated with not more than 2 prior regimens were enrolled to receive docetaxel (60 mg/m^2 on day 1) and everolimus (5 mg PO QD, daily for 19 days) combination on a 3-week cycle schedule. The primary endpoint was response rate and secondary endpoints included PFS, OS and safety assessment. Archival diagnostic tumor samples were evaluated for upstream and downstream markers of mTOR pathway activation (total and phosphorylated mTOR, Akt, S6, eIF4e and 4EBP1) by immunohistochemistry. The staining intensity of biomarker expression was used for this analysis. General linear models were employed to test differences in biomarker expression across different categories of tumor response and histology. The relationship between biomarker expression and patient age was assessed by Spearman correlation coefficient while the median PFS and OS were estimated by Kaplan Meier method.

Results: Twenty-eight patients were enrolled. Median age was 64 years; gender: male/female (13/15), Caucasian 19; histology: adenocarcinoma-17, squamous-8, NOS-3; ECOG performance status: 0 – 4, 1 – 20 and 2 – 2 patients.

A median of 3.5 cycles of therapy was administered. Grade 3/4 toxicities (n=11) included neutropenia, anemia, headache, fatigue, hyperglycemia, mucositis, and dyspepsia. Two patients experienced partial response and 13 had stable disease (clinical benefit rate 54%). The median PFS and OS were 2.3 months and 12 months, respectively. Tumor samples were available for biomarker analysis in 13 of 28 patients. High p-Akt expression was observed in patients with response outcome classification of progressive disease (p=0.01) and in patients with squamous or NOS histology (p=0.04). High p-Akt also showed a negative correlation with age (p=0.03). Similarly, cytoplasmic and nuclear staining intensity for total Akt showed significant negative correlation with age (p=0.002 for nuclear staining and p=0.05 for cytoplasmic staining). The levels of expression of S6 (p=0.08), pS6 (p=0.09) and p-mTOR (p=0.07) were different between disease response categories. There was no significant correlation between the tested biomarkers and patients survival outcomes (PFS or OS).

Conclusion: Expression level of p-Akt in diagnostic tumor tissue may predict for response in advanced NSCLC patients treated with the combination of everolimus and docetaxel. The biologic significance and treatment implication of the correlation observed between biomarkers of mTOR pathway activation and patient age, tumor histology and disease response is worthy of further study in future trials of agents that target this pathway. Acknowledgements: This study was supported by NCI grant P01 CA116676. Everolimus was provided by Novartis Oncology. FRK, TKO, SS, and SSR are Georgia Cancer Coalition Distinguished Cancer Scholars.

Keywords: Biomarkers, Lung cancer, docetaxel and everolimus, mTOR pathway

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P2.174 IKBA - A MECHANISM OF RESISTANCE TO CISPLATIN IN NSCLC

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer morbidity and mortality among western men and women, with an overall 5 year survival of <15%. The most effective systemic chemotherapy for NSCLC is cisplatin-based combination treatment. However, chemoresistance is a major therapeutic problem and understanding the mechanisms involved is critical to the development of new therapeutic strategies, including novel biological targeted agents. It has been shown that AKT amplification and the mammalian target of rapamycin (mTOR) pathway play an important role in cisplatin resistance in NSCLC. The PI3K/AKT/mTOR pathway represents a novel therapeutic target for overcoming cisplatin resistance in NSCLC, and currently there are several PI3K inhibitors in clinical trials.

Methods: A panel of cisplatin resistant NSCLC cell lines (H460, SKMES1, A549) were developed in our laboratory. H460 parent & resistant cell lines were screened for changes in mRNA expression using the PI3K Profiler array (SABiosciences). Gene expression changes between the two cell lines were validated by QPCR. IkBa protein expression was examined by Western blot analysis and High-Content Analysis (HCA). IkBa exons 3-5 were amplified by nested PCR and sequenced using the AB3130 sequencer.

Results:

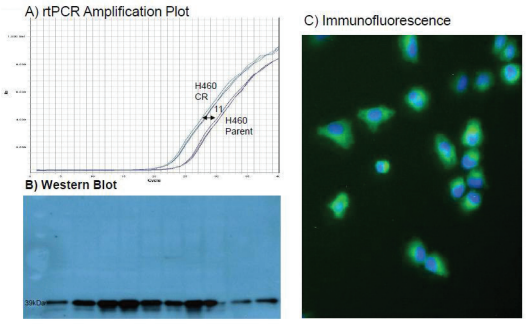

Figure 1. *The Role of IκBα in Cisplatin Resistance.* A) rtPCR amplification plot, showing an 11 fold increase in expression of IκBα in Cisplatin resistant cells (H460 CR) compared to parental lung cancer cells (H460 Parent). B) Western blot analysis showing IκBα protein expression in a panel of lung cancer cell lines. C) Immunofluorescence assay using High Content Imaging, showing IκBα antibody in H460 cells. (Blue: Nucleus, Green: IκBα)

The PI3K array identified no difference in NFkB mRNA expression between parent and cisplatin resistant H460 cells. However an 11.99 fold increase in IkBa mRNA expression was identified in the cisplatin resistant H460 cells. This was validated by QPCR which showed an 11 fold increase in expression of the gene (Fig. 1a). Western Blot analysis of a panel of cisplatin sensitive and resistant lung cancer cells also showed differences in expression of IkBa protein (Fig.1b). HCA confirmed increased levels of IkBa in H460 cisplatin resistant

cells compared to parent cells (Fig 1c). No gene mutations or deletions were identified in exons 3-5 of the IkBa gene

Conclusion: The transcription factor NFkB is involved in cell growth and proliferation and regulates the transcription of its own inhibitor IkBa. IkBa binds to and retains NFkB in an inactive complex in the cytoplasm. Over-expression of IkBa has been shown to decrease cell proliferation and increase apoptosis. However, here we show IkBa over-expression in cisplatin resistant cells compared to sensitive cells. No evidence of a truncated IkBa protein was detected by Western blot and no gene deletions or mutations were detected in exons 3-5. Therefore, further work is warranted to elucidate whether post-translational modifications of IkBa may result in its inability to inhibit NFkB in cisplatin resistant cells.

Keywords: NSCLC, Cisplatin resistance, IkBa, PI3K/AKT/mTOR pathway

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P2.175 TUMOR MARKER INDEX (TMI) BASED ON CYFRA21-1 AND CEA IDENTIFIES P-STAGE I NSCLC PATIENTS WITH HIGH RISK OF RECURRENCE AND POOR PROGNOSIS.

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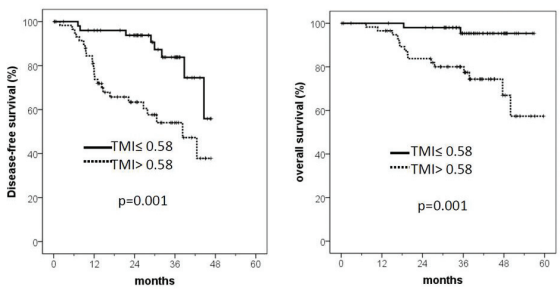
Background: TMI has been shown to be a valuable tool for risk evaluation in early stage NSCLC. The purpose of the prospective study was to analyse the value of TMI to predict tumour relapse in p-stage I NSCLC patients.

Methods: 112 completely resected patients (71 male/41 female; 37 SCC, 59 AC, 16 other NSCLC) entered the study. 23 patients received adjuvant chemotherapy based on clinical considerations. Preoperative markers were measured with Elecsys Bioanalyzer 2010 (Roche, Mannheim, Germany). TMI is defined as the geometric mean of normalized tumour marker data (Muley et al., Lung Cancer, 2008) Follow-up data were actualized in Feb 2011 (median follow-up: 39.3 months). Thirty three patients experienced tumour relapse. 17 patients died from lung cancer and 3 patients from other causes. Statistical analysis was done with SPSS 18.0 (Chicago, Illinois, USA).

Results: CEA (cut-off 5.0 ng/ml) and CYFRA 21-1 (cut-off 3.3 ng/ml) significantly differentiated between patients with low and high risk of tumour relapse (univariate HR: 2.3 [95%CI: 1.2-4.5], p=0.015 and HR: 3.0 [1.4-6.4], p=0.002, respectively). The power of differentiation was considerably improved by using TMI at a cut-off-point of 0.58. The 3-year disease-free survival rate was 83.8% and 54.0%, respectively (p=0.001) (Fig.).The univariate hazard ratio (DFS) was found to be 3.6 [95%CI: 1.6-8.1]. Eight out of 53 patients in the low risk group and 25 out of 59 patients in the high risk group experienced tumour recurrence. The tumor specific overall survival rate was significantly better (p=0.001) in the low risk group (95.4%) compared to high risk patients (77.5%) as defined by TMI (Fig.). TMI was shown to be a significant prognostic factor for DFS and OS in the multivariate analyses.



A small positive effect of adjuvant chemotherapy could be seen in the high risk group (TMI>0.58; n=59). The relapse rate was 2 out of 8 patients receiving adjuvant chemotherapy compared to 23 out of 51 patients without adjuvant chemotherapy. Surprisingly, patients receiving adjuvant chemotherapy in the low risk group (TMI<0.58; n=53) had a higher recurrence rate (5/12) as compared to patients without adjuvant chemotherapy (3/41).

Conclusion: Stage I patients with elevated TMI levels were shown to be at an increased risk of tumour relapse and early death and might therefore be appropriate candidates for adjuvant therapy. A

small positive effect of adjuvant chemotherapy could be seen in high risk patients. The latter should be validated in a larger patient group receiving adjuvant chemotherapy.
Keywords: Tumor marker index, Stage I, risk prediction, Prognosis

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P2.176 EARLY DETECTION OF LUNG CANCER BY MOLECULAR MARKERS IN EDOBRONCHIAL LINING FLUID

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Background: Molecular biomarkers in tissues and body fluids represent a promising source to improve cancer diagnosis and risk assessment. In the lung, early detection of malignancies by less invasive methods aims at achieving efficient intervention and subsequently a reduction of the high mortality rate. We investigated whether biomarker analysis in endobronchial epithelial lining fluid (ELF) collected by bronchoscopic microsampling may be useful for a definitive preoperative diagnosis.
Methods: ELF was collected from subsegmental bronchi close to the indeterminate pulmonary nodule, which was detected by CT scans, and from the contralateral lung. Diagnosis was confirmed by transbronchial biopsy or surgery. The study included 51 non-small cell lung cancer patients and 20 benign cases. Total RNA was isolated from ELF samples and biomarker candidate selection was based on Affymetrix U133 Plus 2.0 microarray analysis of a subset of ELF samples. Potential biomarkers have been further analyzed by rt qRT-PCR in independent ELF samples.
Results: Thirteen potential biomarkers have been identified. Notably, one biomarker candidate was clearly up-regulated in ELF samples of NSCLC patients independent of the tumor subtype. Combined analysis of clinical parameters like nodule size and biomarker expression further improved the prediction of early malignancies.
Conclusion: Our study indicates that specific marker genes in ELF collected by bronchoscopic microsampling may be useful to distinguish between malignant and benign pulmonary nodules.
Keywords: Endobronchial lining fluid, Molecular biomarkers

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P2.177 VEGF EXPRESSION IN NON-SMALL CELL LUNG CANCER: CORRELATION WITH EFFECTORS OF ARACHIDONIC ACID METABOLISM

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Background: It is well known that the angiogenic factor, VEGF promotes tumour survival in NSCLC, with some reports also demonstrating that it is prognostic in the disease. The monoclonal anti-VEGF antibody, bevacizumab can improve NSCLC patient survival when used in combination with conventional chemotherapy. However, the benefits of this new agent are generally modest, suggesting that novel approaches are warranted. Arachidonic acid-derived cyclooxygenase (COX) and lipoxygenase (LOX) pathways have been investigated in a number of cancers and play a role in tumour progression, potentially via increased angiogenesis. The aim of this study was to investigate the expression profile of VEGF in NSCLC and to correlate with both COX (COX-2, thromboxane synthase) and LOX (12-lipoxygenase) pathways. We also wished to investigate the effect of these enzymes on overall patient survival.
Methods: A 200-patient NSCLC TMA was stained for VEGF, COX-2, TXS and 12-LOX. Staining was correlated with clinical parameters, including 5-year patient survival. VEGF expression pattern was correlated with COX-2, TXS, and 12-LOX. VEGF,

TXS, and 12-LOX metabolite levels (VEGF, TXB_2, 12-S-HETE) were measured in human NSCLC serum samples by ELISA. VEGF metabolite levels were correlated with both TXB_2 and 12-S-HETE. Over-expression of TXS and 12-LOX was carried out in NSCLC cell lines (A-549, SKMES-1). The effects of over-expression on VEGF secretion was examined by ELISA.
Results: All four survival factors (VEGF, COX-2, TXS, 12-LOX) were expressed to a varying degree in NSCLC tissue. Expression of TXS was significantly ($p<0.001$) correlated with VEGF in the same patients. 12-LOX levels were not quite significantly correlated with VEGF ($p=0.17$). At the serum metabolite level, both TXB_2 and 12-S-HETE levels were significantly ($p<0.05$) correlated with VEGF, while both TXB2 and VEGF levels were higher in adenocarcinoma. A similar pattern was observed in tissue, with COX-2, TXS and VEGF expression levels also significantly higher in adenocarcinoma ($p<0.001$) and female patients ($p<0.05$). In support of our observations of a correlation between VEGF, TXS, and 12-LOX, both TXS and 12-LOX over-expression increased VEGF secretion in-vitro.
VEGF was not associated with survival in our patient cohort ($p=0.4$). While COX-2 was associated with short-term survival ($p<0.01$), no association with overall survival was observed ($p=0.2$). Neither TXS nor 12-LOX were associated with patient survival, either alone, or in combination with VEGF.
Conclusion: Our study also demonstrates a link between VEGF expression and that of arachidonic-acid derived TXS and 12-LOX in NSCLC, with the strongest association observed between VEGF and TXS. The increased VEGF secretion observed following overexpression of these enzymes suggests that they may play a role in tumour angiogenesis. While we did not observe an association with patient survival in our cohort, our findings suggest that these enzymes may promote tumour progression in NSCLC, potentially *via* increased VEGF expression and subsequent angiogenesis. This novel concept warrants further investigation.
Keywords: 12-lipoxygenase, VEGF, COX-2, thromboxane synthase

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P2.178 GENETIC VARIATIONS AND PATIENT-REPORTED QUALITY OF LIFE AMONG NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Recent evidence has suggested a relationship between a cancer patient's self-reported baseline quality of life (QOL) and genetic disposition. We report an analysis exploring the relationship between baseline QOL assessments and candidate genetic variations in a large cohort of lung cancer patients.
Methods: QOL data was provided by 1299 non-small cell lung cancer patients followed at Mayo Clinic between 1997 and 2007. Overall QOL and subdomains were assessed by either Lung Cancer Symptom Scale (LCSS) or Linear Analogue Self Assessment (LASA) measures with scores transformed to a 0-10 scale with higher scores representing better status. Baseline QOL scores assessed within 6 months of diagnosis were dichotomized as clinically deficient (CD) or not. A total of 470 SNPs in 56 genes of three biological pathways were assessed for association with QOL measures. Logistic regression with training/validation samples was used to test the association of SNPs with CD QOL.
Results: Six SNPs on four genes were replicated using our split schemes. Three SNPs in MGMT gene, (rs3858300 in adjusted analysis, rs10741191 and rs3852507 in unadjusted analysis) from DNA repair pathway were associated with overall QOL. Two SNPs, rs2287396 (GSTZ1) and rs9524885 (ABCC4), from glutathione metabolic pathway were associated with fatigue in unadjusted analysis. In adjusted analysis, two SNPs, rs2756109 (ABCC2) and rs9524885 (ABCC4), from glutathione metabolic pathway were associated with pain.
Conclusion: We identified three SNPs in three glutathione metabolic pathway genes, and three SNPs in two DNA repair pathway genes associated with QOL measures in non-small cell lung cancer patients.

Keywords: Lung cancer, Quality of Life, Clinical Significance

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P2.179 PREDICTIVE VALUE OF KRAS AND BRAF MUTATIONS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH CHEMOTHERAPY

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Background: KRAS mutation is thought to be related with poor outcome of patients with non-small cell lung cancer (NSCLC). The predictive value of KRAS and BRAF mutations for response to and survival following chemotherapy has not been established.
Methods: From a retrospective database consisting of consecutive chemonaive patients with advanced NSCLC treated with a platinum doublet from 2 university hospitals patients cases were selected when archive tumor tissue was available for molecular analysis. Mutation analysis was performed for KRAS exon 1,2 and BRAF exon 15 by high resolution melting following sequencing. Response to chemotherapy was assessed according to RECIST.
Results: FFPE-tumour derived DNA was available from 188 patients. Of 6 cases the DNA was of insufficient quality for KRAS and/or BRAF mutation analyses, leaving a total of 182 patients for further analyses (118 males and 64 females, mean age 60 (range 24-83 years). All patients had advanced NSCLC (34 stage IIIa, 38 IIIb, 110 IV), of which 49% were adenocarcinoma, 27% large cell carcinoma, 20% squamous cell carcinoma and 3% large cell neuroendocrine carcinoma. Of the 182 patients, 56 (31%) had a KRAS mutation, and 1 (0.5%) a BRAF mutation. Mutations were mainly observed in adenocarcinoma (n=36/89), followed by large cell 14/49, squamous cell carcinoma 4/37 and LCNEC 2/6. 30 patients were treated with curative intent (chemo-radiotherapy) and 152 with palliative intent. Response to chemotherapy was evaluable for 163 patients, showing 1 complete response (CR), 39 partial response (PR), 82 stable disease (SD) and 41 progressive disease (PD). Overall objective response rate was 25% (40/163). Median progression free survival (PFS) (n=177)was 7.1 months (95% CI 5.9-8.2). Median overall survival (OS) was 11.4 months (95% CI 8.8-14). Response to chemotherapy was observed in 25% (12/49) of patients with a KRAS/BRAF mutation, and 25% (28/114) of patients with wild type (WT) KRAS/BRAF. There was a trend for higher PD rate in patients with mutated KRAS/BRAF than patient with WT KRAS/BRAF (16/49, 33% versus 25/114, 22%, p=0.148). PFS was significantly shorter in patients with a KRAS/BRAF mutation: 5.4 months (95% CI 2.4-8.3) versus 7.4 months (95% CI 5.8-9.0), p=0.017 for those with wild type KRAS. Although OS was worse for patients with a KRAS/BRAF mutation, this was not significantly different, 6.3 months (95% CI 2.4-10.2) in patients with mutated KRAS/BRAF versus 12.4 months (95% CI 10.2-14.8) in patients with wild type KRAS/BRAF (p=0.082).
Conclusion: In our series, KRAS/BRAF mutation was not predictive for response to platinum-containing chemotherapy in patients with advanced NSCLC. KRAS/BRAF mutation was associated with a significantly shorter PFS but not OS in advanced NSCLC patients treated with platinum-containing chemotherapy.
Keywords: Kras, BRAF, NSCLC, predictive markers

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P2.180 INCREASED BCL-2 EXPRESSION IS ASSOCIATED WITH BAX PROMOTER HYPERMETHYLATION IN NEUROENDOCRINE CARCINOMA (NEC) OF THE LUNG.

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Background: Minimal advances have been made in the treatment of NECs, including small cell lung cancer (SCLC). Bcl-2 and Bax are key regulators

of apoptosis. Previous studies have shown that high Bcl-2 and low Bax expression are associated with worse outcomes in NEC. The objective of our study was to quantify Bax promoter hypermethylation and correlated with Bcl-2 expression.
Methods: Tissues from 150 patients treated as SCLC were stained for multiple molecular makers including Bcl-2 and Bax. Frequency and intensity of expression were measured on a scale of 0-4 (freq 0 = no expression, freq 1=1-10%, freq 2=11-35%, freq 3=36-70%, freq 4=71-100%). Methylation analysis was performed using pyrosequencing.
Results: Of the original 150 tissue samples, 64 samples were analyzed for Bax methylation. Of the Bax hypermethylated samples (overall average CpG methylation >10%), 73% were Bcl-2 positive (freqXint>or=2) vs. 21% of the samples without Bax hypermethylation (Chi square p=0.002). At Bax promoter CpG site -50 (translation start=+1), methylation was 13.0% in the Bcl-2 positive vs. 7.82% for the Bcl-2 negative samples (p=0.005). Analyses of progression free and overall survival are ongoing.
Conclusion: Bax hypermethylation was associated with higher Bcl-2 expression in this group of NEC patients. There results suggest that it would be reasonable to test hypomethylating agents combined with cytotoxic agents or with Bcl-2 inhibitors in NEC of the lung.
Keywords: neuroendocrine carcinoma, Bcl-2, BAX, methylation

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P2.181 FLIP AS A CRITICAL TARGET FOR VORINOSTAT IN MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a rapidly fatal malignancy with a median survival of less than 12 months. One of the main reasons for the failure of anti-cancer therapies is resistance to apoptosis. The caspase 8 inhibitor FLIP is a major anti-apoptotic protein that is over-expressed in several cancer types, including mesothelioma and has been linked to drug resistance. The histone deacetylase inhibitor Vorinostat has been evaluated in a phase III randomised placebo-controlled trial for patients with relapsed MPM, which is due to report in 2011. In order to develop clinically relevant predictive biomarkers of response, understanding the mechanisms involved in Vorinostat-induced apoptosis in MPM is essential.
Methods: The role of FLIP and caspase 8 in mediating the effects of Vorinostat in MPM was assessed in a panel of seven human MPM cell lines and confirmed in spheroid and in vivo models. RNA interference and protein overexpression approaches were used. Cell death was assessed by flow cytometry, Western blotting, caspase activity and clonogenic assays.
Results: We found that Vorinostat potently down-regulated FLIP expression in a panel of MPM cell lines (n=7). Vorinostat-induced apoptosis was found to be highly caspase 8-dependent in 5/7 MPM cell lines examined, and stable FLIP overexpression inhibited Vorinostat-induced apoptosis. Importantly, FLIP down-regulation was a sufficient death signal as RNAi-mediated FLIP silencing also activated caspase 8 and induced apoptosis. In addition, Vorinostat-induced FLIP down-regulation was observed in 3D and in vivo models of MPM. Moreover, Vorinostat was found to enhance cisplatin- and rTRAIL-induced in a FLIP-dependent manner.
Conclusion: These results indicate that FLIP is a major target for Vorinostat in MPM and identifies FLIP, caspase 8 and associated signaling molecules as candidate pharmacodynamic and/or predictive biomarkers for Vorinostat in this disease.
Keywords: Vorinostat, mesothelioma, c-FLIP, caspase 8

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P2.182 MICRORNAS IN PLASMA AS POTENTIAL MARKERS FOR DIAGNOSIS OF MALIGNANT MESOTHELIOMA

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Background: Malignant Mesothelioma (MM) is an aggressive cancer that is primarily caused by asbestos exposure. The median survival duration of MM is less than one year and the 5 year survival rate less than 1%. There is evidence suggesting that when MM is treated at an early stage there will be considerably better survival outcomes. Recently it has been shown that microRNAs (miRNAs) can be detected in a range of biological fluids including serum or plasma, and that these circulating miRNAs represent a class of potential new biomarkers. In addition, specific miRNA expression patterns in plasma or serum have been found to be associated with the presence of (solid) tumours. Recent studies have reported profiling of MM tumour samples, however a specific miRNA pattern in the blood of MM patients has yet to be investigated.
Methods: We have profiled miRNA expression in plasma samples from 3 healthy volunteers and 5 patients with MM using Agilent 8x15k miRNA microarrays. Total RNA from plasma samples was isolated using the mirVana PARIS kit with the additional use of glycogen. MiRNAs were quantified by miRNA specific stem-loop RT-qPCR by absolute quantification using standard curves generated from synthetic oligos. Data were analysed in the GeneSpring software. Candidate miRNAs identified in the arrays were validated by RT-qPCR in a larger sample set of 13 MM patients, 5 healthy controls and 7 patients with coronary artery disease (CAD).
Results: Microarray-based expression profiling of plasma from 5 MM patients and 3 healthy controls identified 17 miRNAs with significantly differential abundance in the two sample groups. 15 of these miRNAs were found at higher levels in MM patients, with 3 of them being exclusively found in patient plasma. Using RT-qPCR we performed first validation studies in a small cohort of 13 MM patient plasma and 12 control plasma (healthy and CAD). These revealed that both miR-92a and miR-29c* were present at significantly higher levels in the plasma of MM patients compared to both healthy and CAD control plasma. Validation of differential expression of further candidates is underway.
Conclusion: MiRNA expression profiling of patient and control plasma identified a number of potential markers for the presence of MM, with preliminary data confirming a significantly higher abundance of both miR-92a and miR-29c* in patient plasma. Taken together these data suggest that circulating miRNAs could represent a promising source of markers to aid in the diagnosis of MM.
Keywords: microRNA, biomarker, Malignant mesothelioma

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P2.183 TREGS IN REGIONAL LYMPH NODES OF PRIMARY NON-SMALL CELL LUNG CANCERS

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Background: CD4+CD25+ Regulatory T cells (Tregs) have been shown to suppress host immune responses to a variety of cancers. Nuclear Foxp3 is currently the only specific marker for regulatory T cells. We previously demonstrated the presence Tregs in human non-small cell lung carcinoma (NSCLC) - infiltrating lymphocytes. All induced lymphoid tissue was positive for Tregs, although there was a trend with greater cell counts in adenocarcinomas (ADC) and lower cell counts in squamous cell carcinoma (SCC). Currently we tested the draining lymph nodes (N1 and N2 stations) from primary lung tumors for the presence and quantity of Tregs.
Methods: After obtaining IRB approval, sixteen cases of formalin fixed paraffin embedded tissue were selected from the pathology archives, [12 primary lung carcinomas (5 squamous cell carcinoma, 7 adenocarcinoma, 2 inflammatory (1 organizing pneumonia and 1 interstitial fibrosis) and 2 sarcoid lymph nodes]. A tissue array was created with two 1.2-mm cores from each: primary tumor, N1 node, N2 node, and control tissue. The array was incubated for 20 minutes with 1:100 dilution of purified anti-Foxp3 antigen (Biolegend, San Diego, CA). The number of positive cells in each array dot was counted and average counts were calculated for all cases and for ADC and SCC separately. Statistics

were calculated from GraphPad Software, Inc.
Results: The mean number of FoxP3 positive cells in the tumors and control lung was 2.7. The average for N1 and N2 draining nodes was 64.3 and 85.1 for all histologies, resp. The average N1 Treg count for ADC alone was 126, and for SCC was 3.5 (p=<0.008, unpaired t-test). The average for N2 for ADC and SCC was similar (83.8 and 86.4, resp.).
Conclusion: These finding demonstrate the presence of Tregs in the draining N1 and N2 nodes of primary lung tumors. The disparity of Tregs between histologies confirms our previous findings. ADC histology appears to be associated with significantly higher numbers of Tregs within the closest N1 nodal basin, compared to SCC.
Keywords: Tregs, FoxP3

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P2.184 CORRELATION BETWEEN PULMONARY FUNCTION TEST AND EGFR MUTATION STATUS IN NON-SMALL CELL LUNG CANCER PATIENTS WITH MODERATE TO HEAVY SMOKING HISTORY

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Background: Epidermal growth factor receptor (EGFR) mutations are reported to be more frequent in non-small cell lung cancer (NSCLC) patients with never and limited smoking history. Although smoking status is the strongest predictor of harboring an EGFR mutation, there are NSCLC patients, albeit a few, who have both moderate-to-heavy smoking history and EGFR mutations. However, the clinical characteristics of those patients are not well established.
Methods: Patients, with both more than a 20-pack year history of smoking and clinically staged I and II NSCLC, were recruited into this study from among those who were evaluated for EGFR mutation status between January 2007 and September 2010 at Ibarakihigashi National Hospital. All eligible patients were divided into two groups: EGFR mutation positive group (positive group) and EGFR wild type group (negative group). The results of pulmonary function test were compared between the two groups.
Results: There were 23 patients who met the criteria, of whom 6 were mutation-positive (all males, median age: 73) and the remaining 17 were the wild type (males: female, 16:1, median age: 72). The median smoking history of the positive group was 46 pack-year and 4 (66.7%) were current smokers, whereas that of the negative group were 40 pack-year and 7 (41.1%) were current smokers. The pathological feature of all patients in the positive group was adenocarcinoma, whereas the negative group was comprised of 10 adenocarcinoma, 6 squamous cell carcinoma, and 2 large cell carcinoma. In pulmonary function test, the median of vital capacity (VC) / predicted VC was 93.5% in the positive group and 94.9% in the negative group (p = 0.70). In forced expiratory volume in a second ($FEV_{1.0}$) / predicted $FEV_{1.0}$, the positive group had better result than the negative group although the difference was not significant (101.3% v.s 87.6%, p = 0.38). On the other hand, $FEV_{1.0}$ / forced VC (FVC) was significantly higher in the positive group than in the negative group (73.6% v.s 68.1%, p = 0.042). The same trend was observed in $FEV_{1.0}$ / FVC, excluding patients with squamous cell carcinoma (73.6% v.s 69.3%, p = 0.092).
Conclusion: Despite moderate to heavy smoking history, the NSCLC patients with EGFR mutation might have normal or mild obstructive defects, compared to those with wild type EGFR. The NSCLC patients with normal or mild obstructive defects should be evaluated for EGFR mutation status irrespective of smoking history.
Keywords: EGFR mutation, smoking history, pulmonary function test, non small lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.185 THE PREVALENCE OF HISTONE DEACETYLASE (HDAC) EXPRESSION IN KOREAN NON-SMALL CELL LUNG CANCER PATIENTS

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Background: DNA methylation and histone modification are dynamically linked in the pigenetic control of gene silencing and they play an important role in tumorigenesis. We evaluated the role of histone deacetylase (HDAC) in the development of lung cancer and the relationship between a HDAC overexpression and survivin, p16 and p53 overexpression.
Methods: We performed immunohistochemical staining for HDAC1, HDAC2, HDAC3, p16, and p53 in 129 lung cancer specimens.
Results: HDAC overexpression was detected in 51% (HDAC1 and HDAC2) and 64% (HDAC3) and it was more frequently seen in the squamous cell carcinomas than in the adenocarcinomas ($p<0.05$). There was statistical significances between HDAC overexpression and survivin overexpression ($p<0.05$), but not with p16 and p53 overexpressions.
Conclusion: HDAC overexpression might be involved in lung carcinogenesis, and especially in a squamous cell carcinoma, and a HDAC overexpression may be associated with survivin overexpression, however, overexpression of these genes are not related with patient survival. These results suggest that HDAC inhibitors are putative therapeutic agents in subgroup of non-small cell lung cancer patients.
Keywords: Non-small cell lung cancer, survivin, histone deacetylase

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.186 ACCURATE ESTIMATION OF DNA METHYLATION FREQUENCY IN NON-SMALL CELL LUNG CANCER

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Background: Promoter hypermethylation is a common epigenetic mechanism for gene silencing in NSCLC. DNA methylation detected in tumour cells has been suggested as a potential biomarker that helps selection of optimal chemotherapeutic agents and stratification of NSCLC patients at high risk of recurrence after surgery. Identifying methylated genes is best done by a methodology that is unlikely to give false positives or negatives. We used methylation sensitive HRM as it can give a methylation portrait for each assayed region and is less prone to false positives than other commonly used methodologies.
Methods: DNA was prepared from FFPE sections of 56 N1 NSCLC tumours and bisulfite modified. MS-HRM assays were performed for two sets of genes; DNA repair genes (BRCA1, MLH1, XPC, MGMT, RAD23B, ERCC1) and genes associated with recurrence after surgery (APC, CDH13, RASSF1A and p16). Selected MS-HRM positive samples were bisulfite sequenced. MGMT methylation was also estimated by SMART-MSP and samples were genotyped for the rs1690625 MGMT promoter SNP.
Results: We were unable to replicate previous reports of a high incidence of XPC, BRCA1 and MLH1 methylation in NSCLC as no methylation was detected for any of these genes. One tumour showed RAD23B methylation and one tumour showed ERCC1 methylation. These are the first reports of the methylation of RAD23B and ERCC1 in NSCLC. A high frequency of DNA methylation in the CDH13, APC, CDH13, RASSF1A, and CDKN2A (p16) genes was confirmed giving an overall methylation frequency of 25%, 50%, 32%, and 25% respectively. MGMT methylation was seen in 7 (12.5%) of tumours but some of these seem to be false positives due to constitutional MGMT methylation predominantly associated with the T allele of the rs1690625 SNP in somatic tissues.
Conclusion: Methodology is critical in accurately

assessing methylation status. Detectable methylation of the XPC, BRCA1 and MLH1 DNA repair genes was absent indicating that their methylation frequency is overestimated in the literature. Methylation in ERCC1 and RAD23B, although rare, was demonstrated for the first time, and may offer intriguing boutique targets for therapy. When measuring MGMT methylation, it will be important to distinguish those tumours that are truly methylated from those tumours in which there are background levels of constitutional methylation.

Keywords: DNA methylation, Predictive biomarkers, prognostic biomarkers

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P2.187 EXTENDED MUTATION PROFILING OF THE EGFR SIGNALLING PATHWAY IN NON-SMALL CELL LUNG CANCER SENT FOR EGFR MUTATION TESTING.

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Background: The EGFR signalling pathway is a pivotal signalling axis for initiation, progression, and survival of non-small cell lung cancer. Frequent dysregulation of the EGFR signalling pathway by gain-of-function mutations makes it an attractive target for therapeutic intervention. The establishment of cost-effective and sensitive methodology for profiling of somatic mutations in the clinically important genes is highly desirable for current and future molecularly tailored therapies.
Methods: 200 formalin-fixed paraffin-embedded NSCLC tumours selected for diagnostic EGFR mutation testing were included. The histological subtype was predominantly adenocarcinomas (141 cases) but also included 24 large cell carcinomas, 10 squamous cell carcinomas, and 25 cases with unknown histology. One hundred twenty cases were female and 80 cases were male in gender. The mutation status of seven selected genes (EGFR, KRAS, HER2, PIK3CA, AKT1, AKT3, and BRAF) was profiled using high resolution melting. The exons examined for each gene were as follows: EGFR exons 18-21, HER2 exon 20, PIK3CA exons 9 and 20, AKT1 exon 4, AKT3 exon 3, KRAS exons 2 and 3, and BRAF exon 15. All HRM positive samples were confirmed by Sanger sequencing.
Results: Gain-of-function mutations from the genes in the EGFR signalling pathway were detected in 54% of the NSCLC samples. Forty nine per cent of the NSCLC tumours harboured either EGFR (36.5%) or KRAS codons 12 and 13 mutations (12.5%), which were mutually exclusive. EGFR mutations were also detectable in 8.5% of tumours with non-ADC histologies and in 21.3% of male patients. PIK3CA (3.5%), BRAF (3%), and AKT1 (0.5%) mutations were less frequently detected. No HER2 mutation was identified. EGFR, KRAS, and BRAF mutations were mutually exclusive whereas concomitant PIK3CA and EGFR mutations were detected in four NSCLC tumours.
Conclusion: High resolution melting is a sensitive, cost-effective, closed-tube method suitable for mutation detection at multiple genes in FFPE NSCLC samples. KRAS mutation testing may be useful to exclude EGFR mutation positivity in some difficult clinical samples. Testing for the other mutations may be useful where they indicate the use of specific therapies.

Keywords: Predictive biomarkers, mutation detection, EGFR mutations, high resolution melting

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P2.188 B-CELL LYMPHOMA/LEUKEMIA 11A (BCL11A) PROTEIN EXPRESSION IS ASSOCIATED WITH SURVIVAL IN EARLY STAGE NON-SMALL CELL LUNG CANCER:A COMPARISON BETWEEN BCL11A GENE COPY NUMBER, MRNA EXPRESSION AND PROTEIN EXPRESSION.

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Background: Lung cancer is leading cause of cancer-related death both worldwide and in China, but we continue to have limited understanding of the pathophysiology of this disease.The purpose of this study was to characterize B-cell lymphoma/leukemia 11A (BCL11A) mRNA expression ,protein expression and gene copy number in surgically resected non-small cell lung cancer(NSCLC) in relation to patient characteristics and prognosis.
Methods: One hundred and fourteen patients with NSCLC who underwent curative pulmonary resection were studied(median follow-up 47.2 months). BCL11A mRNA expression was evaluated by quantitative reverse transcription polymerase chain reaction(qRT-PCR) from 114 corresponding fresh-frozen saples. BCL11A protein expression was assessed by Immunohistochemistry staining (n=113).BCL11A gene copy number was extracted from previous array-based comparative genome hybridization (aCGH) data from the same samples.
Results: BCL11A copy number, gained more frequently in squamous-cell lung cancer(SCC) than lung adenocarcinoma(AC)(t=2.97,P=0.005). BCL11A gene expression by RT-PCR have an oppositive correlation with , A significantly higher average expression level was observed for BCL11A in the SCC samples with amplifications as compared to those SCC samples without amplifications(t=3.54,P=0.023).BCL11A protein expression was also higer in SCC than AC ,and BCL11A protein localized predominantly in cellular nucleus of SCC, but in AC, the immunohistochemical staining was detectable predominantly in cytoplasm of cancer cells. Mutivariate analysis demonstrated that in early stage patients(IA-IIB), BCL11A protein was not only a significant prognostic factor for disease free survival [Hazard ratio (HR) 0.176, 95% confidence interval (CI) 0.047-0.658, P=0.01], but also for overall survival [Hazard ratio (HR) 0.171, 95% confidence interval (CI) 0.059-0.498,P=0.001].
Conclusion: BCL11A protein expression is higher in squamous-cell lung cancer than lung adenocarcinoma and harbors a positive prognostic value for early stage(IA-IIB) NSCLC patients.
Keywords: B-cell lymphoma/leukemia 11A, Prognosis, Non-small cell lung cancer

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P2.189 PRACTICE AND PITFALLS OF MUTATION TESTING USING FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUES.

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Background: Tumour tissues are routinely archived after fixation with 10% buffered formalin and embedding in paraffin. The formalin fixation causes chemical damage to the genetic material. Molecular biomarker testing is increasingly performed with FFPE samples in both research and diagnostic settings. Appropriate design and interpretation of assays based on DNA from FFPE tissues, particularly when the amount of tumour material is limited, is thus essential. In some cases, template derived artifacts will be common. These probably account for most of the non-canonical mutations reported in the literature.
Methods: A range of methodologies are useful for assessing the quality of FFPE specimens. A multiplex PCR generating amplicons at different sizes (100, 200, 300, 500, 600 bp) was performed to assess the degradation of FFPE DNA. A real-time amplification step allows the determination of the amount of amplifiable template. Low copy number-high resolution melting (LCN-HRM) followed by sequencing enables the detection of low frequency variants outside the normal analytical sensitivity of sequencing.
Results: FFPE DNA samples that were negative by sequencing but positive by high resolution melting analysis were further analysed using low copy number-high resolution melting (LCN-HRM). Approximately, a range from one to four copies of template was added in individual LCN-HRM reactions. There was a high intra-sample variation in the size of amplifiable template. Smaller amplicon sizes increased the success rate of assays. When positive LCN-HRM were Sanger sequenced, multiple non-identical sequence changes, predominantly transitional base changes (G>A or C>T), were often detected. In other cases true mutations were detected.
Conclusion: PCR amplification using FFPE DNA can generate multiple template-mediated artefacts. This is particularly a problem when there is a low

mutation frequency and/or limited material for analysis. Non-canonical or novel sequence variants, especially found with FFPE DNA, need to be adequately confirmed by testing of independent PCR products.

Keywords: mutation detection, EGFR mutations, FFPE, Predictive biomarkers

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P2.190 PREDICTIVE FACTORS OF ERCC-1 AND EGFR MUTATION IN ADVANCED NSCLC: A SINGLE CENTER RETROSPECTIVE STUDY.

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Background: Overexpression of ERCC-1 gene has been reported to be associated with platinum resistance in both early and advanced NSCLC patients whereas the mutations at tyrosine kinase domain of EGFR gene especially exon 19 deletion and exon 21 missense mutation are associated with TKI responsiveness. This study is aimed to investigate the prevalence of EGFR mutations in association with ERCC-1 protein expression in advanced NSCLC Thai patients and analyze the correlation between ERCC-1 and EGFR mutation status to the overall survival after platinum-based chemotherapy.
Methods: There were 29 cases of advanced NSCLC patients who had sufficient tumor tissues and had been treated with platinum-based chemotherapy as the first-line treatment in Maharaj Nakorn Chiangmai Hospital between Jan.2006-Dec.2008. The ERCC-1 expression had been assessed with immunohistochemistry whereas the EGFR gene mutation was performed by conventional PCR followed by direct sequencing to identify the mutation.
Results: Twenty-nine tumor tissues have been analysed. There are 11 cases of squamous cell carcinoma and 18 cases of adenocarcinoma . Seven cases (63.6%) of squamous cell carcinoma and nine cases (50%) of adenocarcinoma were ERCC-1 positive. EGFR gene products could be amplified and completely sequenced in only nineteen cases. There were four cases of exon 19 in-frame deletion only in adenocarcinoma subtype and three exon 21 missense mutations, two in the adenocarcinoma as L858R and P848S whereas one squamous cell carcinoma displayed L858R mutation. All exon 19 deletion mutations were ERCC-1 negative. Exon 21 mutations were founded in both ERCC-1 positive (one cases) and ERCC-1 negative (2 cases). Survival of patients having ERCC-1 negative and EGFR wild type is compared with those having ERCC-1 negative and EGFR mutation positive.
Conclusion: Patients having adenocarcinoma subtype with ERCC-1 negative and EGFR mutation wild type seemed to live longer than those having EGFR mutation positive in comparison to double negative tumors. However, this is a single center study with limited number of cases. Further study with high number cases recruited are in cintinuum.
Keywords: Advanced NSCLC, ERCC-1, EGFR mutation

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P2.191 PERFORMANCE OF A COMBINATION OF SERUM BIOMARKERS, INCLUDING SOLUBLE MESOTHELIN-RELATED PEPTIDE (SMRP), IN DIAGNOSING MALIGNANT MESOTHELIOMA

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Background: Malignant mesothelioma (MM) is a rare, progressive malignancy causally linked to asbestos exposure. Currently, there are no approved screening modalities for the early detection of MM. However, recent studies have provided evidence that soluble mesothelin-related peptide (SMRP) and megakaryocyte potentiating factor (MPF) can be useful biomarkers for the serum diagnosis of MM. The aim of this study is to evaluate SMRP as a

diagnostic marker for MM and investigate whether its diagnostic value is enhanced by combination with other biomarkers.
Methods: Serum SMRP levels were measured using a quantitative enzyme-linked immunosorbent assay, in 96 patients with MM, 55 patients with lung cancer, and 39 individuals with asbestos exposure. Receiver operating characteristic curves were constructed for performance evaluation. Stepwise logistic regression analysis was used to select marker combinations (MCs).
Results: The sensitivity of SMRP for diagnosing MM was 56%, and its specificity for MM versus lung cancer and individuals with asbestos exposure was 87% and 92%, respectively. The area under the curve (AUC) was 0.76 (95% confidence interval [CI], 0.68–0.83; $P < 0.0001$) for differentiation between MM and lung cancer and 0.78 (95% CI, 0.71–0.86; $P < 0.0001$) for differentiation between MM and asbestos exposure. For the MC of fluid retention, SMRP, and carcinoembryonic antigen (CEA), the AUC for differentiation between MM and lung cancer (0.92 [95% CI, 0.88–0.97; $P < 0.0001$]) and differentiation between MM and asbestos exposure (0.93 [95% CI, 0.87–1.0; $P < 0.0001$]) was significantly higher than that for SMRP alone ($P = 0.0001$ and 0.0058, respectively).
Conclusion: Combining CEA with SMRP improves the diagnostic performance of SMRP alone. Therefore, a combination of serum biomarkers, including SMRP can facilitate early diagnosis of MM.
Keywords: Malignant mesothelioma, mesothelin, soluble mesothelin-related peptide, serum biomarker

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P2.192 SARCOIDAL REACTIONS IN REGIONAL LYMPH NODES OF EARLY STAGE NON-SMALL CELL LUNG CANCER PATIENTS PREDICT IMPROVED DISEASE-FREE SURVIVAL: A PILOT CASE-CONTROL STUDY

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Background: Sarcoidal reactions occuring in regional lymph nodes of patients with non-small cell lung carcinoma (NSCLC) appear to be limited to patients with Stage I disease. The prognostic significance of this remains unknown. Such reactions are thought to represent a cell-mediated anti-tumour response, and have been associated with improved outcomes in other solid organ malignancies.
Methods: We performed a retrospective chart review of all patients undergoing lobectomy with curative intent for NSCLC. Eligible cases were selected on the basis of pathologic reports noting, with matched controls then drawn from the same surgical cohort
Results: 157 patients underwent lobectomy and lymph node dissection. Eight patients with sarcoidal granulomas present in regional lymph nodes were idenfied as cases, and matched to 16 control subjects. All subjects were staged pN0. Disease recurrence was noted in no case subjects, but in 7 (44%) of control subjects ($p=0.044$, $c^2=4.051$).
Conclusion: The presence of sarcoidal reactions within regional lymph nodes of NSCLC patients predicts a lower rate of disease recurrence following definitive surgical resection. The exact mechanism by which anti-tumour immunity is achieved remains to be elucidated.
Keywords: Granuloma, Anti-tumour immunity, recurrence

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P2.193 IMPACT OF DIHYDROFOLATE REDUCTASE EXPRESSION FOR CLINICAL BENEFIT FROM PEMETREXED IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: The antifolate pemetrexed (PMX) targets multiple enzymes involved in pyrimidine and purine synthesis, including thymidylate synthase (TS) and dihydrofolate reductase (DHFR). TS expression might predict outcome in patients (pts) suffering from malignant pleural mesothelioma (MPM) and non-small cell lung cancer (NSCLC) who are treated with pemetrexed. In contrast to pemetrexed's main target, TS, there is little information about the impact of DHFR expression on the efficacy of PMX. We hypothesized that DHFR protein expression may also predict outcome following PMX treatment of MPM pts.
Methods: Tumor samples from 60 pts with MPM, treated with PMX combined with platinum (57/60) or as a single agent (3/60) were retrospectively analyzed. Pre-treatment tumor samples from 33 pts, post-treatment samples from 11 pts, as well as pre- and post-treatment samples from 16 pts were considered. DHFR protein expression levels were evaluated by immunohistochemistry using the H-Scoring system (ranging from 0 to 300), which relies on the product of intensity of specific tumor cell immunoreactivity (range 0 to 3) and the percentage of positive tumor cells. Radiographic evaluation of response was performed according to RECIST.
Results: The median pre-treatment H-score for DHFR was 105 (range: 40-215) and the median post-treatment H-score was 110 (range: 10-215). There was no significant association between pre-treatment DHFR expression and response or outcome. But there was a significant association between improved progression-free survival (PFS) and low DHFR protein expression after PMX-treatment using the median H-score as the cut-off (median PFS of 254 vs 123 days; hazard ratio [HR] 0.484, 95% CI, 0.057 to 0.912). The comparison between the survival curves was statistically significant by using the Wilcoxon test (P=0.036) and borderline significant by using the log-rank test (P=0.061). Prolonged overall survival (OS) was also associated with low DHFR protein expression (median OS of 810 vs 672 days) using both tests (P=0.035 by the Wilcoxon test and P=0.012 by the log-rank test).
Conclusion: Here we report the most thorough investigation of DHFR expression in tumor specimens from pemetrexed-treated MPM pts to date. Based on our retrospective study, post-treatment DHFR protein expression is associated with prolonged PFS and OS from PMX-based therapy. Further prospective investigation of DHFR expression in MPM pts treated with PMX is warranted.
Keywords: malignant pleural mesothelioma, biomarker for clinical benefit, Pemetrexed, dihydrofolate reductase (DHFR)

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P2.194 STATHMIN – DRUG SENSITIVITY ASSOCIATED PROTEIN OF LUNG CANCER

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Background: The sensitivity of chemotherapy to lung cancer is still very low except small cell lung carcinoma (SCLC). We planned to find some specific proteins related to chemosensitivity from SCLC and apply them to non small cell lung carcinoma (NSCLC)
Methods: We have selected relatively specific proteins from formalin fixed paraffin-embedded (FFPE) tissues of histologically diagnosed as SCLC (n=5), LCC (n=5) and LCNEC (n=4) by laser microdissection, liquid chromatography / mass spectrometry and semi-quantified method. We have knocked out one of characteristic proteins in lung cancer cell lines and checked the change of sensitivity to usual chemotherapeutic agents.
Results: We identified one of common characteristic proteins of SCLC and LCNEC, stathmin, which has been reported as one of drug sensitivity associated proteins. Stathmin was more expressed in SCLC compared to LCNEC immunohistochemically. Stathmin was also expressed in NSCLC cell lines, H838 and H1299. After knocking out of stathmin by siRNA technique, the sensitivity to VP-16 was decreased, while the sensitivity to CDDP was increased.

Conclusion: In this study, our findings suggested that stathmin may be one of proteins associated to the chemosensitivity not only SCLC but also NSCLC.

Keywords: stathmin, drug sensitivity, Lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.195 EGFR-ACTIVATING MUTATIONS, DNA COPY NUMBER ABUNDANCE OF ERBB FAMILY, AND PROGNOSIS IN LUNG ADENOCARCINOMA

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Background: Epidermal growth factor receptor (EGFR) belongs to the ErbB family which comprises four members (EGFR, ERBB2, ERBB3, and ERBB4). Mutations of EGFR are present in a subpopulation of lung adenocarcinomas and showed sensitive to EGFR-TKIs treatment. Recent studies showed that members of ErbB family had associated with prognosis in lung cancer in RNA expression level. However, the association of DNA copy number (CN) abundance of ErbB family and prognosis is still needed to investigate. In this study, EGFR-activating mutation status and DNA abundances of ErbB family were measured in 261 lung adenocarcinomas and association of prognosis will be explored.

Methods: 261 lung adenocarcinomas with stage I to stage IIIa were enrolled in this study and patients with less than 6 months follow-up and died within 1 month were excluded. The identification of EGFR-activating mutation was genotyped by MASS spectrum or Sanger sequence assays. Genomic real-time quantitative PCR was performed to measure DNA copy number abundance of each member of ErbB family. Kaplan-Meier survival analysis was used to generate the survival curve and the survival difference between groups was tested by log-rank test. Multivariate Cox proportional hazards regression was carried out to test the independent prognostic factors.

Results: The proportion of EGFR-activating mutations were 118 wild type (45.2%), 70 L858R (26.8%), and 73 exon 19 deletion (28.0%), respectively. Patients with higher EGFR CN had shorten overall survival (p=0.032) and adjusted hazard ratio (HR) is 1.89 (95% CI=1.16 to 3.10, p=0.011) in all 261 patients. In stratification analysis of EGFR-activating mutation status, EGFR CN was not significant in wild type group and adjusted HRs were 2.96 (95% CI=1.02 to 8.57, p=0.046), 7.25 (95% CI=1.74 to 30.27, p=0.007), 3.53 (95% CI=1.58 to 7.87, p=0.002) for L858R, exon 19 deletion, and all EGFR-activating mutation groups, respectively. ERBB2 showed poor prognosis in all patients (HR=1.68, 95% CI=1.03 to 2.74, p=0.038) but not significant in wild type or EGFR-activating mutations. ERBB3 had significantly association with prognosis in all patients (HR=1.65, 95% CI=1.02 to 2.68, p=0.042), L858R mutation group (HR=3.98, 95% CI=1.02 to 15.63, p=0.047), all EGFR-activating mutation group (HR=2.64, 95% CI=1.17 to 5.95, p=0.019), respectively but no significant findings in wild type and exon 19 deletion groups. The similar results were also found in ERBB4 with significantly association with prognosis in all patients (HR=1.62, 95% CI=1.01 to 2.61, p=0.047), L858R mutation group (HR=7.22, 95% CI=2.23 to 23.36, p=0.001), all EGFR-activating mutation group (HR=3.40, 95% CI=1.55 to 7.48, p=0.002), respectively but no significant findings in wild type and exon 19 deletion groups.

Conclusion: ErbB family had associations with prognosis in lung adenocarcinoma. In addition, the effect modifications are found in EGFR, ERBB3, and ERBB4 in different EGFR-activating mutation status.

Keywords: EGFR mutation, ErbB family, DNA copy number, Prognosis

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P2.196 GENOME-WIDE DNA METHYLATION ANALYSIS OF SMALL CELL LUNG CANCER

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Background: Small cell lung cancer (SCLC) is a highly aggressive form of lung cancer, with a patient median survival of just over one year. There is increasing evidence to suggest that dysregulation of the epigenome is involved in lung carcinoma. We investigated whether DNA methylation profiles can provide useful molecular subtyping of SCLC in terms of etiology and prognosis of SCLC.
Methods: We analyzed tumor and normal samples of 25 patients with SCLC undergoing surgery at the Cancer Institute Hospital. Among them, six were treated with chemotherapy before surgery. All tissues were grossly dissected and snap-frozen in liquid nitrogen. Female: male ratio was 8:17 and the average age was 68.2 years old. Initial diagnosis of each tumor from frozen section was later confirmed by detailed analysis of paraffin-embedded sections and immunohistochemistry as necessary. Following WHO guidelines, the 25 tumors were classified as SCLC. 500 ng bisulfite-converted genomic DNA was used for the illumina Infinium HumanMethylation27 BeadChip, which enables the direct investigation of 27,578 individual cytosines at CpG loci throughout the genome.
Results: Unsupervised hierarchical clustering of methylation data from SCLC samples reveals two major subgroups with different prognosis: Group 1 had a significantly worse prognosis than Group 2, i.e. the overall survival (OS) for 2 years was 45.0% and 80.7%, respectively (p=0.008). Methylation status of normal lung was quite homogenous (n=12). Univariate analyses for OS showed that sex, preoperative and postoperative chemotherapy, pT factor, and methylation status were significant prognostic factors ($p < 0.10$). By multivariate analysis for OS, only postoperative chemotherapy was a significant prognostic factor ($p = 0.036$). Estimated 2-year disease-free survival (DFS) for Group 1 and Group 2 were 14.3% and 76.0%, respectively ($p=0.002$). Univariate analysis for DFS determined that postoperative chemotherapy, pT factor, and methylation status were significant ($p < 0.10$). Of these factors, both postoperative chemotherapy and methylation status were independent prognostic factors in multivariate analysis ($p=0.007$ and 0.023, respectively).
Conclusion: By comprehensive DNA methylation profiling, we identified two subgroups of surgically-resected SCLC with significant differences of both OS and DFS. Multivariate analysis revealed that methylation status was an independent prognostic factor for DFS. DNA methylation profiling will allow the subclassification of SCLC to guide therapy.
Keywords: Prognosis, Small cell lung cancer, methylation, epigenome

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P2.197 GENE EXPRESSION-BASED APPROACHES IN DIFFERENTIATION OF METASTASES AND SECOND PRIMARY TUMOUR

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Background: A 64-year-old male patient was diagnosed with 3 consecutive non-small cell lung carcinomas (NSCLC). In the current study, we applied whole-genome gene expression analysis to control, primary and locally recurrent cancer, and supposed metastasis samples of a single patient. According to our knowledge, there are no published papers describing the gene expression profiles of a single patient's squamous cell lung cancers.
Methods: As the histology and differentiation grade

of the primary cancer and the supposed metastasis differed minimally, but local recurrence was poorly differentiated, molecular profiling of the samples was carried out in order to confirm or reject the hypothesis of second primary cancer.
Results: Principal component analysis of the gene expression data revealed distinction of the local recurrence. Gene ontology analysis showed no molecular characteristics of metastasis in the supposed metastasis.
Conclusion: Gene expression analysis is valuable and can be supportive in decision-making of diagnostically complicated cancer cases.
Keywords: Metastasis, Gene expression profile, local recurrence

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P2.198 CYCLIN D1 A870G POLYMORPHISM AND PROGNOSIS OF NON-SMALL CELL LUNG CANCER

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Background: The cyclin D1 (CCND1) A870G gene polymorphism is associated to the prognosis in patients with resected non-small cell lung cancer. Here, we investigated the potential role of Cyclin D1 (CCND1) A870G gene polymorphisms on prognosis in patients with locally advanced and metastatic non-small cell lung cancer.
Methods: CCND1 A870G genotype was determined by polymerase chain reaction and restriction fragment length polymorphism analysis of DNA extracted from blood. Blood samples were collected from newly diagnosed 53 patients with lung cancer.
Results: In patients with non-metastatic group (n=33), frequency of cyclin D1 genotype was 30.3% for A/A, 51.5% for A/G, and 18.2% for G/G. In patients with metastatic disease (n=20), cyclin D1 genotype was 45.0% for A/A, 40.0% for A/G, and 15.0% for G/G. There was no correlation between CCND1 A870G polymorphism status and age, sex, and smoking rate both in metastatic and non-metastatic groups. In non-metastatic group, median overall survival was 7.96 (1.13-21.47) months and there was no statistically significant correlation between overall survival and CCND1 A870G polymorphism status. In metastatic group, median overall survival was 5.03 (1.33-14.80) months and median overall survival was significantly shorter in patients with A/A genotype than in patients with A/G+G/G genotype (2.96 months vs. 8.0 months, p=0.006).
Conclusion: CCND1 A/A genotype might be a poor prognostic factor in patients with non–small cell lung cancer, who has a metastatic disease.
Keyword: Lung cancer cyclin D1 gene polymorphism prognosis

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P2.199 NF-KAPPAB ACTIVATION AND DISTINCT EXPRESSION OF UBIQUITIN E3 LIGASES IN SKELETAL MUSCLE OF PATIENTS WITH NON-SMALL CELL LUNG CANCER CACHEXIA

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Background: Cachexia is a frequent paraneoplastic feature of lung cancer (NSCLC) and is characterized by progressive body weight loss and skeletal muscle wasting. The presence of cachexia is associated with lower responses to therapy and increased morbidity and mortality. In addition, patients with lung cancer cachexia report significantly reduced quality of life. Experimental research has shown that increased muscular Nuclear Factor kappa B (NF-κB) and subsequent ubiquitin (Ub) proteasome system (UPS) activity plays a causal role in lung cancer-induced muscle wasting but this needs verification in human lung cancer cachexia. The aim of this study is to investigate muscular NF-κB activity and expression of E3 Ub-ligases in skeletal muscle of cachectic patients with advanced NSCLC.
Methods: In this prospective study, 14 cachectic patients (defined by >5% body weight loss in preceding 6 months) and 12 non-cachectic patients with newly diagnosed advanced stage NSCLC

and 22 age and gender matched healthy controls were included. Body composition was assessed by dual energy X-ray absorptiometry (DEXA) and biopsies were obtained from vastus lateralis muscle. IkappaBalpha (IκBα) and Tumor Necrosis Factor alpha (TNF-α) mRNA expression levels were determined as indirect indices of NF-κB activity. UPS activity was evaluated by mRNA expression of four E3 Ub-ligases: neural precursor cell expressed developmentally down-regulated 4 (NEDD4), Atrogin-1, Tripartite motif-containing protein 32 (TRIM32) and Muscle RING-finger protein-1 (MuRF1).

Results: Mean weight loss was 13.1 ± 4.9% in cachectic patients compared with 2.1 ± 2.0% in the non-cachectic group. Cachectic patients had significantly decreased skeletal muscle mass content of upper and lower extremities compared with non-cachectic patients ($p=0.02$) and healthy controls ($p<0.001$). Muscle IκBα ($p=0.04$) and TNF-α ($p=0.03$) mRNA expression and NEDD4 ($p=0.03$) were significantly increased in cachectic patients compared with healthy controls. No increase was observed in the other E3 Ub ligases. In contrast, TRIM32 ($p<0.01$) showed a significant decrease in non-cachectic patients compared to both cachectic patients and healthy controls, whereas MURF-1 levels were unchanged.

Conclusion: These results indicate that NF-κB activity is increased in lung cancer cachexia but show that E3 Ub-ligases are expressed differently. As all assessed E3 Ub-ligases have shown to be important regulators in experimental models of cachexia, the observed distinct regulation in cachectic patients with NSCLC has implications for understanding the mechanism of human lung cancer cachexia. Further research is required to investigate the potential contribution of individual E3 Ub-ligases to human cancer cachexia in order to develop therapeutic interventions to prevent or reverse cachexia and increase survival of lung cancer patients.

Keywords: Non-small cell lung cancer, Cancer cachexia, Ubiquitin proteasome system, Skeletal muscle

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P2.200 IGF-1, IGFBP-3 AND VEGF IN SMALL CELL LUNG CANCER PATIENTS.

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Background: The insulin-like growth factor system: two peptide ligands (IGF-1 and IGF-2), their cell surface receptors (IGF-1R and IGF-2R) and at least six specific binding proteins (IGFBP1 – IGFBP-6), in the opinion of some investigators, plays important role in stimulation of proliferation and cell survival. Moreover, it is suggested that IGF-1 may participate in the development of angiogenesis in cancer, by regulation of VEGF expression and secretion via HIF-1-dependent and independent manner. The subject of the presented study was the evaluation of IGF-1, IGFBP3 and VEGF in respect to factors characterizing both insufficient supply and the developing of acute phase reaction in small cell lung cancer patients.

Methods: The study of IGF-1, IGFBP3 and VRGF were studied in 49 small cell lung cancer patients (LD-34, ED-19) before treatment and in the reference group of 29 healthy persons. For each investigated person Nutritional Risk Index (NRI). was evaluated The serum levels of IGF-1 and IGFBP-3 were determined using RIA and VEGF applyingg ELISA methods.

Results: In SCLC patients as compared with the reference group, there were found significantly higher IGF-1 and VEGF levels and lower NRI value, at lack of significant differences for IGFBP-3. Significant positive correlations between IGF-1 and IGFBP-3 ($r = 0.623$ $p = 0.0001$), and between IGFBP-3 and NRI ($r = 0.386$ $p = 0.006$) as well as negative correlation between IGFBP-3 and VEGF in small cell lung cancer group were observed. In the SCLC group no significant differences were found in the analyzed growth factors and binding protein in relation to stage of disease, probably due to low number of SCLC patients with extensive disease. However, the analysis of prognostic value of extent of disease, performance status, pretreatment

IFG-1, IGFBP-3, VEGF levels and NRI values revealed that presented worse prognosis patients with extensive disease as well as patients with low levels of IGFBP-3. The median survival of patients with limited and extensive disease was 23.0 and 6.5 months respectively and for patients with IGFBP-3 level higher than 3090 mg/L were 19.0 months, whereas with lower level of this binding protein - only 9.5 months (fig.1). Fig. 1

Conclusion:

- In SCLC patients with worse nutritional status there seems to be a characteristic tendency to decrease of IGFBP-3 and growth of VEGF levels
- Small cell lung cencer patients with low levels of IGFBP-3 have relatively increased risk of death.

Keyword: SCLC, insulin-like growth factor, angiogenesis

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P2.201 SERUM BIOMARKERS IN LUNG CANCER PATIENTS FROM TWO CLINICAL TRIALS OF CHEMOTHERAPY WITH OR WITHOUT THALIDOMIDE

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Background: Thalidomide, a drug with immuno-modulatory and anti-angiogenic activity was evaluated in combination with chemotherapy in two phase III, double-blind, randomized controlled trials in patients with advanced small cell lung cancer (SCLC) (n = 724) and non-small cell lung cancer (NSCLC) (n = 722). No survival benefit was found in either study.

Here, we investigate potential predictive and prognostic biomarkers in sera from a subset of the patients.

Methods: Serum samples were collected from a subset of patients with SCLC (n = 50) or NSCLC (n = 50) enrolled into the thalidomide studies, pre-treatment (C1) and / or before the fourth cycle of therapy (C4). Concentrations of vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor-2 (sVEGFR-2) and interleukin-8 (IL-8) were determined using enzyme-linked immunosorbent assay and correlated with clinical data including stage, response rate and progression-free survival (PFS).

Results: Baseline values of angiogenic factors are summarised in Table 1. Table 1: Baseline levels of angiogenic factors

	Small cell lung cancer			Non-small cell lung cancer		
Angiogenic factor	**n**	**Median (pg/mL)**	**Range (pg/mL)**	**n**	**Median**	**Range (pg/mL)**
VEGF	46	148	23.2 - 912	48	150	10.3 - 1361
sVEGFR-2	46	7909	90 - 13711	48	8243	3302 - 14515
IL-8	46	22.8	0 - 336	48	30.7	5.78 - 198

Limited stage SCLC was associated with a below median level of VEGF at baseline ($p = 0.041$). Baseline VEGF significantly correlated with IL-8 ($r = 0.496$, $p < 0.001$). Univariate analysis demonstrated that patients with low VEGF or IL-8 at baseline, had improved PFS compared to those with high values (median PFS 9.3 months versus 6.3 months for both markers ($p = 0.055$ and 0.068, respectively)). SCLC patients demonstrating a partial response (PR) had a lower mean baseline VEGF than those with stable disease (SD) or progressive disease (PD) (117 versus 196 pg/mL ($p = 0.047$)). In both SCLC and NSCLC, patients demonstrating a PR had a greater mean reduction in IL-8 compared to those with PD or SD (35 pg/mL from C1 to C4 versus 0.80 pg/mL ($p = 0.018$)). There were no significant associations between baseline sVEGFR-2 levels and outcomes. Changes in biomarker levels in the thalidomide and placebo groups were similar; for VEGF from C1 to C4 there was an insignificant mean reduction: 29.36 versus -32.93 pg/mL, respectively ($p = 0.465$).

Conclusion: Baseline serum VEGF is associated with disease stage in SCLC. Insufficient changes in serum VEGF levels may partially explain the lack of significant activity of thalidomide in the clinical trials. Our analysis supports the further study of IL-8 and VEGF as potential biomarkers in lung cancer. Additional biomarkers are being analysed, including basic fibroblast growth factor, soluble intracellular

adhesion molecule-1 and tumour necrosis factor-α.
Keywords: angiogenesis, thalidomide, Biomarkers, Lung cancer

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P2.202 PROGNOSTIC SIGNIFICANCE OF OSTEOPONTIN LEVELS IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH RADIO-AND RADIO-CHEMOTHERAPY

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Background: Hypoxia impairs susceptibility of tumor cells to cytotoxic drugs and ionizing radiation, causing an increase resistance to chemotherapy and radiotherapy, thus influences survival of patients. Osteopontin (OPN), multifunctional cytokine, is associated with tumor hypoxia and angiogenesis, and is related to more aggressive phenotype of tumor cells, metastasis and tumor progression.
The aim of this study was to evaluate prognostic importance of OPN non-small cell lung cancer patients treated with radio- and radio-chemotherapy.
Methods: The study included 173 patients treated in the Cancer Center and Institute of Oncology Gliwice Branch, between 2006 and 2010. Clinical stage was assessed (according to the TNM classification) as III-IV. The median age was 63 years (range 33 to 83 years). In this analyzed group 72% were male, 28% women. Performance status was assessed as: Zubrod 1-2: 78%, Zubrod 3-4: 22% of patients. All patients underwent radiotherapy for lung tumor and the regional lymph nodes, 82% of patients were treated with chemo-radiotherapy, 3% of patients underwent intrabronchial brachytherapy, 9% underwent surgery. The concentration of OPN was determined in plasma of patients, before treatment, using ELISA test (Human Osteopontin Immunoassay, R&D Systems). Statistical analysis was performed using STATISTICA (version 7.1). Influence of concentration of OPN on overall survival was assessed using log-rank test.
Results: The concentration of OPN in the analyzed group was within the range 14,9 – 619,1 ng/mL (median 101,7 ng/mL). OPN concentration values were significantly higher ($p<0,0001$) than in the reference group. The reference group consisted of 114 healthy persons, with a median concentration of OPN 47,85 ng/mL.
Only 21 patients (12%) patients in the study group OPN levels did not exceed the designated cut-off value (68,4 ng/mL). The remaining patients OPN concentrations exceeded this value several times. The present study demonstrated a statistically significant unfavorable impact of high initial concentration of OPN in the plasma on overall survival of the patients ($p<0,0001$).
Conclusion: The analysis has shown that high OPN level negatively affects survival in non-small cell lung cancer patients treated with radio- and radio-chemotherapy. This supports the studies that suggest the prospect of using OPN as prognostic marker in such therapy.
Keywords: osteopontin, Radiotherapy, Non-small cell lung cancer

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P2.203 PROGNOSTIC IMPLICATIONS OF EPIDERMAL GROWTH FACTOR RECEPTOR, KRAS AND BRAF GENE MUTATIONS IN RESECTED NON-SMALL CELL LUNG CANCER PATIENTS.

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Background: Surgery is considered the treatment of choice for early stage non-small cell lung cancer (NSCLC). However Ì´ 30% of early stage (IA) patients die within 5 years. The identification of biomarkers that will predict patients with a poor outcome and who may benefit from adjuvant therapies is crucial to improve patient survival. The epidermal growth factor receptor (EGFR) and its downstream factors KRAS and BRAF are mutated with different frequencies in non small cell lung cancer and such mutations predict clinical response to EGFR inhibitors. Because the prognostic role of these mutations remain unclear we undertook this study to evaluate the incidence of EGFR and KRAS mutations and their correlation with clinicopathological parameters and outcome in resected stage I-III NSCLC.
Methods: A cohort of 232 patients were evaluated; median age was 67 (range 30–84), Male/Female: 50/182; squamous/ADC/BAC/other: 98/100/4/30; smoker/never smoker:194/38, and stage I/II/III: 141/49/49. EGFR (exons 18 to 21), KRAS (exons 2 and 3) and BRAF (exons 11 and 15) genes were amplified by nested PCR and sequenced in both sense and antisense direction using 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA). Kaplan-Meier estimates of overall survival (OS) and disease free survival (DFS) were calculated for clinical and biologic variables using Cox model for multivariate analysis.
Results: EGFR mutations were present in 22 patients (9.6 %): 12 delections in exon 19, 10 point mutations in exon 21 (L858R). KRAS mutations were present in 39 patients (19.3 %): the most common KRAS mutations were G12C (42.0 %), G12V(23.0%) and G12D (7.6%). BRAF gene was wild type in all patients. Both EGFR and KRAS mutations were associated with adenocarcinomas (19/22, 86.4% p<0.000 and 24/39, 61.5%, p=0.002, respectively). EGFR mutations in adenocarcinomas were more frequent in women (P =0.001) and in never-smokers (P =0.003) whereas patients with KRAS mutations were more likely to be former/current smokers (92%). In the patients with ADC, EGFR exon 19 delections and L858R mutations were associated with better disease free survival (p=0.03). No difference in outcome was seen between patients harboring KRAS mutations.
Conclusion: Our findings suggest that the EGFR and KRAS mutations are frequent in adenocarcinomas while BRAF mutation is not present. KRAS is not a prognostic factor for survival. EGFR mutations could be used to identify patients with potential better outcome.
Keywords: EGFR, KRAS, BRAF mutations, Early Stage NSCLC, prognostic factors

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.204 ANALYSIS OF THE EXPRESSION OF REGULATORY T-LYMPHOCYTE ASSOCIATED MARKERS IN PERIPHERAL BLOOD SAMPLES FROM ADVANCED NSCLC

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Background: T-cell tolerance is an important mechanism for tumor escape. An imbalance of regulatory T-lymphocytes (Treg) could promote peripheral immune tolerance to tumor cells. Marker genes associated with the presence of Treg are CD127, CD8a, Foxp3, CD4, CD25 and TGF-β1. The aim of this study was to determine the expression level of these marker genes by qPCR in patients with non-small cell lung cancer (NSCLC) in advanced stages and to correlate them with clinic-pathological and prognostic variables.
Methods: 54 control individuals and 50 patients with advanced-NSCLC (IIIB-IV) treated with cisplatin and docetaxel were studied. Blood samples were collected at baseline and after 3 cycles of

chemotherapy in PAXgene Blood RNA Tubes and stored at -80ºC until RNA isolation. mRNA was reverse transcribed and RT-PCR was performed to analyze the expression of CD127, CD8a, Foxp3, CD4, CD25 and TGF-β1. Relative expression was normalized by endogenous genes (GAPDH and β-actin) using the Pfaffl formulae. Statistical analyses were considered significant at $p<0.05$
Results: The characteristics of the studied patients were: median age: 57.8 years [37.7-75.1], 89% males, 55% adenocarcinomas. We found significant differences in the expression levels of CD4 ($p<0.0001$), CD8 ($p=0.019$), CD25 ($p=0.003$), CD127 ($p=0.031$), Foxp3 ($p< 0.0001$) and TGF-β1 ($p<0.0001$) between patients and controls. Pair-matched samples comparing pre and post-treatment expression of TGF-β1 showed that it was significantly reduced after chemotherapy. Additionally, patients with higher ratios (baseline/post-treatment) of CD4 and TGF-β1 were associated with local metastasis and progression, respectively. Survival analysis revealed that patients with combined high expression of CD25 and low expression of CD127 (reflecting a Treg phenotype), had significantly reduced TTP (median 2,40 months vs 5,47 months, $p=0.001$) and a trend in OS (median 3.87 months vs 9.80 months, $p= 0.078$).
Conclusion: Based on gene expression analysis, it seems that the presence of a "Treg profile" in peripheral blood is associated with a poor prognosis in patients with advanced NSCLC. (This work was supported in part, by a grant [RD06/0020/1024] from Red Temática de Investigación Cooperativa en Cáncer, RTICC, Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Science and Innovation & European Regional Development Fund (ERDF) "Una manera de hacer Europa")
Keywords: prognostic, regulatory T-lymphocytes, Advanced NSCLC, Treg

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P2.205 ANALYTIC PERFORMANCE OF A NOVEL REAL-TIME PCR METHOD FOR THE DETECTION OF MUTATIONS IN EGFR IN FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE (FFPET) SAMPLES OF LUNG CANCER.

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Background: EGFR mutation testing is rapidly becoming a part of the standard diagnostic workup of non-small cell lung carcinomas (NSCLC), although there is currently no standardised method to perform the mutational analysis. Direct sequencing is still a commonly used method despite its low sensitivity, long turn around time and labour requirements. Recent advancements in molecular technologies such as real-time PCR have enabled the design of rapid and sensitive detection assays for genetic alterations, but typically with a limited degree of mutation coverage. This is the first report of the clinical testing of a novel real-time PCR assay with comprehensive EGFR mutation coverage.
Methods: The cobas EGFR Mutation Test (Roche Molecular Systems Inc, Pleasanton, CA, USA) is an investigational real-time PCR assay which is designed to detect 43 mutations within exons 18, 19, 20 and 21 of the EGFR gene. The assay can be performed on DNA isolated from a single 5 micron FFPET tissue section, and provides an automated test result. This assay was used to assess EGFR mutation status of 51 NSCLC samples, which had been previously tested by direct sequencing using published primers (Conde et al. Clin Cancer Res 2006), as part of clinical care (lung cancer specimens received at Laboratorio de Dianas Terapeúticas between 2007-2011). The tumor content of the samples ranged from 20 to 90%, and macrodissection was performed in eight cases. DNA extraction for the original sequencing was performed with the QIAamp DNA FFPE Tissue kit and automated on the QIAcube robot (QIAGEN, Valencia, CA). This previously isolated DNA was adjusted to the required volume for the cobas test prior to PCR amplification and detection.
Results: The test gave valid test results in 50/51 samples (98%), and detected 8 EGFR mutations (16%) including three E746-A750del, three L858R, one D770-N771insSVD, and one V769-D770insASV, all of which were confirmed by the prior Sanger sequencing results. Sanger sequencing had also identified a rare D770_N771insN, which the cobas test was not designed to detect. The analytical run time for the cobas test was ≤ 2.5 hours, including PCR set-up, and the post-analytical phase was fully automated. The results of testing in a larger cohort of samples, together with a sensitivity study, will be presented.

Conclusion: Our preliminary study indicates that the test has a low failure rate and provides rapid results (≤ 2.5 hours). Furthermore the reagents in the test kit are configured in a manner to reduce the need for batching samples. The rapid turnaround time and the ability to offer the test more frequently offers a significant improvement over current laboratory turn around times for direct sequencing of 7-10 days.
Acknowledgment: Testing reagents were provided by Roche Molecular Systems. This work was partially funded by Fundación Mutua Madrileña.
Keywords: lung carcinoma, EGFR, real-time quantitative PCR

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P2.206 SOX2-RELATED MICRORNAS AS PROGNOSTIC MARKERS OF RECURRENCE IN SURGICALLY TREATED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: SOX2 is a transcription factor essential for early mammalian development and for maintenance and regulation of stemness in human embryos and adult tissues. SOX2 overexpression has been observed in NSCLC and other solid tumors. miR-145 and the miR-302-367 cluster are involved in stemness through SOX2 regulation. miR-145 plays an important role in SOX2 translation, and SOX2 regulates the expression of the miR-302-367 cluster. We have analyzed the expression of miR-145 and the miR-302-367 cluster in tumor and paired normal tissue samples from 70 surgically treated NSCLC patients (p) and correlated our findings with time to recurrence (TTR).
Methods: We analyzed the expression of miR-145 and miR-302-367 cluster (miR-302b*,b, c*,a, a*,d and 367) in 70 tumor and 70 paired normal tissue samples from NSCLC p who had undergone complete surgical resection from 2006 to 2009. RNA was obtained from fresh frozen tumor and normal tissue using the Trizol method and microRNA expression was detected using TaqMan MicroRNA Assays (Applied Biosystems).
Results: p characteristics: mean age, 67 (46-83); 83% male; all p were PS 0-1; 44 (62.9%) stage I, 12 (17.1%) stage II, 14 (20%) stage III; 36 (51.4%) adenocarcinoma, 28 (40%) squamous cell carcinoma; 18 (25.7%) received adjuvant treatment. With a mean follow-up of 17 months (m), 23 p (32.9%) had relapsed. miR-145 expression was downregulated (P<0.001), and miR-367 expression was upregulated (P<0.001) in tumor compared to normal tissue samples. Mean TTR for p with low miR-145 levels was 18.4 m vs 28.2 m for p with high miR-145 (P=0.015). Mean TTR for p with low miR-367 levels was 29.1 m vs 23.4 m for p with high miR-367 (P=0.048). In the multivariate analysis, high miR-145 expression (OR, 0.33; 95%CI, 0.13-0.82; P=0.018), low miR-367 expression (OR, 0.297; 95%CI, 0.09-0.94; P=0.038), and stage I disease (OR, 0.22; 95%CI, 0.07-0.73; P=0.013) emerged as independent markers for longer TTR.
Conclusion: p with high miR-145 or low miR-367 expression have a longer TTR. For the first time, we show that miR-145 and miR-367 are involved in NSCLC and could be novel markers for tumor relapse in surgically treated NSCLC p.
Keywords: miR-367, NSCLC, miR-145, SOX2

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P2.207 INSULIN-LIKE GROWTH FACTOR RECEPTOR 1(IGF1R) AND EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) AMPLIFICATION AND EXPRESSION IN SURGICALLY RESECTED NSCLC.

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Background: IGF1R represents a novel molecular target in non-small-cell lung cancer (NSCLC). IGF1R and EGFR activation is essential to mediate tumor cell survival, proliferation and invasion. This study investigates the prognostic role of IGF1R and EGFR copy number gain (CNG) by fluorescence in situ hybridization (FISH) and protein overexpression by immunohistochemistry (IHC) in surgically resected NSCLC.
Methods: 114 NSCLC patients were evaluated; median age was 66y (range 40–84), Male/Female:96/18; squamous (SCC)/adeno/BAC/other:59/34/9/12; smoker/never smoker:105/9, and stage I/II/III:71/18/25. IGF1R and EGFR FISH were tested by customized and commercial probes, respectively; positive specimens showed gene amplification or polysomy (≥4 copies in ≥10% of tumor cells). IGF1R and EGFR protein expression were evaluated using mouse antibodies (clones 24-31 and 3147, respectively); overexpression was defined by ≥10% positive cells. Kaplan-Meier estimates of survival and time to recurrence were calculated for clinical and biologic variables using Cox model for multivariate analysis.
Results: 46 tumors (40%) were IGF1R FISH+ and 76 (77%) were EGFR FISH+. IGF1R FISH+ was associated with EGFR FISH+ (p=0.03) and co-amplification was observed in 34 cases (30%). IGF1R and EGFR FISH+ were associated with SCC (p=0.01 and p=0.05, respectively). IGF1R and EGFR overexpression was detected in 36% and 55% of NSCLC patients and co-expression was detected in 25%. Co-amplification and co-expression of both receptors were significantly associated (p=0.045). IGF1R and EGFR co-amplification and co-expression associated with shorter disease free survival (DFS; p=0.05, p=0.05 respectively), also at multivariate analysis adjusting for stage (p=0.0002).
Conclusion: IGF1R and EGFR are frequently co-amplified in NSCLC and CNG correlates with protein overexpression. Both co-amplification and co-expression of IGF1R and EGFR predicts shorter DFS. These results provide a strong rational for targeting simultaneously EGFR and IGF1R in clinical trials for NSCLC. We thank Italian Association for Cancer Research (AIRC) for supporting the study (AF Fellowship)
Keywords: IGF1R, EGFR, NSCLC, Early Stage, Prognosis

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P2.208 ERBB2 AND ERBB3 EXPRESSION IN RESECTED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS)

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Background: EGFR deregulation has been extensively studied in NSCLC, but less is known about the expression and role of other ErbB receptors. The aim of this study is to determine ErbB2 and ErbB3 expression in NSCLC and to explore their clinical and pathological features.
Methods: Tumor samples from 126 NSCLC pts who underwent complete resection in our institution from October 2007 to September 2010 were analyzed. Tissue microarrays were used to study ErbB2 and ErbB3 expression by immunohistochemistry; expression was graded by two independent observers and tumors with a 2+/3+ score were classified as "high
expression". ErbB2 by FISH was analyzed in pts with high ErbB2 expression. EGFR-mutation (mut) status was determined in selected pts.
Results: Pts characteristics: median age 67 yrs, 81% male, 6% never smokers, 40% adenocarcinoma (ADC)/ 39% squamous-cell (SCC)/ 21% others, p-stage 33% I/28% II/30% III/ 9% IV. High ErbB2 expression was found in 5 (4%) pts: all 5 male, 1 never smoker, 3 ADC/2 SCC. None of these pts was ErbB2 FISH+. High ErbB3 membranous and cytoplasmic expression was found in 27% and 21% of samples, respectively, with 10% of samples having high expression at both sites. No correlation was found between ErbB3 expression and age and p-stage. High ErbB3 expression was more frequent in females than in males (membranous 46% vs 22% p= .038; cytoplasmic 33% vs 18% p= .099, respectively), in ADC than in the other histologies (membranous 36% vs 21% p= .07; cytoplasmic 32% vs 13% p =.014, respectively). Five of 23 pts had EGFR-mut (2 del exon 19, 3 L858R exon 21): all 5 female with ADC, 4 never smokers. No EGFR-mut pt had concomitant high ErbB2. Four EGFR-mut pts had high cytoplasmic ErbB3

expression (80%), 3 (60%) had membranous expression. With a median follow up of 17 months there was no association between ErbB3 expression and disease-free or overall survival.
Conclusion: High ErbB2 expression is infrequent in NSCLC. Interestly, ErbB3 can be highly expressed in NSCLC and seems more frequent in females, ADC and EGFR-mut tumors. ErbB3 expression and its use as therapeutic target warrants further study in NSCLC.
Keywords: EGFR, NSCLC, ErbB2, ErbB3

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P2.209 MYC AND HUMAN TELOMERASE GENE (TERC) GENE COPY NUMBER GAIN IN RESECTED NON-SMALL CELL LUNG CANCER (NSCLC).

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Background: Long-term survival of resected NSCLC is disappointing and the identification of biological prognostic factors is critical. Abnormalities in MYC are well known in lung cancer and TERC maps in chromosomal region with frequent copy number gain (CNG) in NSCLC. This study investigates the incidence of MYC and TERC CNG and evaluates their correlation with clinicopathological parameters and outcome in resected NSCLC
Methods: 113 NSCLC patients subjected to curative pulmonary resection were tested for TERC and MYC CNG by fluorescence in situ hybridization (FISH) using commercial probes. Median age was 66 years (range 40–84); most patients were male (84%), former/current smokers (92%), had poorly differentiated histology (42%) and stage I disease (62%). The histological types included 51% squamous cell carcinoma (SCC), 30% adenocarcinoma, 8% BAC, and 11% of other subtypes. CNG was determined when ≥4 gene copies were displayed in ≥40% of tumor cells. Kaplan-Meier estimates of survival and time to recurrence were calculated for clinical variables and biologic markers using the Cox model for multivariate analysis.
Results: Forty-one (36%) patients showed CNG for MYC and 41 (36%) for TERC. MYC and TERC gene amplification (GA) were found in 9 (8%) and 15 (13%) cases, respectively. MYC and TERC contemporary CNG was observed in 12 cases (11%): 2 (17%) cases with GA vs 10 (83%) high polysomy. TERC CNG was associated with SCC histology (80% vs 20% in non-SCC; p=0.001). In univariate analyses, both MYC CNG and GA were associated with shorter disease free survival (DFS, p=0.032 and p=0.022, respectively) and overall survival (OS; p<0.032 and P<0.000, respectively) while TERC CNG or GA showed no association. In multivariate analysis including stage and age, MYC CNG and GA remained significantly associated with worse DFS (p=0.022; p= 0.011 respectively) and OS (p=0.026; p<0.000), respectively).
Conclusion: Our results indicate that MYC and TERC are frequently amplified in NSCLC. TERC CNG shows phenotypic properties strongly associated with SCC and is not a prognostic factor. CNG for MYC is a strong predictor of worse survival. We thank Italian Association for Cancer Research AIRC (AF Fellowship).
Keywords: TERC, MYC, Early Stage NSCLC, Prognosis, FISH

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P2.210 INCREASED CD8+ T CELL PROLIFERATION FOLLOWING CHEMOTHERAPY PREDICTS IMPROVED SURVIVAL IN PATIENTS WITH THORACIC MALIGNANCIES

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Background: Chemotherapy and immunotherapy have historically been considered antagonistic,

partly because lymphopaenia is a toxicity of most cytotoxic drugs. Recently, research in animal models has demonstrated that chemotherapy may actually enhance anti-tumour immunity by altering both the level and context of antigen presentation. However, despite increasing interest in combining chemo and immunotherapy, little is known of the effects of chemotherapy on the human anti-tumour immune response. This study investigated the longitudinal effects of standard chemotherapy regimens on T cell subsets in patients with malignant mesothelioma (MM) and advanced non-small cell lung cancer (NSCLC). CD8+ T cells, which drive anti-tumour immunity, and regulatory T cells (Treg), which play a suppressive role, were specifically assessed.
Methods: 43 patients (27 MM and 16 NSCLC) were enrolled between 2007 and 2009. Serial blood samples were collected over four treatment cycles (baseline, cycle 1 day 8, post cycle 1, and post cycle 3) and analysed using multi-parameter flow cytometry.
Results: Total lymphocyte numbers were significantly reduced one week following the first dose of chemotherapy (mean 1.50 x 10^9/L (baseline) versus 1.30 (cycle 1 day 8); $p<0.01$) and then continued to decline at a slower rate throughout the course of treatment (1.23 (post cycle 1); 1.21 (post cycle 3); $p<0.001$ relative to baseline). Proliferating CD8+ T cells and Treg were almost entirely depleted at cycle 1 day 8, but rapidly recovered with higher than baseline levels of proliferating cells at the end of each treatment cycle (mean Ki67+ CD8+ T cells 5.6% (baseline) versus 7.6% (post cycle 1); $p<0.05$ and Ki67+ Treg, 17.8% versus 26.9%; $p<0.001$). Treg numbers were most profoundly affected, with a decline in the relative size of this population one week after chemotherapy (mean of CD4+ T cells 6.3% (baseline) versus 5.1% (cycle 1 day 8); $p<0.01$). Activated effector CD8+ T cells were detected both before and after treatment, suggesting a degree of antigen-driven activation. Tumour antigen - specific CD8+ T cells were identified in 10% of patients but did not alter following chemotherapy. Higher proportions of proliferating CD8+ T cells and activated effector CD8+ T cells and Treg at baseline were predictive of poorer overall survival in univariate regression analyses ($p<0.05$, $p<0.05$ and $p<0.01$ respectively), suggesting that greater immune activity may be present in patients with more advanced disease. Conversely, increased CD8+ T cell proliferation following one cycle of chemotherapy was predictive of improved survival in both univariate ($p<0.05$) and multivariate analysis including both immunological and clinical variables ($p<0.05$). Chemotherapy-induced change in CD8+ T cell proliferation was more predictive of outcome than any baseline clinical variable included in the model, including performance status.
Conclusion: Lymphodepletion following chemotherapy was not found to be detrimental but instead appeared to reset the stage, temporarily removing Treg mediated suppression and enabling regeneration of the CD8+ T cell pool. This may represent a window of opportunity for manipulating these newly reconstituted T cells by combining chemotherapy with immunotherapy to skew the immune response in favour of effective anti tumour immunity.
Keywords: T cells, Chemotherapy, Non-small cell lung cancer, mesothelioma

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P2.211 SYSTEMATIC EVALUATION OF GENETIC VARIANTS IN THREE BIOLOGICAL PATHWAYS ON PATIENT SURVIVAL IN EARLY-STAGE NON-SMALL CELL LUNG CANCER

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Background: Studies from selected candidate genes suggest that single nucleotide polymorphisms (SNP) in genes involved with glutathione metabolism, DNA repair, or inflammatory responses may affect survival in early-stage non-small cell lung cancer (NSCLC). In this study, we took a systematic pathway-based approach to evaluate the impact of genetic variation from these

three pathways on survival for early-stage NSCLC.
Methods: DNA from 647 patients with Stage I and II NSCLC was genotyped for 480 SNPs (tagSNPs) tagging 57 genes from the three candidate pathways. Associations of tagSNPs with patient survival were assessed at the individual SNP and whole gene levels adjusting for age, tumor stage, surgery type and adjuvant therapy. The association of genotype combinations of the SNPs associated with post-diagnosis survival was also estimated.
Results: Among the 412 tagSNPs that were successfully genotyped and passed all quality assessments, 28 showed association with survival ($p<0.05$). Two of the 28 were estimated to have less than a 20% chance of being false positive (rs3768490 in GSTM4 gene: $p=1.32\times10^{-4}$, $q=0.06$; rs1729786 in ABCC4 gene: $p=9.25\times10^{-4}$, $q=0.20$). Gene-based analysis suggested that, in addition to GSTM4 and ABCC4, variation in two other genes, PTGS2 and GSTA2, was also associated with survival following detection of early-stage NSCLC.
Conclusion: We describe further evidence that variation in genes involved in the glutathione and inflammation pathways is associated with survival in early-stage NSCLC. Further study is warranted to verify our findings and elucidate the functional mechanisms of how these risk variants may influence survival in NSCLC patients.
Keywords: genetic polymorphisms, DNA repair, inflammation response, glutathione metabolism

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P2.212 COMPARISON OF TWO DIFFERENT EGFR GENE MUTATION TESTS FOR RESECTED LUNG ADENOCARCINOMA

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Background: Information of epidermal growth factor receptor (EGFR) gene mutation status is crucial for non non-small lung cancer patients in selecting their therapy, because it is a predictor for the efficacy of EGFR tyrosine kinase inhibitors. Four EGFR gene mutation tests are commercially available in Japan. However differences in sensitivity between these tests have not been investigated. This study compared the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp assay (PNA-LNA PCR-Clamp) with the cycleave polymerase chain reaction assay (Cycleave-PCR) using formalin-fixed paraffin-embedded (FFPE) tissue samples of resected lung adenocarcinoma.
Methods: We examined the EGFR gene mutation status in 42 lung adenocarcinoma patients who underwent curative operation at Tokushima University Hospital from 2004 to 2010. They included 15 males and 27 females and their mean age was 67 (range; 29 - 82). In these 42 patients, there were 15 smokers (35.7%). Pathologic staging was IA in 15, IB in 13, IIB in 5, and IIIA in 9. FFPE tissue was sliced at 10-μm thickness and five sections were used for each test (PNA-LNA PCR-Clamp assay and Cycleave-PCR assay). Fixation time was usually one week. Each sample was tested in a blinded manner by each laboratory
Results: PNA-LNA PCR-Clamp assay detected 25 (61.0 %) EGFR gene mutation-positive samples and failed in 1 (2.4 %) case. Cycleave-PCR assay detected 28 (66.7 %) EGFR gene mutation-positive samples without failure. Concordance rate between the two methods was 95.1 % (39/41). Among the concordant cases, 14 (35.9 %) EGFR gene mutations were found at exon 19, and 11 (28.2 %) mutations were found at exon 21. According to the discordance, two samples with EGFR gene mutation-negative in PNA-LNA PCR-Clamp assay were revealed to have EGFR gene mutations at exon 19 in Cycleave-PCR assay.
Conclusion: Cycleave-PCR assay demonstrated higher EGFR gene mutation-positive rate than PNA-LNA PCR-Clamp assay without failure. These discordances need confirmation by other EGFR gene mutation tests.
Keywords: EGFR, Adenocarcinoma, EGFR gene mutation test

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P2.213 TOPOISOMERASE II, CARBONYL REDUCTASE I, CHEMOSENSITIVITY AND TOXICITY FOR AMRUBICIN IN THE SECOND-LINE TREATMENT OF PATIENTS WITH SMALL-CELL LUNG CANCER. THE RESEARCH FROM TORG 0301

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Background: Amrubicin (AMR) has been suggested to provide a new effective therapeutic option for small-cell lung cancer (SCLC). It is a totally synthetic 9-aminoanthracyclin and converted by carbonyl reductase I (CBR-I) to its active form, amrubicinol, that has higher potent activity than the parent drug and inhibits purified human topoisomerase II (topo-II). We previously reported the promising result of a prospective phase II trial for AMR monotherapy in patients with second-line SCLC (Thoracic Oncology Research Group Study 0301). Using blood samples at enrollment in this trial, the clinical significance of topo-II and CBR-I expression levels on antitumor effect as well as toxicity has been examined.
Methods: Total RNA was extracted from the blood with an RNeasy Mini Kit (Qiagen Inc.) and DNase treatment was performed using the RNase-Free DNase Set (Qiagen Inc.). RT-PCR analysis was performed using TaqMan technology. Quantification of target cDNA (Top-II alpha, CBR-I and beta-actin gene) was conducted using an ABI PRISM 7700 Sequence Detection System (Applied Biosystems Inc.). Quantification was performed using the relative standard curve method.
Results: The trial registered a total of 60 patients, of which 40 blood samples were available. Nineteen patients achieved a CR or PR to AMR according to the RECIST assessment and 21 did not. Patients with tumor response had a significantly lower Topo-II level than those without (p=0.0465, Wilcoxon test), although there was no association between tumor response and the level of CBR-I (p=0.3229, Wilcoxon test). We did not find any significant association between the levels of the two enzymes and toxicity.
Conclusion: Topo-II may be a potential predictor of response in the treatment of AMR for second-line SCLC. Further investigations in larger patient materials are warranted.
Keywords: SCLC, amrubicin

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P2.214 EVALUATION OF VERISTRAT® SIGNATURE IN ADVANCED BRONCHIOLOALVEOLAR CARCINOMA (BAC): A POOLED ANALYSIS OF IFCT 0401 AND 0504 TRIALS

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Background: Based on results from Phase II trials, it was suggested that EGFR-TKIs have reduced activity in mucinous BAC, while taxane-based chemotherapy could have some effect both in mucinous (M) and nonmucinous (NM) cytological subtypes. Two phase II trials conducted by French Intergroup of Thoracic Oncology (IFCT) evaluated first-line gefitinib (IFCT0401) and first-line erlotinib or carboplatin/paclitaxel (C/P) (IFCT0504). VeriStrat is a pretreatment mass spectrometry-based test that assigns a "Good" or "Poor" classification, shown to correlate with survival on EGFR-TKIs therapies

in advanced NSCLC with a hazard ratio (HR) of approximately 0.5. This study aimed to evaluate the VeriStrat test in advanced BAC patients included in IFCT 0401 and 0504 trials.
Methods: Pretreatment samples (64 from IFCT0401 and 114 from IFCT 0504) were available for VeriStrat testing. The only population difference between the two trials was the proportion of men (45.5% vs. 60.9%); there was no difference in age, smoking status, or proportions of cytological subtypes.
Results: 175 samples were assigned VeriStrat classification; 148 were classified as "Good", 27 as "Poor". No significant correlation was found between VeriStrat classification and M and NM cytology, or other patient characteristics. In the combined population there was no significant difference in PFS between "Good" and "Poor" patients (p=0.26, median PFS: 100 days in "Good", 66 days in "Poor") or between treatments (p = 0.095, HR = 1.32; 95%CI 0.95-1.83; PFS 201 days in C/P, 90 days in EGFR-TKIs). Patients with M cytology had significantly longer PFS when treated with C/P than EGFR-TKIs (p = 0.0002, HR=0.39; 95%CI 0.24-0.64; PFS 143 days in C/P, 64 days in EGFR-TKIs); no significant difference between "Good" and "Poor" was found in M patients treated with P/C or with EGFR-TKIs. Patients with M cytology identified as "Good" benefited more from chemotherapy than from EGFR-TKIs (p = 0.0001; HR= 0.33, 95%CI 0.19-0.58; median PFS: 198 days in P/C, 81 in EGFR-TKIs); no difference in PFS between treatments was found in "Poor" M patients. In NM patients there was no significant difference between treatment arms; no comparison between VeriStrat groups was done in the NM subset treated with EGFR-TKIs due to an insufficient number of "Poor" subjects; PFS in the NM P/C-treated subset was significantly different between "Good" and "Poor" (p=0.039, HR= 0.17, 95%CI 0.03-0.91; median PFS: 269.5 days in "Good" and 70.5 days in "Poor"). There was no treatment-related difference in PFS in the NM "Good" group.
Conclusion: In contrast to previous results, in non-BAC NSCLC VeriStrat did not separate PFS in the EGFR-TKI-treated population of ADC-BAC, but did show significantly different PFS in NM patients treated with P/C. M and NM patients presented different susceptibilities to chemotherapy and EGFR-TKIs. Patients with M cytology classified as VeriStrat "Good" may benefit more from chemotherapy than from EGFR-TKIs, while NM patients derive similar benefit from both treatments; the predictive value of VeriStrat in BAC needs validation in larger studies.
Keywords: bronchioloalveolar carcinoma, Mass spectrometry-based test VeriStrat, Mucinous cytological subtype, Nonmucinous cytological subtype

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P2.215 HIGHLY EXPRESSED ADAM9 IN COMPLETELY RESECTED STAGE I NON-SMALL CELL LUNG CANCER CASES PREDICTS A SHORTENED SURVIVAL

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Background: A disintegrin and metalloproteinase-9 (ADAM9) was recently found highly expressed in some malignant solid tumors, correlates with cancer progression, metastasis, and predicts a shortened patients' survival. However, the expression of ADAM9 in human resected lung cancer tissues, and its clinical significance are not clear. Here, we investigate the abnormal expression of ADAM9 on protein level in human resected non-small cell lung cancer (NSCLC) tissues, to evaluate the significance of ADAM9 expression in surgically resected NSCLC.
Methods: Sixty-four cases of completely resected stage I NSCLC with mediastinal N2 lymph node dissected were immunohistochemically analyzed for ADAM9 protein expression. Survival analysis, univariate and multivariate analysis were conducted to asses the significance of ADAM9 expression and the relationship with other clinicopathological characteristics.
Results: In 64 cases of completely resected stage I NSCLC, 53.1% (34/64) was found with ADAM9 protein highly expressed (ADAM9+), significantly higher when compared with normal control lung tissues (P=0.001). In 48 adenocarcinoma cases, 66.7% (32 cases) was found with ADAM9 protein

highly expressed, however, in 16 cases of squamous cell carcinoma, only two cases (12.5%) showed ADAM9 highly expressed, the difference was statistically significant (P=0.000). There is no difference found between ADAM9 high expression rates in stage IA and IB group (P>0.05). The overall 5-year survival rate was 71.8% for this group of 64 completely resected stage I NSCLC cases with lobectomy and local hilar (N1) and mediastinal (N2) lymph nodes dissection performed. The 5-year survival rate in ADAM9 low expression (ADAM9-) group (30 cases) was as high as 88.9%, however, the 5-year survival rate was sharply decreased to 56.9% in ADAM9 high expression (ADAM9+) group (34 cases), the difference was statistically significant (P=0.012). There is no statistically significant effect of ADAM9 expression on the survival of patients found in different histological types, pathologic stages. In 24 stage IA cases, the 5-year survival rate for ADAM9 low expression group (8 cases) was 100%, it sharply decreased to 55.0% for ADAM9 high expression group (16 cases), the difference was statistically significant (P=0.049). In the 40 stage IB cases, the 5-year survival rate for ADAM9 low expression group (22 cases) was as high as 84.8%, but it decreased sharply to 55.6% for ADAM9 high expression group (18 cases), the difference was statistically significant (P=0.030). Cox regression model was used for multivariate survival analysis: patients' gender, age, smoking status, histological types, pathologic stages (IA and IB) and ADAM9 high/low expression, were entered into Cox proportional hazard regression model. The results showed that ADAM9 high/low expression was the independent predictor of prognosis for this group of completely resected stage I NSCLC (HR=3.385, 95% CI: 1.224-9.360; P=0.019).

Conclusion: The results showed clearly for the first time that ADAM9 is highly expressed in NSCLC and highly expressed ADAM9 correlates with shortened survival, suggesting that ADAM9 is a novel biomarker for predicting the prognosis in resected stage I NSCLC, and ADAM9 might become a useful predictive biomarker for selection of adjuvant chemotherapy treatment.

Keywords: immunohistochemistry, ADAM9, lung neoplasm, Prognosis

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P2.216 ESTROGEN HORMONE RECEPTOR EXPRESSION IN WOMEN WITH NON-SMALL CELL LUNG CANCER.

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Background: Non-smal cel lung cancer (NSCLC) is the leading cause of cancer death in men and rates second among women in Brazil. It has been reported that women tend to develop NSCLC at an earlier age, have increased susceptibility to cancer and have better survival when compared with men. The biological reasons for these differences remain unknown. The aim of this study is to explore the expression of ER and its relationship with clinical factors in women with NSCLC.

Methods: This is a descriptive analysis of 53 consecutive female patients (pts) diagnosed with NSCLC at the Oncology Service, Hospital São Lucas, PUCRS, between January 2007 and April 2010. ER was analyzed by Immunohistochemistry (Rabbit IGG, Biocare Medical). Positive ER expression was considered if >1% cells showed nuclear staining.

Results: Mean age at diagnosis, 58.9y (35-89) and about 30% of pts were non-smokers. Nine records had no information on smoking. Adenocarcinoma (49,1%), squamous cell carcinoma (24,5%), adenosquamous carcinoma (1,9%) and NSCLC NOS (24,5%) were the reported histological subtypes. At baseline, 45,3% had stage IV and 60,4% performance status of 0-1. A total of 9/56 pts (17%) showed ER expression by IHC. Of the early stage pts (I-IIIA) ER positive pts represented 10% of cases while they were 19,4% of cases with advanced stage (IIIB-IV). The distribution of ER expression according to histology was equal in Adenocarcinoma and Squamous (15,4%). The 3 other positive pts had NSCLC-NOS. A total of 19,4% of smokers were ER positive while there were no positive cases among non-smokers. The distribution of ER positive cases according to age was 16,6% in pts <50y and 17% in pts >50%. Considering the whole group of pts, median survival was 7,5 months in ER positive cases

vs 10,4 months in pts with no ER expression. Median survival of ER positive stage IV pts was 4,7 months while it was 6,0 months in ER negative patients. In the older women (>50y) median survival of ER positive pts was 6.8 months while it was 11,9 months in ER negative pts. In the younger cohort (<50y) median survival was 9,5 months in ER positive and 5,7 months in ER negative cases.
Conclusion: This retrospective analysis does not seem to identify a clear relationship of ER expression and survival in women with NSCLC. Small numbers in this subgroup of pts compromises definitive conclusions. Larger prospective trials addressing clinical factors to ER expression in NSCLC are needed.
Keywords: Estrogen Hormone Receptor, Lung cancer, Women

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P2.217 VARIOUS SENSITIVE MOLECULAR DETECTION TECHNIQUES FOR EGFR MUTATIONS IN NSCLC, BY 20 FRENCH CENTERS – PRELIMINARY RESULTS ON CELL LINES OF ERMETIC-2/PREDICT.AMM STUDIES.

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Background: EGFR Tyrosine Kinase Inhibitors (TKIs), gefitinib or erlotinib, is an effective treatment for patients with non-small cell lung cancer (NSCLC) tumors expressing EGFR-sensitizing mutations. Molecular selection should be performed since clinical characteristics were shown to be insufficient to accurately select patients harboring EGFR mutations. After direct sequencing, various more sensitive and less time-consuming molecular methods have been developed for EGFR detection because gefitinib obtained restrictive EMA/FDA approval for first line treatment of patients with EGFR mutated NSCLC.
Methods: Three EGFR mutated NSCLC cell lines, SW48 (G179S), H1650 (DE746-A750), H1975 (T790M, L858R) and three wild-type DNA were blinded and simultaneously analyzed. DNA from each mutated cell line was diluted into wild-type DNA (100%, 20%, 10%, 5%). Twenty French molecular laboratories from ERMETIC-2 (Evaluation of the EGFR Mutation status for the administration of EGFR-TKIs in non-small cell lung Carcinoma) and PREDICT.amm (Prediction of treatment of extended NSCLC – using of molecular markers) national studies used their current molecular sensitive techniques for EGFR mutation detection.
Results: The table indicated by molecular technique, the number of centers which were able to detect the mutation related to the number of centers using the technique.

Cell line	Direct sequencing	Targeted techniques	Fragment analysis	HRM	Pyrosequencing
EGFR exon18, SW48, G719S		(*)			
100%	10/10	4/4	NR	5/5	1/2
20%	8/10	4/4	NR	4/5	2/2
10%	2/10	4/4	NR	3/5	2/2
5%	0/10	2/4	NR	1/5	0/2
EGFR exon19, H1650, (DE746-A750)		(**)			
100%	9/9	1/1	10/10	5/5	3/3
20%	7/9	1/1	10/10	5/5	2/3
10%	1/9	1/1	8/10	2/5	2/3
5%	0/9	1/1	5/10	1/5	0/3
EGFR exon20, H1975, T790M		(***)	NR		
100%	7/9	5/5	NR	4/5	2/3
20%	3/9	4/5	NR	3/5	2/3
10%	1/9	4/5	NR	0/5	2/3
5%	0/9	3/5	NR	0/5	0/3
EGFR exon21, H1975, L858R		(****)	NR		
100%	9/9	7/7	NR	5/5	2/3
20%	3/9	5/7	NR	3/5	2/3
10%	1/9	5/7	NR	1/5	1/3
5%	0/9	4/7	NR	0/5	0/3

NR: Not Relevant; (*) snap-shot analysis (1 center), real-time PCR (2 centers), short sequencing (1 center); (**) real-time PCR (1 center); (***) snap-shot analysis (1 center), real-time PCR (4 centers); (****) real-time PCR (5 centers), RFLP (1 center), snap-shot (1 center) For EGFR exon 18 analysis, one false positive result was observed with HRM analysis. For EGFR exon 19 analysis, one false positive result was observed with fragment analysis. For EGFR exon 20 T790M mutation analysis, 5 false-positive results (one center) were observed with HRM. For EGFR exon 21 analysis, no false-positive result was detected.

Conclusion: Conclusions and perspectives: In routine analysis of mutated cell lines, alternative molecular techniques for mutation detection in NSCLC cells are more sensitive than direct sequencing, but sensitivity could be different among techniques. Furthermore, some false-positive results could be observed. The next step is to use these techniques in the "real-life" on paraffin-embedded NSCLC samples, as in ERMETIC-2 and in PREDICT.amm studies in order to analyze these techniques in the context of poor tumor cells and lower DNA quality samples.

Keyword: EGFR, mutation, molecular methods, ERMETIC-2, PREDICT.amm, NSCLC

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P2.218 PROTEOMICS ANCHORED SYSTEMS BIOLOGY ANALYSIS OF PROGNOSTIC FACTORS IN PRIMARY LUNG ADENOCARCINOMA TUMOURS

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Background: Protein level analysis has several benefits; proteins can be measured both in tissue and plasma and the majority of novel cancer drugs target proteins. Mass spectrometry (MS) is a powerful technology for the analysis of large numbers of endogenous proteins. We have developed methods to improve proteome analysis in lung cancer tissue[1], plasma and pleural effusion samples[2]. We have previously used these methods to detect proteome changes in lung cancer cells[3] and further validated these in tumor tissue[4]. In this study we performed a proteomics anchored systems biology analysis of tumor tissue to elucidate the molecular profiles of lung adenocarcinoma. In addition to comprehensive proteomics data, mRNA and miRNA expression and gene copy number alterations from same samples have been analyzed in relation to the proteomics data to elucidate the mechanisms behind tumor progression. The data has been correlated to clinical data on relapse and node invasion at time of surgery.

Methods: Surgical samples (n=8 relapse free and 8=relapse cases) were analyzed. Samples were fractionated by two dimensional fractionation using peptide isoelectric focusing followed by nLC-MS/MS analysis. Quantitative proteomics data was generated using isotopic labelling (iTRAQ). Proteome was analysed by mass spectrometry based proteomics. Multivariate data analysis (PLS) was used to select significant protein level

alteration between the groups. Further, biological interpretation of data was performed by pathway analysis. Early validation of marker profiles and altered pathways were performed using western blot and IHC.
Results: We identified and quantified over 3500 proteins. This is a one of the most comprehensive tumor proteomics data sets and to analyze it we used significance analysis between the groups but also characterized tumor specific protein profile analysis to detect pathways driving tumor growth. The distribution of the GO terms is similar between the proteomics and the transcriptomics data. We identified a substantial amount of membrane proteins, which are usually difficult to identify with global proteomics methods (36% of the proteins). Among the altered pathways, glucose and amino acid metabolism very commonly altered in all tumors. However, we could also detect tumor specific cancer related pathways potentially powerful for molecular sub-typing of lung adenocarsinoma. Finally, the combined statistical and pathway analysis revealed ten potential markers for relapse in early stage adenocarsinoma with indications on MYC, HIF1a and metabolic switch related pathways.
Conclusion: Here we have performed comprehensive tumor proteomics comparing lung adenocarsinoma proteome between relapse free and relapsed cases. The proteomics data is related on genomics and transcriptomics data from same samples creating unique molecular landscape of altered pathways. This data can help to classify lung adenocarsinoma tumours based on pathway alteration and gain knowledge on proteome changes to direct the therapy. [1] De Petris, L. et al., Proteome Sci (2010) [2] Pernemalm, M. et al., Proteomics (2009). [3] Orre, L. M. et al., Mol Cell Proteomics (2007). [4] De Petris, L. et al., Lung Cancer (2009).
Keywords: proteomics, Lung adenocarsinoma, Pathway analysis, Molecular systems biology

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.219 RELATIONSHIP BETWEEN PTEN AND EGFR EXPRESSION, AND ITS CLINICAL SIGNIFICANCE IN SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER

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Background: Epidermal growth factor receptor (EGFR) is involved in cellular proliferation and differentiation. Increased expression of EGFR has been reported in squamous cell carcinomas of the lung. Serine/threonine kinase Akt is known to be a downstream mediator of phosphatidylinositol 3-phosphate kinase (PI3K), a critical element in cancer development. Activity of AKT is mainly inhibited by phosphatase and tensin homologue (PTEN), a tumor suppressor gene that inhibits PI3K levels. The author hypothesizes that PTEN inhibition and subsequent PI3K-Akt signal transduction are major constituents in tumorigenesis. This study observes the expression patterns of EGFR and PTEN in non-small cell lung cancer patients by immunohistochemical stains, and analyzes the relationship between biological markers and clinical parameters.
Methods: Lung cancer tissues obtained from surgical specimens of 178 patients who were diagnosed as non-small cell carcinoma and underwent curative operation were assessed by tissue microarray. The EGFR and PTEN expression patterns were examined by immunohistochemical stains and were statistically analyzed.
Results: There was an inverse correlation between EGFR and PTEN expression patterns. With immunohistochemical stain, EGFR was expressed in 17% of adenocarcinoma and 44% of squamous cell carcinoma cases ($p<0.001$), while PTEN was expressed in 85% of adenocarcinoma and 23% of squamous cell carcinoma ($p<0.001$). Age, sex, degree of histological differentiation, lymph node invasion, and stage were not significantly different between positive and negative groups.
Conclusion: There is an inverse correlation between EGFR and PTEN expression patterns in non-small cell carcinoma patients.

Keywords: EGFR, Non-Small-Cell Lung, PTEN

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.220 DEVELOPMENT OF A LUNG CANCER BIOSIGNATURE FROM PLASMA USING CIRCULATING MICROVESICLES

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Background: Early detection is one of the key elements to the successful treatment of NSCLC. In the past, individual biomarkers have failed to exhibit sufficient sensitivity or specificity to allow for the detection of non-small cell lung cancer (NSCLC) at a stage that could be cured by surgical intervention. A multiplex approach with sub-cellular vesicles secreted into the plasma by tumor cells offers an exciting potential solution to this dilemma. Circulating microvesicles (cMV) are lipid bilayer vesicles ranging in size from 40-1000nm in diameter. cMVs are secreted by most cell types, including tumor cells, through multiple mechanisms and contain membrane bound proteins that are characteristic of their cell of origin. This suggests that cMV surface protein composition and quantity can be used to evaluate the risk for the presence of disease and possibly to characterize disease sub-types such as NSCLC. In this study, we demonstrate that a novel protein biomarker signature is associated with NSCLC by analysis of multiple protein markers found in circulating microvesicles in plasma of patients.
Methods: A novel multiplexed platform for quantifying and profiling cMVs from plasma was used to develop a cMV-derived biosignature. We isolated cMVs from plasma of patients both with and without NSCLC, including both smokers and non-smokers. Beads coated with antibodies against surface proteins were used in a multiplex assay to capture and detect cMVs. Quantification of cMVs with significant concentrations of these surface proteins led to the development of a specific biosignature that differentiated NSCLC samples from control samples.
Results: A biosignature of 6 different proteins was found that differentiated patients with biopsy-confirmed NSCLC (n=20) from individuals from the general population (n= 25) with a sensitivity of 85% and specificity of 92%. The NSCLC samples analyzed were comprised of AJCC/UICC stage IA/B (n=7), IIA (n=4), IIB (n=7) and IIIA (n=2). Half of these patients were positive for lymph node involvement. The biosignature found is composed of 6 different surface membrane protein markers, which include both microvesicle and cancer-associated proteins. Three of the proteins are members of the tetraspanin transmembrane family (CD9, CD63 and CD81) that are found on microvesicles. Three other protein markers are DR3 (death receptor 3, a protein involved in apoptosis), PRB (progesterone receptor B) and MS4A (Membrane-spanning 4 domain subfamily A from the multigene family of proteins involved in signal transduction of which CD20 is one member).
Conclusion: In this small retrospective analysis, we have shown for the first time that a unique cMV-based biosignature derived from the blood is able to differentiate NSCLC patients from normals. These results may serve as the foundation to develop a diagnostic test for NSCLC.
Keywords: blood based diagnostics, circulating microvesicles, Non small cell lung cancer

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P2.221 ERCC1-GENE EXPRESSION AS A RESPONSE PREDICTIVE MARKER TO NEO-ADJUVANT THERAPY WITH CISPLATIN AND DOCETAXEL IN STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: 30% of patients (pts) affected by NSCLC presents with locally advanced stage for

which a multidisciplinary therapeutic approach is recommended. Standard treatment is a neo-adjuvant platinum-based chemotherapy followed by local treatment. When surgery is not feasible, due to comorbidity, compromised lung function, unresectable disease, integrated chemo-radiotherapy is the best approach. Several studies show a correlation between response to platinum and ERCC1 expression levels determined when an adequate tumor specimen is suitable. Data suggest low ERCC1 levels correlate with better response to treatments, while high levels link to resistance to platinum therapy.

Methods: We enrolled 39 pts affected by NSCLC (18 pts with stage IIIA and 21 with stage IIIB), receiving neo-adjuvant chemotherapy with Cisplatin (CDDP) 75mg/m2 and Docetaxel (DOC) 75mg/m2 day 1, q21. We evaluated objective response rate (ORR) and its correlation with ERCC1 expression, progression free survival (PFS) and overall survival (OS) at 24 months. ERCC1 mRNA levels were determined in peripheral blood cells samples using RT-PCR.

Results: 38 pts completed planned chemotherapy. We observed partial response (PR) in 23 pts (60%), stable disease (SD) in 10 pts (26%) and progressive disease (PD) in 5 pts (13%). 11 pts underwent surgery (followed by adjuvant irradiation in 3 cases), 17 received sequential radiotherapy; 7 patients stopped their treatments after chemotherapy. 2 years OS was 76% ; PFS was 46% for the whole cohort (75% for surgically treated patients, 42% for patients receiving sequential radiotherapy). In patients who didn't received any local treatment 2 years OS was 20%, with PFS of 31% (OS p-value=0.02, PFS p-value<0.001). ERCC1 gene expression was collected in 24 patients, with the following **Results:**

	Partial Response (PR)	Stable Disease (SD)	Progression (PD)
Low ERCC1 levels (expression ≤0.215)	10 (41.6%)	2 (8.4%)	0 (0%)
High ERCC1 levels (expression >0.215)	5 (20.8%)	5 (20.8%)	2 (8.4%)

OS and PFS were not statistically different in the two groups.

Conclusion: Neo-adjuvant CDDP-DOC schedule obtains good response rate (60%) expecially in low ERCC1 level subgroup. At a 2 years follow up, surgery and radiotherapy show similar efficacy in terms of OS and PFS. Peripheral blood ERCC1 expression seems to have a potential role in predicting response to platinum based chemotherapy in NSCLC but a larger population is required to validate these preliminary results.

Keywords: locally advanced NSCLC, combined modality, ERCC1

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.222 EGFR MUTATION STATUS AMONG PATIENTS IN LITHUANIA: A SINGLE INSTITUTION EXPIERENCE

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Background: Activating mutations within the tyrosine kinase domain of Epidermal Growth Factor Receptor (EGFR) are found in approximately 10-20% of non-small cell lung cancer (NSCLC) patients and are associated with response to EGFR tyrosine kinase inhibitors (TKIs). The aim of this study is to examine the prevalence of EGFR 18-21 among patients with histologically confirmed non-squamous NSCLC treated in our institution.

Methods: We report the data of NSCLC patients of a single institution experience enrolled from April 2010 to January 2011. We examined the mutation status of EGFR patients with newly diagnosed non-squamous NSCLC. The formalin fixed, paraffin embedded tissue samples were obtained from tumor biopsy. These were sequenced to look for mutations in exons 18 - 21 of EGFR.

Results: 67 patients were examined for EGFR mutations: 13 (19.4%) patients with stage IIIB and 54 (80.6%) patients with stage IV. Age median was 63 years (range 34-80); male/female: 51/16; smokers/ex-smokers/never-smokers: 41/13/13; adenocarcinoma/large cell carcinoma/no otherwise specified NSCLC: 44/19/4. The EGFR mutations (L858R in Exon21) were found in 5 patients (7.5%): female 12.5% (2/16), male 5.9% (3/51); adenocarcinoma 9.1% (3/44), large cell carcinoma 10.5% (2/19); never-smokers 23.1% (3/13), smokers 4.9% (2/41) (p>0.05). First-line treatment with EGFR-TKI was started for these patients.

Conclusion: In comparison with literature data the frequency of EGFR gene mutations among non-squamous NSCLC patients was very low.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.223 THE PROLIFERATION MARKER KI67 PREDICTS SURVIVAL IN MALIGNANT PLEURAL MESOTHELIOMA PATIENTS

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Background: Malignant Pleural Mesothelioma (MPM) is an aggressive disease with increasing incidence and poor therapy response. The prognosis of patients suffering from MPM strongly depends on pathological variables including histological subtype and TNM stage. Despite of a wide panel of diagnostic immunohistochemical (IHC) markers used in MPM patients, none of them proved to have prognostic significance in the clinical practice.
Methods: The prognostic power of the routine IHC proliferation marker Ki67 was studied in paraffin-embedded tissue samples of 49 MPM patients who underwent tumor resection between 01/1994 and 06/2009 at the Department of Thoracic Surgery of the Medical University of Vienna. Interpretation of the results was limited to proven tumor tissue. The results were documented as the percentage of Ki67 nuclear stained tumor cells and correlated with patients' clinical data using the SPSS 17 software package.
Results: Of all 49 patients (mean age: 61±9 years; 10 female, 39 male), 30 exhibited epithelial, 14 biphasic and 1 sarcomatous histology. Furthermore, in 4 patients, pseudomesotheliomatous adenocarcinoma was found. Ki67 labeling was significantly decreased in the 25 patients who received chemotherapy before surgery compared with those who did not (10±8% vs. 19±16%, all patients: 14±13%, p = 0.017). Patients whose tumor samples were categorized by low Ki67staining intensity (≤ 10% of Ki67 positivity) had significantly longer survival times than those with high staining intensity (median overall survival: 470 vs. 197 days; log rank test: p = 0.004). The same was observed when the analysis was done within the pretreated patient subgroup (median overall survival: 806 vs. 334 days; log rank test: p = 0.039). Finally, in the multivariate analyses, we could prove the prognostic power of Ki67, independent from sex, age, treatment, TNM-stage and histology. Treatment (p=0.009), histology (p=0.040) and Ki67 (p=0.012) were the remaining significant prognosticators in the Cox regression model. Data of an independent Hungarian collective will be available until June to validate our results.
Conclusion: This study reveals Ki67 as a novel, independent prognostic factor in MPM and warrants its further investigation in larger series of patients with this malignancy.
Keywords: Ki67, malignant pleural mesothelioma, Biomarkers

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P2.224 THREE-MICRORNA EXPRESSION PROFILE IS RELATED TO THE RISK OF DISSEMINATION AND PROGNOSIS IN EARLY STAGE SQUAMOUS CELL LUNG CANCER (SQCLC)

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Background: About 50% of NSCLC patients (pts) will develop distant metastases following pulmonary resection. Currently, apart from clinical stage at diagnosis, there are no reliable clinical factors to select high risk pts for adjuvant chemotherapy. We previously demonstrated high prognostic value

of selected microRNAs (miRs) in frozen tissues of early stage SqCLC and the feasibility of their expression assessment in formalin fixed paraffin embedded (FFPE) samples (Skrzypski et. al. J Clin Oncol 28;521s:2010). In this study we validated the prognostic value of the 3-microRNA expression signature assessed in the FFPE samples in an independent patient population.
Methods: FFPE tumor tissue was obtained from 89 stage I-II SqCLC pts. Of those, 40 pts developed distant metastases and 49 had no relapse after a median follow-up of 5.4 years (range, 3.4-8.2 years). MicroRNA was isolated from paraffin blocks after macrodissection of tumor tissue, and extracted with RecoverAll kit (Ambion). Expression of miR-10b, miR-532-3p and miR-192* was analyzed by RT-PCR assays (Applied Biosystems). Raw data were normalized vs. the expression of U6 RNA and calibrated by deltadeltaCt method. After z-score transformation, the risk score was calculated based on the expression of these 3 miRs.
Results: The median metastasis-free survival was not reached in the low risk group according to 3-microRNA expression signature, whereas it was 26 months in the high risk group. The three-microRNA (10b, 532-3p and 192*) expression signature was significantly related to the time to distant metastases (log-rank; p=0.013). With the median of the risk score as a cut-off value, the test sensitivity for distant relapse prediction was 66% at the specificity of 64%. After exclusion of stage IA patients, the corresponding values were 73% and 69%.
Conclusion: Three-miRNA expression profile (10b, 532-3p and 192*) has been successfully validated as a strong predictor of distant metastases in operable early stage squamous cell lung cancer.
Keywords: Prognosis, Adjuvant chemotherapy, microRNA, NSCLC

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P2.225 CIRCULATING TUMOR CELL CYTOKERATIN-19 GENE EXPRESSION AS A PROGNOSTIC FACTOR IN LUNG CANCER: ANALYSIS BASED ON NORTH CENTRAL CANCER TREATMENT GROUP (NCCTG) CLINICAL TRIALS (N0423/426)

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Background: Biologic characterization of circulating tumor cells (CTCs) is becoming important in determining prognosis, monitoring response, and tailoring treatment strategies for lung cancer patients. The objectives of this study were to examine the CTC gene expression of cytokeratin-19 (CK-19) throughout treatment of advanced cancer patients with extensive-small cell lung cancer (ES-SCLC; N0423) or advanced non-small cell lung cancer (NSCLC; N0426) and to investigate associations between baseline and post-treatment gene expression and patient outcome.
Methods: Blood was obtained at local sites (community-based sites that enroll patients) from advanced lung cancer patients before or during treatment with first-line pemetrexed plus carboplatin (N0423) or second-line pemetrexed plus bevacizumab (N0426). CTC processing was performed at a central laboratory (Mayo Clinic, Rochester, MN). CTCs were enriched from 10mls of EDTA blood using CD45-depletion 24-30 hours after blood collection. CK-19 mRNA levels were determined using quantitative RT-PCR in CTC samples of 45 (N0423) and 42 (N0426) patients. The relative gene expressions were normalized to β_2-microglobulin and calibrated to healthy blood using the $2^{-\Delta\Delta Cq}$ algorithm. Cut points for CTC CK-19mRNA positivity were explored. Cox proportional hazards models were used to compare the progression-free survival (PFS) and overall survival (OS) distributions for the baseline CTC subgroups. A landmark analysis was utilized for post-baseline CTC analyses.
Results: In ES-SCLC patients, at baseline, CK-19mRNA was detected in 58% and 44% using ≥2 and ≥5 cutpoints, respectively. On day 1 of cycle 2, CK-19mRNA was detected in 54% and 41% of ES-SCLC patients using ≥2 and ≥5 cutpoints, respectively. ES-SCLC patients with higher CK-

19mRNA at baseline and at follow-up had worse prognosis, ie., patients with CK-19mRNA ≥5 at baseline had significantly worse PFS (HR=2.17; 95%CI: 1.15-4.10; p=0.013) and OS (HR=4.23; 95%CI: 2.05-8.72; p<0.001). Similarly, patients with follow-up (cycle 2, day 1) CK-19mRNA ≥5 also had significantly worse OS (HR=2.81; 95%CI: 1.30-6.08; p=0.0064) compared to those patients with CK-19mRNA <5. Patients that were positive (CK-19mRNA ≥5) at both baseline and follow-up had significantly worse PFS (p=0.0071) and OS (p=0.0096) as compared to patients that were negative (CK-19mRNA <5) at baseline and follow-up. In NSCLC patients, CK-19mRNA was detected in 45% using the ≥2 cutpoint. A significant increase in CK-19mRNA levels was observed from baseline to 24 hours post-treatment initiation (absolute change p=0.038; percent change p=0.002) in NSCLC patients. Although no significant associations were observed between baseline CK19mRNA ≥2 (or ≥5) and PFS or OS, a borderline association was observed between baseline CK-19mRNA level, treated as a continuous variable, and OS (p=0.07) of NSCLC patients.

Conclusion: In ES-SCLC patients, higher levels of baseline and follow-up CK-19+mRNA CTCs were associated with poor prognosis. CTC gene expression analysis by a reference laboratory is feasible when blood is collected from community-located, trial-enrolling sites.

Keywords: circulating tumor cells, Lung cancer, gene expression, prognostic factor

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Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.226 SERUM MICRORNAS AS BIOMARKER FOR EARLY RELAPSE IN NON-SMALL CELL LUNG CANCER

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Background: Lung cancer is world-wide the leading cause of cancer related death. About 50% of lung cancer patients are diagnosed at late stages, when metastases have already been established, followed by a very bad outcome. Therefore, early detection of malignancies in the lung aims at achieving efficient intervention and subsequently a reduction of the high mortality rate. microRNAs have been searched in tissue and serum of cancer patients, and represent promising diagnostic and prognostic biomarkers. The aim of the study was to identify microRNAs in serum associated to early relapse in non-small cell lung cancer.

Methods: Serum samples and RNA extracts were collected from 232 patients including NSCLC disease and control samples (e.g. COPD and benign cases). We performed qRT-PCR based microRNA screening from a subset of 40 patients based on a low-density array including 667 microRNAs. microRNA candidates were further validated in serum samples of an independent patient cohort. For the statistical analyses, we used a modified t-test (LIMMA) for the microarray analysis and Wilcox test in the validation experiment.

Results: The screening experiment revealed six potential microRNA biomarker to be associated with early relapse in NSCLC. One microRNA could be validated in an independent patient cohort. Furthermore, several microRNAs were deregulated in benign lung diseases like COPD, or associated to epidemiological parameters like gender and age.

Conclusion: MicroRNAs may be promising prognostic biomarkers in early stage lung cancer. The combination of biomarker profiles, clinical and epidemiological parameters may improve the diagnosis of severe cancer diseases and patient care.

Keywords: microRNA, serum biomarker, Lung cancer, early relapse

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Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.227 EVALUATION OF BETAV-TUBULIN EXPRESSION AS NOVEL PREDICTIVE BIOMARKER FOR CLINICAL BENEFIT FROM TREATMENT WITH TAXANES IN NON-SMALL CELL LUNG CANCER

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Background: Microtubule-binding agents (TBA) like taxanes and vinca alkaloids act to impair the normal function of mitotic spindles and are well established agents for treatment of non-small cell lung cancer (NSCLC). These drugs target microtubules, which are composed of αβ-dimers, form the fibers of the mitotic spindle and change their polymerization or depolymerization dynamics, subsequently leading to mitotic arrest and cell death. Increased expression of the betaIII-tubulin isotype (TUBB3) has been inconsistently associated with a poor outcome in NSCLC patients (pts) treated with TBAs. Beta-tubulin isotypes (TUBBs) present a family of 8 members and are separated into biologically different subfamilies. In particular, the subfamily of TUBB3/TUBB5 leads to resistance against TBAs in vitro. Both of these isotypes are expressed in cancer cells and their patterns of expression seem to be complementary. Because of their similarities, it is conceivable that expression levels of TUBB5 would also alter the sensitivity of cancer cells to TBAs. We hypothesized that combined TUBB3/TUBB5 protein expression may predict outcome and response following TBA treatment of NSCLC pts.

Methods: Pre- and post-treatment samples from 92 locally advanced or oligometastatic NSCLC pts who were treated with paclitaxel combined with platinum (91/92) as an induction treatment and who received vinorelbine combined with platinum for concomitant radiotherapy were retrospectively analyzed. Due to high homology between human and murine TUBB5 (97.7%), we used a murine TUBB5 plasmid to produce the target protein in FNX cells, with which we established an antibody suitable for immunhistochemical staining. TUBB3/TUBB5 protein expression levels in NSCLC were evaluated by immunohistochemistry using the H-Scoring system (ranging from 0 to 300), which is determined by the product of intensity of a specific tumor cells immunoreactivity (range 0 to 3) and the percentage of positive tumor cells. Radiographic evaluation of response was performed according to RECIST.

Results: Median pre-treatment H-score for TUBB3 was 110 (range: 0-290) and 150 for TUBB5 (range: 0-280). Using the log-rank test and the median H-score as cut-off, we found a borderline significant association between improved overall survival (OS) and low TUBB3 protein expression (median OS of 1,776 vs 642 days; hazard ratio [HR] 0.370, 95% CI, 0.133 to 1.013; P=0.056). Surprisingly, prolonged progression-free survival (PFS) was associated with high TUBB5 protein expression (median PFS of 539 vs 227 days; hazard ratio [HR] 2.139, 95% CI, 1.144 to 4.001; P=0.017). Using a t-test we found an association between high TUBB5 protein expression and objective response to induction chemotherapy (mean H-score 160 for responders vs 113 for stable disease and progressive disease pts, P=0.005).

Conclusion: This is the first report of TUBB5 examination in NSCLC. Based on our retrospective study, base line determination of TUBB5 expression may be predictive for outcome of TBA-based therapy in NSCLC. TUBB5 expression might explain the inconsistency of results from studies evaluating the predictive value of TUBB3 protein expression. In contrast to TUBB3, protein expression of TUBB5 is a more significant predictor for response to TBA therapy. Confirmation of the prognostic and predictive value of combined TUBB3/TUBB5 expression in NSCLC by prospective studies is warranted.

Keywords: Non-small cell lung cancer (NSCLC), taxanes and vinca alkaloids, predictive biomarker for response and outcome, beta-tubulin isotypes III/V (TUBB3/5)

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P2.228 POTENTIAL DIAGNOSTIC AND PROGNOSTIC ROLE OF THE LONG PENTHRAXIN PTX3 IN RESECTABLE NON-SMALL CELL LUNG CANCER

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Background: C-Reactive Protein (CRP) and other acute phase proteins are elevated in patients with lung cancer and high levels correlate with more aggressive disease suggesting a potential role as prognostic markers. Both malignant and normal cells express a wide array of inflammatory mediators. Penthraxin 3 (PTX3) is an acute phase protein produced mainly by endothelial cells, fibroblasts, macrophages and granulocytes. Its prognostic role in lung cancer has never been investigated before. The purpose of this study was to evaluate the role of CRP and PTX3 as diagnostic and prognostic markers in resectable non-small cell lung carcinoma (NSCLC).
Methods: Patients with completely resected NSCLC were identified from two groups: a retrospective one derived from a randomized trial of lung cancer screening with spiral-CT (DANTE Trial), and a prospective group of consecutive patients who underwent resection for lung cancer between February and July 2009 in our institution. Intratumour expression of PTX3 was assessed by immunohistochemistry with a specific antibody and evaluated semiquantitatively. In the prospective cases, serum samples were collected immediately before surgery and levels of CRP and PTX3 were determined by specific and validated assays. Relationships between PTX3 and CRP serum levels, intratumour PTX3 expression and survival were analyzed by the Cox proportional-hazards model.
Results: Seventy cases (34 retrospective and 36 prospective, average age 69,6) were analyzed. The screening-detected group showed a higher rate of IA stage (44,1%), while among prospective patients the rate of stage IA was only 13,8%. PTX3 and CRP serum levels did not correlate significantly with survival (p=0,08 and p=0,06 respectively) in the prospective group, while PTX3 expression in the tumour stroma significantly correlated with post-treatment survival in both groups and in the whole series (p=0.0008).
Conclusion: Our results show that PTX3 is often highly expressed intralesionally in NSCLC suggesting that inflammatory signals produced by neoplastic cells induce the formation of a cellular infiltrate responsible for PTX3 production. Serum levels were not significantly correlated with survival in this series (although there was a trend towards significance) while higher expression of PTX3 in the tumour stroma was shown to be a strong prognostic indicator, independent from the pathologic stage, in patients who had undergone potentially curative surgery. This is the first study that investigates tumour stroma expression of Long Penthraxin 3 and its relationships with treatment outcomes in patients with resectable lung cancer. These results, if confirmed, may represent a first step toward new diagnostic and therapeutic strategies in NSCLC
Keywords: Prognosis, Lung cancer, Surgery, PTX3

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P2.229 EXPRESSION OF MIR-497 IN CIRCULATING MICROVESICLES IS A POTENTIAL BIOMARKER FOR THE EARLY DETECTION OF NSCLC

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Background: Currently, early detection facilitating complete surgical resection remains the best hope for a cure for NSCLC. Therefore, finding biomarkers for the early detection of NSCLC has become an important goal in lung cancer research. Recent research with micro RNAs (miRs) has suggested that quantification of miRs in blood may be an attractive avenue for discovering such biomarkers. In recent years, microRNAs and circulating microvesicles (cMVs) have shown promise for detecting and classifying a variety of cancer types.

A proprietary method for isolating cMVs from plasma and extracting microRNAs from cMVs was used to explore microRNA expression differences between healthy individuals and those with NSCLC. In particular, we found significant differential expression of miR-497.
Methods: cMVs from 24 NSCLC patients of primarily early stage disease (IA = 9, IB = 9, IIA = 1, IIB = 2, III = 1, IV = 2) and 26 healthy individuals were isolated from 1 ml of frozen plasma. RNA was then extracted from the cMVs using a Trizol and affinity bead based extraction method. A quantitative Taqman® assay was constructed with a calibration curve for the determination of the number of copies per ml of mir-497 in each sample.
Results: Median normalized copy number for normal individuals was 9000±307 copies per ml (±95% CIM) and 27,500±1298 copies per ml (±95% CIM) for patients with NSCLC. Expression levels did not correlate to disease stage. Setting a threshold of 15,700 copies per ml, this assay had a sensitivity of 79% and specificity of 81% and an AUC of 0.89.
Conclusion: While further study is warranted due to the small sample size in this exploratory analysis, it demonstrates the promise of using cMVs in combination with microRNA expression for the early diagnosis of NSCLC.

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P2.230 ASSESSMENT OF MET AMPLIFICATION IN NON-SMALL CELL LUNG CARCINOMAS BY SISH: CORRELATION WITH EGFR AND KRAS MUTATIONS IN EARLY STAGES

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Background: The amplification of the MET gene is one of the main mechanisms responsible for resistance to EGFR-tyrosine kinase inhibitors (TKIs) in patients with non-small cell lung carcinoma (NSCLC). Some authors have suggested that: (a) there is a reciprocal and complementary relationship between MET amplification and the T790M EGFR mutation, (b) there are minor clones with such alterations even before EGFR-TKI treatment, (c) only 4-fold MET amplification is clinically relevant and (d) the alteration may depend on the lesion site within each patient. With the above facts in mind it is obvious that targeting MET necessitates the development of companion diagnostics that optimize the tissue sample and are rapid. Although MET gene amplification has been studied with various assays, all of which have yet to be standardized, there are no publications using SISH. We sought to evaluate a novel dual-color brightfield approach (SISH) in a series of early stage untreated NSCLCs and to correlate this alteration with EGFR and KRAS mutations.
Methods: MET gene amplification was analyzed in 108 surgically resected untreated NSCLCs, including 60 SCCs and 48 adenocarcinomas (ACs). Automated SISH was performed on Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ), following manufacturer´s protocols with few variations. The entire assay procedure was fully automated and was performed on a single 5 micron slide. Amplified cases were confirmed by FISH (Kreatech, Amsterdam, The Netherlands). EGFR and KRAS mutations were studied by direct sequencing in ACs.
Results: SISH was successfully performed on all samples. The turnaround time was ~14 hours. The median mean MET gene copy number was 3.075. Using this cutoff, a total of 54 cases (50%) were MET SISH positive, including five cases (4.6%) with true gene amplification. Among those amplified cases, three ACs (EGFR and KRAS wild type) exhibited high amplification (ratio > 3) and two SCCs showed low amplification (ratio ≤ 3). Interestingly, two of the three EGFR mutant ACs were non-amplified positive as were four of the seven KRAS mutant ACs.
Conclusion: In early stage untreated NSCLCs, true MET gene amplification is an uncommon event and our study suggests that it is mutually exclusive with EGFR and KRAS mutations in ACs. MET amplification in SCCs should also be considered. Dual color SISH represents a robust method for the determination of MET status in NSCLC. This rapid test helps in the strategic time management when dealing with NSCLC targeted therapies.
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Keywords: MET, amplification, Lung cancer

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P2.231 HIGH ALK GENE COPY NUMBER IS A FREQUENT EVENT IN NON-SMALL CELL TUMORS AND CELL LINES OF LUNG CANCER

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Background: The anaplastic large cell kinase gene (ALK) rearrangement is a rare event, described in approximately 4-6% of lung adenocarcinoma. ALK translocation is described as mutually exclusive with EGFR and KRAS mutations. ALK activation may depend however, on alternative mechanisms, such as an increase in gene copy number (GCN). We propose in this study to describe ALK GCN among non small cell lung cancer (NSCLC) cell lines and patients with advanced disease.

Methods: ALK status was evaluated by fluorescence in situ hybridization (FISH) in paraffin embedded specimens from advanced NSCLC patients. Lung cancer cell lines were screened by FISH-ALK after cytospin. ALK scoring was performed following Cappuzzo criteria established for EGFR and HER2 in lung cancer. High GCN was defined as the presence of ≥ 6 copies of ALK per cell in ≥ 10% of analyzed cells. FISH with CEP2 was performed to determine the ploïdy status in samples with high GCN. EGFR and KRAS mutational status were determined on DNA extracted from the paraffin embedded tumor specimens. All coding sequences of exon 18 to 21 of EGFR , exon 2 and 3 of KRAS were analyzed by Sanger direct sequencing performed after Polymerase Chain Reaction amplification of targeted exons.

Results: Among 96 NSCLC tumors, FISH ALK was contributive in 75. There were ten cases (13%) of EML4-ALK translocation which were EGFR and KRAS wild type. Eleven cases (15%) exhibited high ALK GCN and 38 (51%) copy number gains, whereas two exhibited monosomy. The ALK high GCN were associated with polysomic status as revealed the FISH with CEP2.EGFR was mutated in seven cases, two exhibiting high ALK GCN and five with unless 3 gains ALK copy number.Among lung cancer line cells, 4 (15%) display over of six copies number of ALK and 20 (75%) presented a gain of over three ALK copy number.

Conclusion: The increased ALK copy number was close to a polysomy of the chromosome 2 and seem to be not exclusively to EGFR wild type. ALK amplification in preclinical models of neuroblastoma harbour a good sensitivity to ALK inhibitors. Further preclinical studies in lung cancer models are ongoing to determine the prognostic and predictive value of this event.

Keywords: anaplastic lymphoma kinase, Lung cancer, new predictive marker, high gene copy number

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.232 THE EXPRESSION OF RCAS1 MOLECULE IN LUNG CANCER AND ITS CLINICAL SIGNIFICANCE

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Background: RCAS1 (Receptor-binding Cancer Antigen expressed on SiSo cells) is a membrane protein that is expressed in different types of cancer. It halts the cell cycle and/or induces the apoptosis of the immune system cells within the tumour microenvironment. Hence, it is possible that this molecule is involved in the mechanism of the tumour cells' escape from the immune system surveillance (immunoescape).The aim of this study is the measurement the RCAS1 molecule's expression in primary lung cancer and the evaluation of its clinical significance.

Methods: Patients with primary lung cancer, eligible for surgical treatment, were included in the study.

The tissue samples (paraffin cubes) were processed using the Tissue Micro-arrays Method. Then, an immunohistochemical study followed, specific for the RCAS1 and the Ki-67 (a cell proliferation marker). The image analysis was feasible due to a special program. In addition, a database was created that included the clinical and pathological characteristics of the patients.
Results: In total, 108 patients were examined (81 men and 27 women), mean age 62 years old. Almost 44% of the cases were adenocarcinoma, 31% squamous cell, 9% large cell, and 16% other types of lung cancer. The results of the immunohistochemical and statistical analysis that followed will be ready shortly.
Conclusion: The conclusions according to the results of the study will be ready to announce shortly.
Keywords: RCAS1, Lung cancer, Tissue microarrays, Biomarkers

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.233 INCIDENCE OF MOLECULAR TARGETS (EGFR-MUTATION, EML4-ALK, BRAF AND KRAS) IN METASTATIC NSCLC IN A CERTIFIED LUNG CANCER HOSPITAL.

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Background: NSCLC has become a molecularly defined disease with the discovery of activating mutations within the EGFR gene, inversions of EML4 –ALK as well as the description of B-RAF and k-ras mutations. The incidence of these targets is not well known in the Caucasian population. Therefore, we have in part retrospectively, in part prospectively screened patients with predominantly non-squamous cell NSLCLC with a tumor stage M1a or M1b for the occurrence of these molecular alterations.
Methods: Archived formalin fixed paraffin embedded tumor material was microdissected and studied for activating mutations in EGFR exons 18-21 using Sanger sequencing. Direct sequencing (Sanger method) was also used to evaluate codons 13, 13, and 61 of the KRAS gene for mutations. The BRAF mutation V600E was detected using a PCR based allelic discrimination assay and screening for EML4-ALK translocation was done by RT-PCR assays spanning all 12 relevant exons of EML4 and exon 20 of ALK. Smoking status was defined according to the criteria in the IPASS trial (Mok et al., NEJM 2009).
Results: 88 patients were screened for the genetic alterations. Patient characteristics were: male/female: 42/46, median age: 62, non-squamous/squamous: 80/8, never smoker/light smoker vs. smoker:37/42 . In 8 patients, the amount of tumor material was not sufficient to carry out the molecular analyses. In 18/80 patients, EGFR mutations were found, in 5/80 patients, EML4-ALK inversions were detected, in 0/59 patients, B-RAF mutations and in 5/53 patients, k-ras mutations were found. Patient characteristics of the EGFR mutated patients were: male/female:4/14, non-squamous vs. squamous: 17/1, never/light smoker vs. smoker:14/4. Median age of the EGFR-MT group was 66, the distribution of e19 mutations/ L858R mutations/vs. other mutations was: 8/7/3. Median time to progression in e19/e21 EGFR-MT pts was 14 months (6-24 months). Patient characteristics in the EML4-ALK positive group were: male/female 1/4, median age 77 years (33-80) and never/light smoker vs. smoker: 4/1. Patient characteristics of the KRAS mt patients were male/female 3/2, never/light smoker vs smoker: 2/2, and median age was 66 years. EGFR mutations did not occur in combination with k-ras, BRAF or EML4-ALK alterations. Within the group of 35 never/light smokers, successfully analyzed for the molecular targets, the incidence of EGFR mutations was 14/35 (40%), of EML4-ALK 4/35 (16%) and KRAS 2/35 (8%).
Conclusion: Recurrent mutations were detected in this screened population diagnosed and treated at a certified lung cancer center with an incidence of 23% (EGFR-MT), 6% (EML4-ALK) and 9% (KRAS). An association with smoking status, gender and histology was found for EGFR and EML4-ALK alterations. The EML4-ALK population had a higher median age than the EGFR-MT group and seemed

to be more frequently detected than in most reported series.

Keywords: EGFR mutation, EML4-ALK fusion gene, KRAS mutation, BRAF mutation

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.234 EPITHELIAL MESENCHYMAL TRANSITION OCCURS EARLY IN SQUAMOUS CELL LUNG CANCER DEVELOPMENT

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Background: Lung cancer is the commonest cause of cancer death worldwide; there is increasing interest in identifying disease as early as possible in an attempt to improve survival. Squamous cell carcinoma accounts for approximately 35% of all lung cancer and has a well defined pathway of development from basal cell hyperplasia through squamous metaplasia, low- and high-grade dysplasia to invasive disease. Preneoplastic lesions may be detected using autofluorescence bronchoscopy; previous work suggests that some lesions may remain static or even regress rather than proceeding to invasive disease. However, it is unclear what drives these changes. Epithelial mesenchymal transition (EMT) is increasingly recognised as being a key sequence of events in cancer development. It is the process whereby cells lose their epithelial characteristics and dedifferentiate into a more motile, invasive phenotype. Previously this was not thought to occur until carcinoma in situ became invasive disease. We examined EMT during squamous cell lung cancer development.

Methods: We identified areas of squamous cell lung cancer and its precursor lesions from 109 formalin-fixed, paraffin-embedded blocks of bronchial biopsies and lung resection specimens. We stained for the epithelial markers E-cadherin and MNF116 (pancytokeratin), the mesenchymal marker S100A4, and beta-catenin (which translocates from the cell membrane to the nucleus during EMT). Up to three representative areas from each lesion were scored using an aggregate scoring system based on extent and intensity of staining. Where expression was expected to shift from membranous to nuclear, one hundred cells per high power field were counted and the proportion of membranous, cytoplasmic and nuclear staining noted. The majority of lesions were scored jointly by two investigators, one an experienced Thoracic Pathologist.

Results: The 109 blocks came from 70 patients (55 men, 15 women; average age 66.4 years). There was a progressive loss of E-cadherin and MNF116 with increasing grade of dysplasia and a concurrent gain of S100A4 expression. Similarly, beta-catenin showed exclusively membranous expression in normal respiratory epithelium and basal cell hyperplasia but showed progressively more cytoplasmic and nuclear expression as dysplastic grade increased. These changes began as early as squamous metaplasia and consistently reached significance across all markers between low- and high-grade dysplasia.

Conclusion: Our results suggest that EMT may be beginning earlier than previously thought during the development of squamous cell lung cancer. This has implications for future research examining processes determining the temporal behaviour of dysplastic lesions.

Keywords: squamous cell lung cancer, epithelial mesenchymal transition, squamous dysplasia

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.235 CLINICAL STUDY BY THE DUTCH ASSOCIATION OF PULMONOLOGISTS (NVALT) INVESTIGATING THE EARLY IMMUNE TUMOR INTERPLAY DURING CHEMOTHERAPY IN STAGE IV NON-SQUAMOUS NSCLC PATIENTS

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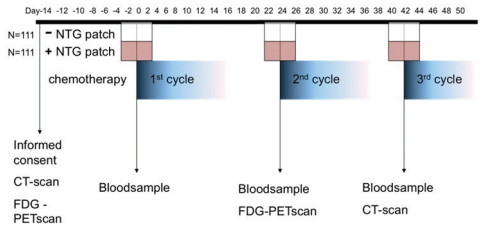
Background: Standard treatment for non-small cell lung cancer (NSCLC) consists of platinum-containing chemotherapy. It has been shown that the addition of bevacizumab to carboplatin-paclitaxel (bevCaTAX) combination chemotherapy improves overall survival in patients with non-squamous NSCLC. Benefit from this treatment is still limited, and therefore a need for better treatments exists. Tumor hypoxia is a common phenomenon in lung cancer; it is a known poor prognostic marker and is related to treatment resistance. Pre-clinical studies have shown that nitric oxide (NO) donating drugs may decrease hypoxia related drug resistance. Nitroglycerin (NTG) is one of those NO donating drugs. Hypothetically NTG increases tumor blood flow, augments antitumor drug delivery and inhibits hypoxia inducible factor (HIF) -1a. HIF-1a is the major factor regulating the response to hypoxia. It has recently been shown in mouse models that the addition of HIF-1 inhibitors to bevacizumab significantly inhibits tumor growth by inducing apoptosis. In vitro testing has also showed an effect of HIF-1a on immune regulatory cells. Our aim is to determine the effect of bevCaTAX chemotherapy ±NTG on immunoregulatory cells (regulatory T-cells and myeloid derived suppressor cells (MDSCs)) and to establish the value of these cells as a predictive marker to bevCaTAX.
Methods: A randomized multi-centre open label phase II study investigating bevCaTAX +/-NTG patches in patients with stage IV non-squamous-NSCLC: "NVALT 12" is open for accrual. Expected enrollment is 222 patients. Immunoregulatory cells blood samples are taken at the start of chemotherapy, in week 3 and week 6 (figure 1). All patients undergo a FDG-PET scan in week 3 and a CT scan in week 6 to determine response to treatment.
Results: Mononuclear cells were purified from peripheral blood by density gradient centrifugation and analysed by flowcytometry. All patients have a significantly increased percentage and number of CD11b+ CD15+ CD33+ HLA-DR- MDSC in their blood compared to healthy controls. These cells produced reactive oxygen species (ROS) at a high level. First results indicate that high levels of MDSC correlate with early tumor progression and poor prognosis. This is in line with our pre-study results. We anticipate that results on NTG patches are available at the time of the conference.



Conclusion: Clear shifts of immunoregulatory cells are observed between patients at the start of treatment and during treatment. This may indicate that immunoregulatory cells in the peripheral blood may be suggestive for response to treatment and for disease progression.
Keyword: Myeloid Derived Suppressor Cells

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.236 CORRELATION OF THYMIDYLATE SYNTHASE GENOTYPE AND PROTEIN EXPRESSION AND ASSOCIATION WITH LUNG CANCER SURVIVAL

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Background: Thymidylate synthase (TS) catalyzes DNA synthesis and is directly inhibited by pemetrexed, a drug used for treatment of lung cancer. The aim of this study is to analyze the association of a TS genetic polymorphism and protein expression with survival in patients with non-small cell lung cancer.
Methods: We performed a retrospective study of

114 patients with NSCLC using paraffin embedded tumor tissue at the University of Colorado. DNA was extracted from each tumor specimen and assessed by fragment analysis for genotype in the TS promoter variable tandem repeat region (VNTR). Thymidylate synthase protein expression was evaluated with immunohistochemistry and percent nuclear positivity was assessed. Survival analysis with the log rank test statistic was performed to compare survival time based on TS genotype and protein expression. The association between TS genotype and protein expression was evaluated by Pearson correlation analysis.

Results: Of the 114 lung tumor specimens, 32 were homozygous for three repeats (3R/3R), 49 were heterozygous (2R/3R) and 33 were homozygous for two repeats (2R/2R). Patients with lung cancer who were homozygous or heterozygous for three repeats in the TS VNTR survived significantly longer than patients homozygous for two repeats (N=114, p=0.007) with death due to lung cancer as an endpoint. Lower than average thymidylate synthase protein expression (<=12% nuclear positivity) was significantly associated with longer survival (N=94, p=0.001). The TS genotype was correlated with TS protein expression (N=94, p=0.03).

Conclusion: This work suggests that TS VNTR may be an important prognostic marker in NSCLC. The TS VNTR genotype and TS protein expression are associated with a significant difference in mortality from lung cancer. The TS VNTR genotype may be associated with survival because of its association with a differential expression of TS protein. Tumors homozygous or heterozygous for three repeats in the TS VNTR are associated with lower TS expression and have a better prognosis than tumors homozygous for two repeats in the TS VNTR. Whether TS VNTR predicts response to pemetrexed is a question that warrants further study.

Keyword: thymidylate synthase, genotype, protein, NSCLC, polymorphism, VNTR

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.237 LUNG CANCER: CORRELATION OF CRP AND SERUM ALBUMIN AT DIAGNOSIS WITH CLINICAL AND PATHOLOGICAL PARAMETERS

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Background: CRP and serum albumin are indicators of systemic inflammatory reaction and the status of patient's nutritional condition respectively. It has been found that CRP has a prognostic value in advanced neoplasms of various types while its combination with serum albumin has additional prognostic value in certain tumours. The aim of this study is to assess the values of CRP and serum albumin in primary lung neoplasms and to evaluate their clinical significance.

Methods: Patients with primary lung cancer and no active infection were included in the study. The diagnosis of the neoplasm was made by means of histology or cytology. A blood sample was taken prior to any therapeutic intervention. The samples were centrifuged and the serum was stored in deep freezer until the measurement. CRP and albumin were assessed using nephelometry and photometry respectively. Finally, a database was created with all the clinical and histological data of the patients.

Results: Overall, 129 patients (114 men and 15 women) with a mean age of 64 years were assessed. The histology types were: 79% non small cell and 21% small cell neoplasms. The results and the respective statistical analysis will be available shortly.

Conclusion: The conclusions of the study will be announced shortly.

Keywords: Biomarkers, Lung cancer, CRP, serum albumin

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.238 INFLUENCE OF CXCR4 AND ER CO-EXPRESSION IN METASTATIC NSCLC AND ASSOCIATION WITH OUTCOME

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Background: CXCR4, a G protein coupled chemokine receptor, and its ligand, stromal cell derived factor-1 (SDF-1), play a critical role in organ specific tumor metastasis. Increasing evidence suggests that it contributes to metastasis in Non Small Cell Lung Cancer (NSCLC) and that its expression may be associated with poor outcome. It was recently demonstrated that a positive regulatory loop exists between the CXCR4/SDF-1 chemokine axis and estrogen receptor (ER) signaling pathways which influences both ER and CXCR4 dependent gene expression and ultimately tumor cell growth in vitro. It is also known that a significant proportion of NSCLC tumors express ERs and that there may be a gender dependent difference in ER expression. We set out to assess the expression of CXCR4 and ERs in stage IV NSCLC diagnostic biopsies to determine if either receptor alone, or co-expression of both CXCR4 and ER is associated with clinical outcome.
Methods: After ethical approval was obtained, demographic details, clinical variables and outcome data were gathered on NSCLC patients diagnosed at the Tom Baker Cancer Centre (TBCC) from 2003 to 2006 (Glans-Look Lung Cancer Database). Formalin-fixed paraffin embedded tumor specimens were obtained from patients diagnosed with stage IV disease and tissue micro arrays (TMAs) were generated. Protein expression of the target biomarkers was analyzed by quantitative fluorescent immunohistochemistry (IHC) using the HistoRx PM-2000 platform. A quantitative AQUA expression score for ERs and CXCR4 was obtained. CXCR4 and ER expression, and co-expression of both receptors was then correlated with clinical outcome. Survival analyses were performed using the Kaplan-Meier method and tested using a log rank test.
Results: 832 patients were diagnosed with stage IV NSCLC, 170 of which had suitable samples for incorporation into TMAs. The overall survival of patients whose tumors were suitable for TMA generation was similar to the general cohort. Automated IHC for CXCR4 and ERs was successfully completed on all samples. CXCR4 expression was seen in the cytomembranous compartment of almost all samples tested. High expressors had a significantly poorer median overall survival (MOS) of 2.7 months vs 5.6 months for the low expressors ($p = 0.0468$). This difference was driven by high expressing females who had a MOS of 1.6 months versus 6.4 months for the low expressors ($p = 0.006$). No significant difference in survival was seen in the males. ERs were expressed in the nucleus in approximately 15-20% of tumor samples. There appears to be more females with expression of ERs than males which may be influencing the observed gender discrepancy in outcome seen in CXCR4 high expressors.
Conclusion: Estrogen receptors (ERs) are expressed in a significant number of NSCLC tumors and are localized to the nucleus while CXCR4 is limited to the non nuclear compartment of tumor cells. We describe a gender dependent effect on the association between CXCR4 and clinical outcome which may be influenced by ER co-expression in stage IV NSCLC. Detailed analysis of the relationship between ER expression, ER/CXCR4 co-expression and outcome is ongoing and will be presented.
Keywords: Non small cell lung cancer, estrogen receptors, outcome, CXCR4

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.239 PREDICTIVE AND PROGNOSTIC ROLE OF GEMCITABINE-RELATED GENES IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Gemcitabine is widely used in the first-line treatment of advanced non-small cell lung cancer (NSCLC), either as a single agent or in combination regimens. Tumour mRNA expression levels of breast cancer susceptibility gene-1 (BRCA1) and ribonucleotide reductase subunits M1 and M2 (RRM1 and RRM2) were recently indicated as useful tools for customising gemcitabine-based chemotherapy in this setting. Furthermore, human equilibrative nucleoside transporter-1 (hENT1), deoxycytidine kinase (dCK) and cytidine deaminase (CDA) have a key role in the cellular transport and metabolism of gemcitabine, thus being implicated in the drug's antitumour activity. We investigated the potential role of tumour expression of the six aforementioned genes in clinical outcome to gemcitabine-based chemotherapy in advanced NSCLC.
Methods: BRCA1, RRM1, RRM2, hENT1, dCK and CDA mRNA expression was retrospectively analysed by RT-qPCR in microdissected, FFPE primary tumour specimens from 138 patients with stage wet-IIIB and IV NSCLC (UICC 6th TNM edition) or recurrent, locally-advanced disease not amenable to surgery or radiation. Patients had participated in clinical trials of the Hellenic Oncology Research Group and received first-line gemcitabine, either as monotherapy (G) or combined with platinum (GC), taxane (GT), vinorelbine (GV) or pemetrexed (GP). Relative gene-expression quantification was performed with the comparative Ct method, using β-actin and 3-phosphoglycerate kinase as endogenous controls. The individual and combined gene expression patterns were statistically evaluated for association with clinicopathological features and outcome endpoints, including overall response rate (ORR), time to progression (TTP) and overall survival (OS).
Results: Patients' and tumour characteristics were as follows: median age 64 years; males 86%; ECOG performance status 0-1 88%; stage IIIB 28% and stage IV 68%; adenocarcinomas 56% and squamous-cell carcinomas (SCC) 30%; treatment with GT and GV 75%, GC 14%, and G 9%. All six target genes were successfully amplified in 78% of the specimens. BRCA1, RRM2, and dCK expression levels were significantly higher in SCC compared with non-SCC ($P < 0.05$). A significant intermediate to strong coexpression was observed between BRCA1/RRM1, BRCA1/RRM2 and dCK/RRM2 (Spearman's coefficient >0.55, $P < 0.001$). In univariate analysis, there was a statistical trend for shorter TTP in patients with high versus low/intermediate RRM2 mRNA levels (2.8 versus 4.17 months, $P = 0.063$). Furthermore, patients with combined overexpression of the genes disfavouring gemcitabine activity, i.e RRM1, RRM2 and CDA, had significantly shorter TTP compared with those with combined low levels of the corresponding genes (0.3 versus 1.82 months; $P = 0.045$). Similarly, OS was significantly shorter in the former group of patients compared with those combining high and low levels (0.6 versus 3.16 months; $P = 0.027$).
Conclusion: The combination of tumour RRM1, RRM2 and CDA expression is a potential biomarker tool for tailoring gemcitabine-based chemotherapy in advanced NSCLC. Prospective cross-validation is required.
Keywords: NSCLC, gemcitabine, tumor biomarkers, clinical outcome

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.240 CONCURRENT TP53 AND TYROSINE KINASE SIGNALING PATHWAY MUTATIONS IN ADENOCARCINOMA OF LUNG

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Background: Emerging data suggests that adenocarcinomas of lung appear to be driven by a small number of mutations that affect tumor behavior and response to treatment. The effect of combinations of mutations is currently being assessed by a consortium of centers in the US, the Lung Cancer Mutation Consortium. It is assessing 1000 adenocarcinomas for the presence of mutations in 15 or more genes by high throughput allele specific technologies including Sequenom and SNaPshot or by direct sequencing.
Methods: In this abstract we report the frequency of TP53 mutation determined by direct sequencing of exons 5, 6, 7, and 8 and their associations with mutations detected in 13 other genes including APC, AKT1, BRAF, CTTBN1, EGFR, FLT3, JAK2, KIT, MAP2K1 (MEK1), Notch1, NRAS, PIK3C,and PTEN by SNaPshot in 44 tumor cases.

Results: SNaPshot detected mutations is 5 genes in this cohort of adenocarcinomas for which data is currently available as shown in the table at the left (n=44). A total of 6 cases with TP53 mutations were identified by direct sequencing in the subset of tumor so far evaluated by both methods. TP53 mutation occurred in approximately 1/6 of the cases, regardless of the presence or type of an associated additional mutation. The single tumor with both EGFR and TP53 mutations had an EGFR exon 19 deletion and a second erlotoinib resistance-associated mutation in EGFR exon 20 (T790M) together with a point mutation at TP53 codon 248 on exon 7 (742 C→G). In 4 of 6 cases with TP53 mutation no additional mutations were found in any of the evaluated targets. Association Between TP53 status And Additional Mutations in Adenocarcinoma

	TP53+	TP53-	Totals
EGFR	1	5	6
KRAS	0	6	6
BRAF	0	3	3
PIK3CA	1	1	2
CTNNB1	0	1	1
Wild	4	22	26
Totals	6	38	44

Conclusion: These data suggest that TP53 may be the only identifiable driver mutation among the 14 genes evaluated in a significant proportion of cases. Further investigation as to the impact of TP53 mutation alone or in combination with other mutations on prognosis and response to therapy is warranted.

Keyword: Adenocarcinoma, mutation, TP53, SNaPshot, sequencing

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Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.241 CORRELATION BETWEEN ATP7A, XIAP AND PAKT EXPRESSION AND CISPLATIN RESISTANCE IN NON-SMALL CELL LUNG CANCER.

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Background: Despite significant advances in non-small cell lung cancer (NSCLC) therapy during the past decade, platinum compounds remain the cornerstone for both early and advanced stages NSCLC management. However, the mechanisms underlying platinum resistance/sensitivity are poorly understood and no major impact in patient selection or treatment modulation has been achieved to date. Anti-apoptotic proteins and platinum-efflux pumps are known mechanisms, therefore we decided to evaluate the role of XIAP and pAkt anti-apoptotic proteins, and ATP7A, a cisplatin-efflux pump, correlating its expression with cisplatin sensitivity in either cell lines or patients.
Methods: We analyzed three human tumor cell lines, ACC-LC94, ACC-LC319 and A549, all comprising adenocarcinoma histology and harboring KRAS mutations. The cisplatin IC50 was assessed using MTT assay after 48 hours incubation. mRNA expression was evaluated by Real-time PCR, while Western blotting was performed to evaluate protein expression. For correlative studies, two distinct cohorts of NSCLC patients were evaluated. The first cohort comprised 39 patients diagnosed at early-stage NSCLC, whereas the second included patients with metastatic disease. In the latter, patients were clinically classified as platinum-sensitive (more than 6-months progression-free interval after platinum-based therapy) and platinum-non-sensitive group (less than 6-months interval). In these two cohorts, we have either analyzed mRNA or protein expression by immunohistochemistry.
Results: The studied cell lines exhibited distinct profiles regarding cisplatin sensitivity. LC94 was especially sensitive to cisplatin (IC50 11.2 mM), in contrast to LC319 (IC50 47.4 mM) and A549 (IC50 63.7 mM). Notably, resistant cell lines (LC319 and A549) showed a positive correlation of high XIAP and ATP7A mRNA expression when compared to LC94. These data was corroborated by XIAP and ATP7A mRNA expression, which also showed a significant positive correlation (R^2=0,88) among early-diagnosed patients. Unfortunately, we were not able to correlate these data to treatment, since only few patients received adjuvant therapy.

Subsequently, the XIAP protein expression was evaluated in cell lines and in the cohort of metastatic patients. XIAP had higher expression in the resistant cell lines when compared to the sensitive cell line. Among metastatic patients, XIAP was expressed in 45% (21/47) in the platinum-non-sensitive group, while no expression was observed in the platinum-sensitive (0/4). Knowing that XIAP is regulated by PI3K/Akt pathway through phosphorylation at the serine-87 residue, which increases XIAP stability and accumulation, we further analyzed the Akt phosphorylation on cell lines. In LC319 and A549, with high XIAP expression, we also observed increased Akt phosporylation, in contrast to LC 94. We also assessed the Akt activation after cisplatin exposure. In fact, cisplatin induced Akt phosphorylation in resistant cell line (A549), but not in the sensitive (LC 94).

Conclusion: XIAP and ATP7A mRNA expression were positively correlated to cisplatin resistance/sensitivity in NSCLC patients and cell lines. Also, we observed a correlation of high XIAP mRNA and protein expression and Akt phosphorylation with cisplatin resistance in the studied cell lines. While further analyses are warranted to validate these findings in larger cohorts, these proteins are putative targets for drug development, since they seem promising for combined therapies directed to overcome cisplatin resistance.

Keywords: Lung neoplasms, Biomarkers, Cisplatin, Predictive

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.242 ASSOCIATION BETWEEN VITAMIN D RECEPTOR GENE POLYMORPHISM AND NON-SMALL CELL LUNG CANCER RISK AND SURVIVAL.

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Background: The effects of 1,25-dihydroxyvitamin D3 are mediated by binding to a specific intracellular vitamin D receptor (VDR), which has been identified in a variety of tissues. Certain polymorphisms in the VDR gene have been associated with various neoplasms. The purpose of this study was to determine whether polymorphism in the VDR gene might also influence non-small cell lung cancer (NSCLC) risk.

Methods: Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP), and agarose gel electrophoresis techniques were used to detect VDR TaqI and Fok I polymorphisms. Sixtytwo NSCLC patients and 74 healthy controls were genotyped for the TaqI and FokI .The survival and staging data of operated NSCLC patients were also recorded. Kaplan Meier analysis, log-rank and Cox-proportional hazard risk test were also used.

Results: The frequencies of the TT, Tt and tt genotypes were 32.0%, 48.0%, 20% in NSCLC cancer patients and 54.8%, 37.1%, 8.1% in healthy controls, respectively. The genotype distribution for TaqI polymorphism was different between NSCLC patients and controls (p =0.015). VDR Taq I TT genotype was significantly associated with a increased risk of NSCLC in our study groups (OR=1.893; 95%CI 1.122-3.192; P = 0.032). On combined genotype analysis, the TTFF combined genotype was associated with NSCLC risk compared with other genotypes (OR=1.788; 95%CI 1.189-2.690; P = 0.004). VDR Taq genotype was also found to be associated with survival (p=0.02) and lymph node involvement (p=0.03).

Conclusion: Our findings suggest that the TT genotype of the VDR TaqI variant was significantly associated with a increased risk of NSCLC. VDR taqI genotype also seemed to be associated with survival.

Keywords: vitamin D receptor, polymorphism, survival, genetic factor

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.243 STUDY OF MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES, AND EGFR AND KRAS STATUS OF PULMONARY ADENOCARCINOMAS WHEN DIAGNOSED ON CYTOLOGY

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Background: Bronchioloalveolar carcinoma (BAC) and mixed-type adenocarcinomas with BAC features are associated with EGFR mutations and a clinical response to tyrosine kinase inhibitors. Tumors that contain KRAS mutations and lack EGFR mutations have different therapeutic implications. In this study we present the cytomorphological and immunohistochemical features of lung adenocarcinomas, that were diagnosed by cytologic methods and their relationship to both EGFR and KRAS mutational status.
Methods: We retrospectively reviewed 50 lung adenocarcinomas that were diagnosed cytologically for cell size, architectural pattern, nucleoli, intranuclear cytoplasmic inclusions (INCI), mucin, necrosis, squamoid features, lymphocytic response, and histologic features of BAC differentiation on FNA and/ or touch imprint of needle core biopsies (NCB) and tested for both EGFR and KRAS mutations. Immunohistochemistry was performed on the cell block or NCB using CK7, CK20, TTF-1 and P63. DNA extracted from paraffin embedded cell block or frozen needle core fragments was studied for exon 19 deletions and the L858R mutation in exon 21 of EGFR (using PCR followed by capillary electrophoresis for fragment sizing). KRAS mutational analysis was performed by real-time PCR using a set of 7 different Taqman(r) allelic discrimination assays to detect 6 mutations in codon 12 and 1 mutation in codon 13.
Results: KRAS mutations were seen in 12 (24%) and EGFR mutations in 6 (12%) patients. Thirty eight (62%) patients were negative for both EGFR and KRAS mutations. Tumors with EGFR mutations were more likely to be well differentiated (P=0.016) and tumors with KRAS mutations were more poorly differentiated adenocarcinomas (P=0.025). Presence of prominent INCI (P=0.036), papillary fragments (P=0.041), and histologic features of BAC on paraffin block (P= 0.039) correlated with EGFR mutations while necrosis (P=0.030), squamoid features (P=0.048), and poorly differentiated tumors (P=0.025) with KRAS mutations. Tumors with EGFR or KRAS mutations were positive with TTF-1 and CK7 immunostains. There was no significant association between lymphocytic response and EGFR or KRAS mutational status.
Conclusion: The distribution of EGFR and KRAS mutations in lung adenocarcinomas when diagnosed on cytology was similar to that reported in prior studies on surgical material. Features of BAC including the presence of INCI, flat sheets and papillary fragments on cytology was associated with EGFR mutations. Tumors with KRAS mutations frequently had necrosis and squamoid features on cytologic material and were almost all poorly differentiated. Tumors with either mutation was immunohistochemically positive with TTF-1 stain. These morphological features may help cytopathologists better triage specimens for molecular studies.
Keyword: Cytology, pulmonary adenocarcinoma, EGFR, KRAS

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.244 TECHNICAL VALIDATION STUDY OF A MULTI-ANALYTE SERUM PANEL FOR LUNG CANCER DETECTION

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Background: Lung cancer is the leading cause of cancer death worldwide primarily due to late stage presentation and no accepted early detection protocol. Preliminary National Lung Cancer Screening results using computed tomography (CT) have shown enhanced detection of early stage disease with better survival. However, a large number of incidentally found benign nodules lead to costly further workups and non-therapeutic invasive procedures. A simple, cost-effective serum test for early detection could improve falsely positive findings on imaging to accurately identify early stage lung cancer patients.
Methods: We reported two individual serum tests for non-small cell lung cancer (NSCLC) using immunobead (Luminex) assays, including one comprised of circulating biomarkers (tumor necrosis factor-α, CYFRA 21-1, interleukin-1ra, matrix metalloproteinase-2, monocyte chemotactic protein-1 and sE-selectin) and one comprised of autoantibodies

(inosine monophosphate dehydrogenase, phosphoglycerate mutase, ubiquillin, annexin I, annexin II, and heat shock protein 70-9B). Each test was validated against separate patient cohorts; the biomarkers were tested against 92 NSCLC and 43 non-cancer controls, and the autoantibodies were tested against 117 NSCLC, 43 non-cancer, and 31 normal controls. The misclassification rate for these independently published panels was 15% and 7%, respectively. Multivariate statistical methods were used to condense these algorithms into a single multi-analyte panel for detecting NSCLC.
Results: Two published serum panels were combined into a single panel for classifying patient disease status, which consists of tumor necrosis factor-α (TNF-α), cytokeratin 19 fragment (CYFRA 21-1), and autoantibodies against endoplasmic reticulum protein-29 (ERP29), inosine monophosphate dehydrogenase (IMPDH), monocyte chemotactic protein-1 (MCP1), ubiquillin, and annexin A2 (ANXA2). Performance of this combined serum panel against our original discovery and validation cohorts revealed a 3.2% (3/94) overall misclassification rate.
Conclusion: Here we report the development of a 7-target panel for the detection of NSCLC that was found to be highly accurate against all cohorts tested except those with inflammatory, benign lesions. Further refinement of this detection algorithm has potential to provide a useful first-line serum screening test for early NSCLC.
Keywords: NSCLC, Early Detection, biomarker, Luminex

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P2.245 FREQUENCY OF EGFR ACTIVATING MUTATIONS IN LUNG ADENOCARCINOMA PATIENTS FROM THE SOUTHWEST REGIóN OF COLOMBIA, LATIN-AMERICA.

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Background: The detection of activating mutations in exons 19 and 21 of the epidermal growth factor receptor (EGFR) gene, which predict sensitivity to treatment with EGFR tyrosine kinase inhibitors, represents a major advance in the treatment of lung adenocarcinoma. The prevalence of these mutations in Colombian patients has not been thoroughly investigated.
Methods: We collected formalin-fixed, paraffin-embedded material from resected lung adenocarcinomas from patients in Cali (Southwest Colombia) for DNA extraction, PCR amplification and subsequent automated sequencing. The frequencies of EGFR exon 19 deletions and exon 21 L858R substitutions in tumor specimens from southwest Colombia patients were compared with data from America and Asian populations.
Results: EGFR mutations were detected in 6 out of the 37 specimens tested from Cali (southwest Colombia) for a frequency of 16,2% (95%IC: 0,86 – 19,03, P=0,0002). All detected mutations were deletions in exon 19. The detected activating mutations were present in non-smoker women. Besides, there was no significant difference between frequencies of EGFR mutations comparing to African American (P=0,8868) or White American (P=0,7630) patients; However, there was a tendency to lower frequencies than in Japanese (P=0,0474) or Korean patients (P=0,0610).
Conclusion: This is the first study to date examining the frequency of mutations in lung adenocarcinomas in patients from southwest Colombia. There was no difference between the frequencies of EGFR mutations in patients outside Asia. These results suggest that, as suggested elsewhere, all Colombian patients with advanced lung adenocarcinomas should undergo mutational analysis before initiation of therapy.
Keywords: EGFR mutations, lung adenocarcinoma, Sothwest Colombia

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P2.246 VALIDATION OF A QPCR-BASED GENETIC ASSAY PROGNOSTIC OF SURVIVAL IN RESECTED NON-SMALL CELL LUNG CANCER

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Background: The large scale validation of genetic assays that provide more accurate prognosis than traditional staging has altered the standard of care for early-stage breast cancer patients. By comparison to most cancers, the five-year survival of patients undergoing an attempt at curative resection for non-small cell lung cancer (NSCLC) is poor. Most treatment failures are due to distant disease, often indicating an inaccurate post-operative staging and a resultant failure to consider adjuvant therapies that might have improved survival. Although numerous studies have established the feasibility of using genetic parameters to differentiate between patients with good and poor prognosis after resection of NSCLC, these studies have generally utilized microarray-based profiling and/or fresh frozen tissues, methods that are difficult to reproduce in a community-practice setting. None have been validated on a large scale. We report the development and initial large scale validation of a straightforward, quantitative PCR-based multi-gene assay using formalin-fixed, paraffin embedded (FFPE) specimens that identifies patients at high risk for treatment failure after resection of NSCLC.
Methods: Specimens were studied from 468 patients who underwent resection and complete surgical staging of stage I-IV NSCLC at University of California, San Francisco. RNA was extracted from FFPE tumor specimens using modifications of previously published methods. Expression of 11 target genes previously identified in a study using frozen tissues was measured using custom-designed TaqMan quantitative PCR assays. Multivariable Cox proportional hazards modeling employing h-fold cross-validation was used to select and validate a prognostic model. Risk scores were assigned using model coefficients and dichotomized. Survival of low- and high-risk category patients was analyzed using the Kaplan-Meier method.
Results: Expression of target genes was reliably measured in 413 FFPE specimens. 5-year overall survival was 41% among high-risk patients and 69% among low-risk patients ($p<0.0005$). Among stage I patients, 5-year overall survival was 46% among high-risk patients and 73% among low-risk patients ($p<0.0005$). After adjusting for patient age, sex, and stage, the hazard ratio of the risk score as a continuous variable was 2.6 (95%CI 1.97-3.43, $p<0.0005$).
Conclusion: We have begun large-scale validation of a practical multi-gene qPCR-based assay that is prognostic of survival in patients with resected NSCLC. Further validation of this assay on a large, independent cohort of patients who have undergone resection for early-stage NSCLC at Kaiser Permanente Northern California is ongoing. This practical genetic assay provides additional prognostic information beyond the traditional TNM staging system that may impact both the use of adjuvant therapy as well as the choice of surgical procedures in patients with NSCLC.
Keywords: genetic, Non-small cell lung cancer, prognostic, biomarker

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P2.247 PREDICTIVE VALUE OF THYMIDYLATE SYNTHASE AND FOLYLPOLY-GLUTAMATE SYNTHETASE FOR CLINICAL BENEFIT FROM PEMETREXED IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: The antifolate pemetrexed (PMX) targets multiple enzymes involved in pyrimidine and purine synthesis including thymidylate synthase (TS). After entry into cells, PMX is converted to more potent polyglutamated forms by folylpoly-γ-glutamate synthetase (FPGS), a critical step to achieve full target inhibition. We hypothesized that FPGS and TS protein expression may predict response and outcome following PMX treatment of patients (pts) with malignant pleural mesothelioma (MPM).
Methods: Pre-treatment tumor samples from 69 pts with MPM, treated with PMX combined with platinum (64/69) or as single agent (5/69), were retrospectively analyzed. TS and FPGS protein expression levels were evaluated by immunohistochemistry using the H-Scoring system (ranging from 0 to 300), which relies on the product of intensity of specific tumor cell immunoreactivity (range 0 to 3) and the percentage of positive tumor cells. Radiographic evaluation of response was performed according to RECIST.
Results: Median pre-treatment H-scores were 230 (range: 50-300) for TS and 240 for FPGS (range: 110-300). Using the log-rank test and the median H-score as cut-off, we found a significant association between improved progression-free survival (PFS) and low TS protein expression (median PFS of 225 vs 190 days; hazard ratio [HR] 0.516, 95% CI, 0.295 to 0.908; P=0.022). High FPGS protein expression was associated with objective response (mean H-score 251 for responders vs 230 for non-responders, P=0.016) as well with absolute clinical benefit including objective response and disease control (mean H-score 244 for responders and stable disease pts vs 215 for progressive disease pts, P=0.009). Moreover, we found an association of high FPGS protein expression with prolonged PFS (median PFS of 218 vs 185 days; HR 0.847, 95% CI, 0.268 to 1.430; P=0.019).
Conclusion: Here we report the most thorough investigation of TS and FPGS expression in tumor specimens from pemetrexed-treated MPM pts to date. Based on our retrospective study, base line determination of TS and FPGS expression may be predictive for clinical benefit of PMX-based therapy in MPM. Confirmation of the prognostic and predictive value of TS and FPGS expression in MPM by prospective studies is warranted.
Keywords: thymidylate synthase (TS) and folylpoly-glutamate synthetase (FPGS), malignant pleural mesothelioma (MPM), predictive biomarker for response and outcome, Pemetrexed

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P2.248 ROUTINE IMAGE-GUIDED DIAGNOSTIC BRONCHOSCOPIES CAN YIELD TUMOR SPECIMEN SUITABLE FOR BROAD PANEL OF IMMUNE AND PREDICTIVE MOLECULAR MARKERS STUDIES IN THORACIC MALIGNANCIES. ROLE OF COORDINATED MULTIDISCIPLINARY THORACIC ONCOLOGY PATHOLOGY TEAMWORK.

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Background: Lung Cancer(LC) fatality remains high, previously prognosis is linked to patients' disease stage and functional status. Recent studies with have highlighted importance of accurately characterizating NSCLC celltypes: distinguishing between squamous and non-squamous carcinomas. Introduction of molecular "targeted" agents (EGFR-TKIs, EML4-ALK antagonists) and proliferation of other prognostic and predictive markers (PIK3CA,BRAF, AKT,etc) requires more tumor tissue for immunohistochemical(IHC) and genetic testing than simple cytologic diagnosis of "lung cancer". Coincidentally, there's a drive to reduce more invasive initial surgical procedures (medianstinoscopies, open lung biopsies) as patients receiving induction-therapy may require re-staging prior to resections. Minimally invasive bronchoscopies have heretofore provided limited diagnostic material. We describe the routine use of Endobronchial Ultrasound (EBUS) Image

Guidance and a coordinated pathology-diagnostic team approach to provide material necessary to guide personalized therapy in thoracic malignancies.
Methods: Retrospective review of database developed to assess impact of bronchoscopic real-team image-guided interventions (BIGI) in improving diagnostic yield. From 2-2008 through 2-2011, 80 cases of suspected thoracic malignancies included. EBUS used as the primary mode of BIGI, plus fluoroscopy for peripheral lesions; bedside cytopathology to provide on-site evaluation available in all cases. Male:female ratio 49:31; age range 17-95, median 6th decade. 34 suspected of primary lung cancers (risk factors); 46 suspected recurrent cancers or new primary lung with prior non-lung cancers: 16lung, 7H&N, 7colorectal, 3RCC, 3pancreatic, 3hematologic malignancies, 2breast, 2melanoma, 1 each bladder, prostate, osteosarcomas. Tissue sample by EBUS guided transbronchial needle aspiration (TBNA) 90 lymph node stations sampled in 76/80 patients, (4/80 without lymphadenopathy); 33 patients have parechymal(29) or central airway masses(4). Transbronchial biopsies (forcep and needle) of peripheral lesions guided by EBUS probe and fluoroscopy.
Results: Diagnosis: Cancer 61/80, 17 benign(granulomatous) 2 false-negative (NSCLC). Malignancies include 49 LCs in 47 patients: 38 new, 9 recurrences; synchronous primaries in 2. 15 thoracic metastases in 30 patients with prior non-lung primaries; other 15 with new primary lung or granulomas (Table). A broad panel of immunohistochemical stains geared to determine cancer origin ordered per pathology staff based on detailed history, additional molecular biomarkers included KRAS 10+/33(30%); EGFR 8+/30(27%); EML4-ALK 2+/4(3.4%,3.5% fusion); BRAF ordered on 1 each lung, melanoma and colon 2+/3(66%); ERCC1/RRM1 high expression in one specimen sent for analysis. HPV16/18+ in two H&N metastases.

LN Station	# attempt	Cancer Dx	Lymphs	Inadequate	Final Diagnosis	IHC /Marker
4R	41	26	15	1	Primary Lung: 49	SCLC 9 Chromogranin Synaptophysin
4L	5	2	2	1	New 38	NSCLC 42 Adenocarcinoma NapsinA,TTF1 KRAS,EGFR, EML4-ALK,ERCC1,RRM1
7	23	8	14	1	Recurrent 9	>1 primary 2 pts
11R	27	10	12	5	Metastatic	Cancers #15
11L	7	2	5	0	Head & Neck squamous cell	P16, HPV16, 18 KRAS, EGFR
9L/10L	2	2	0	0	Colorectal	CDX2, CK20 KRAS
12R/13R	4	1	1	2	Melanoma	S100, HMB45
Extra-thoracic	2	2	0	0	Breast	ER, PR, HER-2 Gross Cystic Dis protein
Lung nodule Endo-bronchial	30 4	26 4	0 0	4 0	Pancreas Renal Cell (RCC)	DPC4 loss PAX8

Conclusion: Tumor specimen from routine EBUS-guided diagnostic bronchoscopies can generate information about cancer-origin, cell-type, and mutation-status to provide guidance for personalized cancer therapy; successful implementation requires close collaborative teamwork between diagnostic-pathology services.
Keywords: Endobronchial Ultrasound (EBUS), Bronchoscopic Image Guided Interventions (BIGI), Prognostic/predictive Markers; Immunohistochemistry (IHC), Molecular Targeted Therapies

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P2.249 KRAS MUTATION STATUS PREDICTS SENSITIVITY TO ANTI-DHFR THERAPY (METHOTREXATE) IN NON SMALL CELL LUNG CANCER CELL LINES

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Background: Somatic genetic mutation in the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene has been linked to resistance to various targeted therapeutics (e.g.Erlotinib, Gefitinib) in Non Small Cell Lung Cancer (NSCLC). Therapeutic strategies that target tumors harboring these mutations represent an unmet medical need. In this study, we have identified higher sensitivity to a dihydrofolate reductase (DHFR) inhibitor, methothrexate (MTX), in KRAS mutant (mut) versus wild type (wt) NSCLC cell lines.
Methods: The NCI Developmental Therapeutics Progam cancer drug screen database was interrogated for association between KRAS mutation status and drug efficacy in NCI60 NSCLC cell lines. Furthermore, ten human NSCLC cell lines (4 KRASwt / 6 KRASmut) were treated with MTX and assayed for proliferation after 72h. Microarray gene expression data from the NCI-60 NSCLC cell lines using Ingenuity pathway analysis was also performed. Finally, expression of genes/

proteins related to folate metabolism and cell cycle progression were examined in KRASmut and KRASwt NSCLC cells with methotrexate treatment and KRAS overexpression or knockdown.
Results: Interrogation of the NCI Developmental Therapeutics Progam cancer drug screen database revealed increased efficacy of MTX in KRASmut versus KRASwt NCI-60 NSCLC cell lines. Furthermore, a similar specificity was revealed for other anti-folate therapies in the NCI cell screen. In our proliferation assays, KRASwt cells did not show response to MTX treatment, however, growth of 4 out of 6 KRASmut cell lines was significantly inhibited. Examination of microarray gene expression data from the NCI-60 NSCLC cell lines demonstrates increased expression of folate metabolism associated genes in KRASmut versus KRASwt cells. Furthermore, we determined that expression of DHFR, TS, E2F-1, phosphorylated Rb and mutant KRAS were decreased by methotrexate treatment in KRASmut but not in KRASwt cells. We also demonstrate that expression of DHFR, TS, E2F-1 and phosphorylated Rb are increased upon KRAS transfection and decreased upon siRNA knockdown of mutant KRAS.
Conclusion: Collectively, these studies highlight increased sensitivity to MTX in KRASmut NSCLC cells. We propose that mutant KRAS drives expression and release of E2F-1 which may in turn lead to increased expression of DHFR / TS and potential dependency on these pathways. The remainder of this study aims to characterize the underlying molecular mechanisms leading to this dependency on folate metabolism. Pemetrexed (Alimta) is a MTX derivative that is currently approved for the treatment of advanced or metastic nonsquamous NSCLC. Surprisingly this is one of the few antifolates from our analysis that do not show a similar enhanced efficacy in KRASmut versus KRASwt NSCLC cell lines which may be due to lower specificity of this drug for DHFR. While Pemetrexed has shown good efficacy in NSCLC treatment, our data suggests that the parental molecule MTX, should be revisited as a potential candidate for the treatment of NSCLC harboring KRAS mutation.
Keywords: Kras, Methotrexate, DHFR

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Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.250 N-NITROSO-TRIS-CHLOROETHYLUREA INDUCES PRE-MALIGNANT SQUAMOUS DYSPLASIA IN MICE

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Background: Squamous cell carcinoma (SCC) is the second-most common form of non-small cell lung cancer, and SCC tumor models have been difficult to develop. Herein, we propose a murine SCC (and pre-malignant precursor lesions) model using topical N-nitroso-tris-chloroethylurea (NTCU) application, and determine the extent to which airway dysplasias develops, and compare immunohistochemical staining patterns to dysplastic lesions from human smokers.
Methods: FVB/N mice were given biweekly topical applications of NTCU for 32 weeks at concentrations of 4mM, 8mM and 40mM, diluted with acetone. Following dorsal coat shaving a 25µl volume was applied to exposed skin. Afterward, formalin-fixed lung was thoroughly examined under bright field microscopy. Three separate H&E slides were examined per animal, taken from a single paraffin block, spaced 50µm apart. Squamous cell lesions were enumerated and categorized as one of the following: flat atypia (FA), low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive SCC (iSCC). Squamous origin of the range of observed lesions was confirmed with immunohistochemical staining for cytokeratin 5/6, p63, thyroid transcription factor-1, and napsin-A. As prostaglandins play a prominent role in lung carcinogenesis, we chose to measure changes in prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2) levels.
Results: Despite the intolerability of 64 total NTCU applications over 32 weeks to the 40mM group, this concentration produced the entire spectrum

of premalignant dysplasias and squamous cell carcinomas. Survival rates were 45.0% (18/40) in 40mM NTCU-treated animals, 77.8% (21/27) in 8mM, 92.3% (24/26) in 4mM, and 84.6% (22/26) in acetone control animals. Lesions detected per square centimeter of lung tissue (±SE) were as follows: FA, 2.96 (±0.63), 2.99 (±0.67), 1.12 (±0.39); LGD, 0.08 (±0.05), 0.15 (±0.06), 1.70 (±0.29); HGD, 0, 0.03 (±0.03), 0.98 (±0.40); iSCC, 0, 0, 0.49 (±0.22), respectively for the 4mM, 8mM, and 40mM groups. Control animals did not develop SCC lesions of any type. Interestingly, animals of the 40mM group that received 33 applications of NTCU over 32 weeks developed more SCC than those of the same group that received 46 applications (0.63±0.36, 0.35±0.36, p=0.39, n=14). Immunohistochemical staining patterns of cytokeratin 5/6, p63, thyroid transcription factor-1, and napsin-A revealed distinct similarities to human predysplastic lesions and SCC. Selected prostaglandin levels of the 8mM group were significantly higher than the 4mM group ($p<0.05$). **Conclusion:** Concentrations of 4mM and 8mM NTCU were better tolerated and produced significant levels of FA but not HGD or iSCC. Data from selected prostaglandin levels is suggestive of an integral relationship between aberrant inflammation involving the COX-2/PGE_2 pathway and cancer-mediated immunosuppression. Alterations in prostaglandin production may be associated with alterations in chemoprotection in lung cancer incidence and progression. Although more data is needed to improve the applicability of this model in the FVB/N mouse, it seems an equivalent degree of SCC development may be possible through fewer NTCU doses over a longer period of time. This study demonstrates that topical application of NTCU produces endobronchial pre-malignant lesions with clear squamous characteristics immunohistochemically comparable to those seen in human smokers and is a useful model in the pre-clinical evaluation of chemopreventive agents.

Keywords: NTCU, squamous cell carcinoma, Lung cancer, prostaglandin

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.251 BRONCHIAL DYSPLASIA IS MORE FREQUENT AND MORE ATYPICAL IN BIOPSY AND SPUTUM MATERIAL FROM HIV INFECTED SUBJECTS: A PRELIMINARY REPORT FROM AN ONGOING STUDY.

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Background: While the era of highly active antiretroviral therapy (HAART) has brought about dramatic improvements in overall life expectancy, the relative importance of non-AIDS-defining malignancies as a contributor to HIV-related morbidity and mortality has grown. Previous studies have demonstrated that carcinoma of the lung occurs in HIV infected individuals with higher frequency and at younger age than is typically observed in the HIV negative population. It has been noted that lung cancer in HIV infected patients is often associated with no observable radiographic abnormality even within the year prior to diagnosis, and HIV infected lung cancer is associated with significantly shorter survival. We have hypothesized that increased development and progression of bronchial dysplasia may have an important role in the observed increase of lung cancer incidence in the HIV infected population.
Methods: HIV infected subjects were recruited to an ongoing study of lung cancer biomarkers in a Colorado Lung SPORE approved protocol for sputum evaluation and potential bronchoscopy. A finding of moderate or worse sputum atypia was an indication for bronchoscopy. Sputum and bronchial biopsy specimens were read by either of two SPORE

pathologists (DTM, WAF) who were blinded to the HIV status of the subject. The frequency of atypical findings in sputum and bronchial biopsies in HIV infected subjects were compared to the frequency of these findings in subjects without a known history of HIV infection that were matched by age, gender and smoking status. In bronchoscopically evaluated subjects, frequencies of atypia were calculated by number of atypical biopsies per total number of biopsies.

Results: 30.8% (4/13) HIV infected subjects screened by sputum cytology showed moderate or higher degrees of dysplasia as compared to 21.7% (97/448) of HIV negative individuals. In addition, the frequency of severe sputum atypia was markedly higher in HIV infected than in HIV negative subjects [15.4% (2/13) vs. 0.9% (4/448)]. Four HIV infected subjects have been evaluated by bronchoscopy to date. The frequency of moderate or higher degrees of dysplasia for these respiratory epithelial biopsies in HIV infected patients was 38.9% (7/18) versus 24.9% (64/257) in age, gender and tobacco status matched non-HIV subjects.

Conclusion: The findings from this small number of HIV positive subjects studied to date supports our hypothesis that there may be more frequent and more atypical bronchial lesions in HIV infected subjects. If these findings are confirmed on extended analyses, it suggests that altered surveillance guidelines may be needed for early lung cancer detection in HIV infected patients and that these patients may benefit from chemopreventive therapy beyond smoking cessation. Recruitment of additional study subjects is continuing to confirm these preliminary findings.

Keywords: HIV infection, Sputum, bronchial biopsy, Bronchial dysplasia

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.252 IDENTIFICATION OF ALTERATIONS IN GENE EXPRESSION THAT DISTINGUISH PERSISTENT FROM REGRESSIVE BRONCHIAL DYSPLASIA

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Background: Bronchial dysplasia (BD) is believed to be a precursor lesion for the development of squamous cell carcinoma (SCC) of the lung. However, the majority of these lesions do not progress to invasive cancer. Identification of features of BD that are associated with risk for progression is essential for effective management of these lesions. Persistence of BD is a characteristic that may indicate increased malignant potential. We have previously found a direct correlation between the degree of atypia at baseline and higher levels of atypia on re-biopsy. Furthermore, in subjects with SCC, follow-up diagnoses are higher than equivalent sites in subjects without cancer. Thus, we hypothesized that differences in gene expression will distinguish persistent from regressive BD and identify markers of malignant potential and targets for therapeutic intervention in these lesions.

Methods: 111 biopsies snap frozen in liquid N2 immediately after collection were chosen for analysis. Expected baseline histology was based on diagnoses in immediately adjacent formalin fixed paraffin embedded (FFPE) biopsies. Gene expression analysis was performed on 64 specimens; 47 were excluded (22 for discrepant frozen and FFPE diagnoses, and 25 for inadequate RNA). Biopsies were classified into four groups based on the diagnosis at baseline and on follow-up at the site: Group 1 – Persistent Dysplasia (follow-up ≥ mild dysplasia; n=24) Group 2 – Regressive Dysplasia (follow-up ≤ hyperplasia; n=15) Group 3 – Progressive Non-dysplasia (follow-up ≥ mild dysplasia; n=9) Group 4 – Stable Non-dysplasia (follow-up ≤ hyperplasia; n=16) Total RNA was extracted from the portion of the biopsy remaining after frozen sectioning. Gene expression profiling was conducted using Affymetrix Human Gene 1.0 ST microarrays, and analyzed using RMA and ANOVA methods. Significant differences in expression were defined using a false discovery rate cutoff of 0.05% based on a corrected t-test.

Results: Groups 1 and 2 were not significantly different in respect to baseline diagnoses (5.08 vs. 4.73, group 1 vs. 2 respectively), gender (67.7% vs. 73.3% male), age (58.9 vs. 63.2 years), tobacco status (50.0% vs. 40.0% current smokers) or history of lung cancer (33.3% vs. 20.0%). The gene

expression analysis comparing group 1 to group 2 revealed 66 genes with statistically significant differential expression of greater than two-fold change. Many genes encode proteins with activities related to known cellular processes including squamous differentiation (13 genes), cellular proliferation (10), invasion (7), inflammation (6), cell-cell adhesion (5), angiogenesis (3) and apoptosis (2). Although 3 of the 5 upregulated genes in the adhesion group promote cell-cell interaction, within the rest of these groups the majority or all of the genes are modulated in a manner that would be expected to promote malignant progression. Group 1 also showed 896 differentially expressed genes compared to group 4. Except for 3 genes differentially expressed when comparing groups 3 and 4, no significant changes were seen in other comparisons.

Conclusion: Gene expression analyses identified several alterations that distinguish persistent BD from regressive lesions. The genes identified in this analysis could provide needed prognostic markers of risk for progression and indicate potential targets for chemoprevention in high risk patients.

Keywords: Bronchial dysplasia, Persistence, gene expression

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.253 REG FAMILY GENES EXPRESSION IN LUNG CANCER

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Background: Regenerating gene (REG) was originally discovered as a gene which related in regeneration of pancreatic ß-cells. REG family genes (REG Iα, REG Iß, REG III, HIP/PAP, and REG IV) encode growth factor family, and they are involved not only in regeneration of damaged tissues but also in tumor growth of gastrointestinal cancer cells. In the present study, we investigated expressions and effects of REG family genes in non-small cell lung cancer in vivo and in vitro.

Methods: We enrolled 47 lung adenocarcinoma (AD) and 21 lung squamous cell carcinoma (SCC) patients who were operated on Nara Medical University (stage I: 42, stage II: 8, stage III: 18). RNA was extracted from tumor and corresponding normal lung tissue, and used for real-time RT-PCR to measure REG family genes expressions. We set the cutoff levels from the expressions of the normal lung tissues and then correlated these expressions of tumors with prognosis of patients. In vitro, we obtained lung adenocarcinoma (HLC-1) and lung squamous cell carcinoma (EBC-1) cell lines and established HLC-1 and EBC-1 expressing REG Iα (HLC-1 REG Iα and EBC-1 REG Iα). Cell growth, cell proliferation, and anchorage independent cell growth of HLC-1 REG Iα and EBC-1 REG Iα were compared with those of control HLC-1 and EBC-1 (HLC-1 mock and EBC-1 mock), respectively.

Results: REG Iα and REG VI genes expressed high rate in tumors than in normal lung tissues. Especially, the survival rate among the stage I patients of AD and SCC expressing higher levels of REG Iα was significantly worse than among those expressing lower levels of REG Iα ($P<0.01$, Kaplan-Meier survival curve). In contrast, the characteristics of expressions of REG Iß, REG III, and HIP/PAP had no difference in normal lung tissues and tumors. In vitro, HLC-1 REG Iα showed significant increases in cell growth, cell proliferation, and anchorage independent cell growth compared with HLC-1 mock. On the other hand, EBC-1 REG Iα showed significant increase only in anchorage independent cell growth compared with EBC-1 mock.

Conclusion: The present results demonstrated that REG Iα expression was correlated with poor prognosis of early stage non-small cell lung cancer because of enhancement of cancer cell progression. REG Iα may be a useful target for anticancer treatment to patients of non-small cell lung cancer.

Keyword: Regenerating gene (REG)

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.254 HISTOLOGIC SUBTYPING AND TUMOR STROMAL RESPONSES IN LUNG ADENOCARCINOMA AND THEIR RELATIONSHIP TO SURVIVAL

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Background: Lung adenocarcinoma (ADC) has variegated histology and diverse clinical behavior. The 2011 IASLC classification of lung ADC recognizes distinctive architectural subtypes but cytological features and tumor stromal responses may be particularly useful for prognosis. The predictive value of these features in relation to erlotinib treatment is unknown. The objectives were to develop a tool for detailed morphologic profiling of ADC and to identify potential features related to outcome in a cohort of patients (pts) with ADC treated with erlotinib following progression.
Methods: This was a retrospective study of ADC from pts who initially underwent resection and then were treated with erlotinib following disease progression (N=51). Subtyping of resected ADC using morphometric profiling (Okudela 2008). Tumor-associated fibrotic focus (FF) and lymphoid responses (TALR) were graded on H&E sections as prominent vs mild/none. The log-rank test was used to compare selected morphologic parameters for their effects on overall (OS) and progression-free survival (PFS).
Results: 51 pts included 29 females, 8 never smokers. ADC with prominent FF (N=33) showed a significant difference for improved PFS (p=0.002) compared with those without (N=5), but there was no difference in OS. No significant differences in survival were found between mixed vs pure ADC types, mixed type with solid pattern vs without, mixed subtype with high columnar cell type vs without, and prominent TALR vs. none.
Conclusion: This is a small, retrospective study but our data show that prominent FF is related to improved PFS in resected ADC pts treated with erlotinib upon progression. This was unexpected given the association of FF with poor outcomes in breast cancer. This suggests that FF in lung ADC may identify tumors with a favorable prognosis but does not appear to be associated with response to erlotinib following progression. These data also suggest that mixed subtype ADC, solid pattern component, variations in tumor cytology and TIR may not be significant for PFS or OS in early stage resectable pts. Detailed morphologic subtyping of ADC, measurement of FF, identification of EMT markers, and qualitative and quantitative assessment of tumor immune responses need to be examined further in a larger group of resected early stage ADC for possible prognostic significance.
Keywords: fibrotic focus, Adenocarcinoma, morphologic subtyping

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.255 USE OF A CONTINUOUS EGFR IHC SCORING METHOD IN NSCLC: FEASIBILITY IN A GENERAL PATHOLOGY DEPARTMENT AND RELATIONSHIP TO EGFR FISH

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Background: Using a continuous Epidermal Growth Factor Receptor (EGFR) immunohistochemistry (IHC) scoring method, high EGFR expression levels were predictive of high response rate and patient benefit from the addition of cetuximab to chemotherapy in the FLEX trial (O'Byrne K et al. JTO 2010; 5(12), LBOA1). We investigated whether this scoring method was feasible in a general pathology department and related IHC scores to patient and tumour characteristics and EGFR FISH analysis.
Methods: Triplicate FFPE samples of resected primary NSCLC tumours were prepared as tissue arrays. The FDA approved Dako PharmDX kit was used for IHC detection of EGFR expression by a senior laboratory scientist skilled in IHC. Expression levels were determined via a continuous scoring system based on membrane staining intensity (0, 1^+, 2^+, 3^+) and percentage of positive tumour cells. The score was calculated as (% 1^+ x 1) + (% 2^+ x 2) + (% 3^+ x 3), with possible scores of 0 (no staining) to 300 (strong staining all cells). The mean of triplicate

specimens was calculated. EGFR FISH was carried out on the same tissue array samples.
Results: Tissue arrays were from tumours resected from 403 patients over the period 1992-2008. Patient and disease characteristics were: median age 68 yrs (range 22 - 102); male 282 pts (70%); TNM – $T_{1-2}N_0$ 344 pts (85.4%), $T_{1-3}N_1$ 56 pts (13.9%) and $T_{1-2}N_2$ 3 pts; smoking – never smoked 26 pts (6.5%), light smoking (≤10 pack years ceased ≥ 10 yrs) 9 pts (2.2%); histology included adenocarcinoma 181 pts (44.9%), squamous cell 142 pts (35.2%) and large cell / LC neuroendocrine 36 pts (8.9%); 5yr survival was 53% (Kaplan-Meier). Low EGFR expression (0-199) was scored for 264 patients and high (200-300) for 139 patients (34.5%), similar to the 31% high EGFR expression for FLEX trial patients (O'Byrne et al). High EGFR expression was more frequent with squamous cell than adenocarcinoma tumours (54% vs 23% respectively, p<0.001), and trended more frequent in heavy smokers than never or light smokers (35% vs 20%, p=0.14 NS). Survival over the 5 years following resection was worse for patients with high EGFR expression (further analysis will be presented). Overall 87 cases (21.5%) were positive on EGFR FISH: 11 and 15 patients showed high and low amplification respectively, 15 polysomy and 46 'Colorado criteria' (≥4 copies in ≥ 40% cells). Nine cases (6.5%) of EGFR high amplification were seen with high EGFR IHC scores compared with 2 cases (0.8%) with low scores. Overall there were 41 FISH positive (15.8%) amongst low IHC score cases and 41 positive (29.9%) amongst high IHC score cases (p=0.0015).
Conclusion: This EGFR IHC scoring system was feasible in a general pathology department. The proportion with high expression was similar in our early stage patients to that seen for patients in the FLEX trial, who were treated for advanced disease. As expected, high expression was more frequent in squamous cell carcinomas. Positive EGFR FISH was significantly associated with high EGFR IHC expression although the overall proportion of cases with FISH positive tumours was low.
Keywords: predictive factors, EGFR IHC, EGFR FISH, NSCLC

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.256 EGFR AND KRAS MUTATIONAL PROFILING IN FRESH NSCLC CELLS

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Background: Correlation between mutations in cancer alleles and drug response is a crucial point to identify drugs or drug combinations that match the genetic profile of individual tumors. In NSCLC genetic lesions affecting EGFR pathway act as predictive markers of response to EGFR inhibitors. Inappropriate EGFR phosphorylation is mainly consequent to somatic mutations in receptor tyrosine kinase (TK) domain. Incidence of EGFR mutations is about 77% among erlotinib/gefitinb responders while it is < 7% in unsensitive cases; mutations are more frequent in adenocarcinomas (ADK) aroused in not smokers and females. Downstream KRAS mutations are highly specific negative predictors of response to single agent EGFR inhibitors
Methods: We planned to evaluate in a cohort of NSCLC patients the EGFR and KRAS mutations prevalence by analyzing tumor cells directly obtained through CT-guided trans-thoracic biopsy, which represents a proper diagnostic tool for peripheral lesions, such as ADKs - actually accounting for 40% of all NSCLC diagnosis. Importantly this procedure allows acquisition of samples enriched by cancer cells captured through CT fluoroscopic guidance.
Results: In an ongoing study we have till now evaluated 134 cases, 88 males and 46 females (mean age = 67 years). 62.9% of them are smokers. We found EGFR somatic mutations in 13 (9.7%) patients affected by ADK, of them 7 were females and 11 never or former smokers. KRAS mutations occurred in 20 (5,95%) patients (F:M=3:2), 3 affected by ADK and 2 by squamous cell (SCC) cancer. As expected EGFR and KRAS mutations are mutually exclusive. Results have been validated by performing the same analysis on corresponding paraffin-embedded samples and obtaining the same mutational results. Clinical response of patients treated with erlotinib will be also presented.
Conclusion: Mutational screening on fresh cancer

cells is an achievable, safe and cost-effective procedure that could be easily integrated to conventional histopathological
Keyword: mutations, fresh cancer cells

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P2.257 BIOMARKER DEVELOPMENT FOR A PHASE II STUDY OF COMBINATION EPIGENETIC THERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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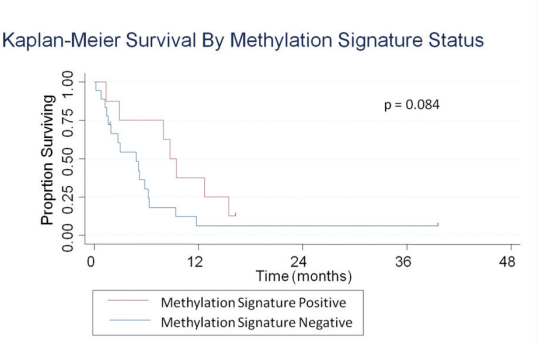
Background: Epigenetic gene silencing is an important contributor to carcinogenesis. Pre-clinical studies suggest that combined inhibition of DNA methyltransferase and histone deacetylase activity can synergistically re-express aberrantly silenced genes. A trial employing the combination of 5-azacitidine (5AC) and entinostat was performed for patients with advanced non-small-cell lung cancer (NSCLC). DNA in circulation was analyzed for hypermethylation of genes known to be critical in NSCLC tumorigenesis.
Methods: Patients with recurrent, metastatic NSCLC having received at least 1 prior chemotherapy regimen were given 5AC 40 mg/m2 SQ days 1-6 and 8-10, and entinostat 7 mg days 3 and 10, on a 28 day cycle. Plasma samples were collected prior to treatment and 28 days later. Single-stage, quantitative-methylation-specific PCR (qMSP) was performed on circulating nucleic acids (CNA) extracted from plasma for the promoter regions of APC, HCAD, and RASSF1A and normalized to circulating Beta-Actin. Patients were considered to have a positive methylation signature if at least 2 of the 3 genes assayed were methylated and showed decreasing detectability at day 29.
Results: 27 patients with a median of 3 prior therapies had both pretreatment and posttreatment plasma available. Median overall survival was 8 months. A complete response was observed in a patient with 3 prior therapies. A second patient with 3 prior therapies and metastases to the liver had a partial response for 8 months, including complete resolution of his liver disease. Nine pts had disease stabilization (SD) over multiple cycles, including 2 patients with SD for 14 months and 16 months respectively. Of 45 detectable methylation events, 30 (66%) showed decreasing methylation detectablity. No patient (0%) responded to therapy if methylation was unable to be detected at baseline. Of the 17 patients with two or more methylated genes, 8/17 (47%) showed demethylation at all detectable loci on day 29. Of these 8 patients, 6 (75%) met RECIST criteria of SD (n=6), PR (n=1), or CR (n=1).



Conclusion: The combination of 5AC and entinostat is safe and well tolerated in advanced NSCLC patients. Durable patient benefit was observed in this extensively pretreated population, including major objective responses. qMSP of plasma CNAs show that patients with more methylated alleles and who show decreasing methylation have a high probability of clinical benefit, while patients without detectable methylation in plasma samples derived no clinical advantage. Overall decreasing levels of methylation and lack of benefit to any with no detectable methylation support the putative pharmacodynamic mechanism of action of epigenetic therapy.
Keywords: Biomarkers, epigenetics, methylation, Lung cancer

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P2.258 SERUM BIOMARKERS FOR APOPTOSIS HAVE VALUE FOR PROGNOSTICATING PROGRESSION-FREE AND OVERALL OUTCOMES IN ADVANCED NSCLC.

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Background: Dysregulation of programmed cell death, or apoptosis, is implicated in the progression of an epithelial-to-mesenchymal transition (EMT) in NSCLC and other carcinomas, creating a permissive environment for uncontrolled cellular proliferation and genetic instability. Despite advancements in therapeutic options, this process may confer resistance to cytotoxic therapy and/or radiation, potentially impacting cancer survival outcomes. In this study we examine whether serum biomarkers of the apoptosis functional pathway correlate with clinical outcome in advanced NSCLC.

Methods: Luminex-based immunoassays were used to evaluate circulating levels of 27 circulating protein biomarkers implicated in the regulation of apoptosis by the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways database. Sera were collected from 146 patients with stage III or IV NSCLC patients immediately prior to treatment initiation. Treatment groups consist of front-line platinum-based chemotherapy (n=43), second-line or greater cytotoxic chemotherapy (n=30), or erlotinib (n=73). Disease progression was measured using RECIST criteria. Differences in progression-free- (PFS) and overall-survival (OS) was assessed by log-rank test and Kaplan-Meier estimates using the R statistical software package. The p-values reported are two-sided with p-values ≤ 0.01, 0.01-0.05, and 0.05-0.10 reported as strongly-significant, significant and marginally-significant (respectively).

Results: Low levels of the pro-apoptotic 'tumor-necrosis factor' family of proteins, including sFas, tumor necrosis factor–alpha (TNF-α) and its receptors (sTNF-RI, sTNF-RII), and high levels of TNF-related apoptosis inducing ligand (TRAIL) were all strongly associated with favorable PFS and OS in all patients. As expected, low levels of anti-apoptotic interleukin-6 (IL-6) and soluble IL-6 receptors (sIL-6R and sgp130) were also associated with improved outcome (e.g. IL-6: PFS - 3.91 vs. 1.74 months, p=0.00048; OS - 10.78 vs. 4.44 months, p=0.00012). Interestingly, although insulin-like growth factors 1 and 2 (IGF-I, IGF-II) are classically protective against apoptosis, here increased levels of these factors strongly-correlated with better survival outcomes. One possible explanation for these findings is the sequestration of circulating IGFs through specific IGF-binding proteins, which high circulating levels were also observed to be positively-associated with outcome (e.g. high IGFBP-3: PFS – 3.68 vs. 5.82 months, p=0.0087; OS – 10.5 vs. 32.8 months, p=0.0012). Increased expression of the anti-apoptotic tumor growth factor–alpha (TGF-α), vascular endothelial growth factor (VEGF) and receptors (VEGFRs 1-3) and fibroblast growth factor-2 (FGF-2) had no survival correlation, but low levels of FasL predicted poor OS in the erlotinib group alone. Matrix metalloproteinases (MMPs) -7 and -10 strongly-correlated with improved PFS and OS; low-levels of MMP-9 were associated with improved OS (p=0.0026). Surprisingly, MMP-2, the MMP commonly associated with increased metastatic potential, was expressed at higher levels in patients with favorable clinical outcomes.

Conclusion: This study used a functional pathway strategy to identify candidate apoptosis-related biomarkers for classifying advanced NSCLC patients according to outcome. Statistical significance for prognosticating outcome was observed by several candidate biomarker families, which include biomarkers related to TNF-α, IL-6, IGF-I, and MMPs, to name a few. Our efforts are currently focused on further examinations of the biological and clinical significance of these findings in relation to our goal of developing a serum 'EMT-biomarker' panel to help individualize treatment selection for advanced NSCLC.

Keywords: apoptosis, EMT, Serum Biomarkers, NSCLC

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P2.259 CORRELATION BETWEEN MET GENE COPY NUMBER BY SILVER IN SITU HYBRIDIZATION AND PROTEIN EXPRESSION BY IMMUNOHISTOCHEMISTRY IN NON-SMALL-CELL LUNG CANCER

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Background: MET is a receptor implicated in the pathogenesis and progression of non-small-cell lung cancer (NSCLC). Clinical trials with MET inhibitors in NSCLC are ongoing or planned with patient selection based on immunohistochemistry (IHC) and/or gene copy number assessment, therefore detailed understanding of relationship between these markers is essential.
Methods: Primary tumors from 189 NSCLC patients who underwent pulmonary resection (median follow-up of 5.3 years) were included in this study. MET expression was evaluated by IHC on tissue microarray and scored according to hybrid (H) score (range: 0-400). MET gene copy number was assessed by silver in-situ hybridization (SISH, N=140 patients).
Results: Median MET IHC score was 60 (range: 0-400; N=174). There were no associations between clinical and pathological characteristics, disease-free or overall survival according to median value (P=0.36 and P=0.38, respectively) or other cut-off points. Of the 140 tumors evaluable for MET copy number, three (2.1%) showed gene amplification and 14 (10%) had an average of 5 or more copies per nucleus. There were no associations of MET copy number with clinico-pathological features, disease-free or overall survival with any analyzed cut-off points. Correlation between MET copy number and protein expression was significant (Pearson's r=0.42, P<0.0001) and detailed analysis of the distribution of these two molecular features will be presented.
Conclusion: There is a significant correlation between MET protein expression and MET gene copy number in NSCLC, but neither are associated with clinical variables or prognosis. Both markers may be considered for patient selection to MET inhibitors and their predictive value for this therapy should be assessed in prospective clinical studies.
Keywords: MET, gene copy number, immunohistochemistry, silver in-situ hybridization

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.260 STUDY OF PHARMACOKINETIC AND PHARMACOGENOMIC CHARACTERISTICS IN PATIENTS WITH ADVANCED NSCLC TREATED WITH ERLOTINIB

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Background: A strong but unexplained association between toxicity and outcome has been noted for patients given Erlotinib in lung cancer. Several potential explanations have been suggested, including pharmacokinetic and pharmacogenomic variability.The purpose of this study was to better characterize Erlotinib pharmacokinetics in patients with advanced NSCLC and to relate Erlotinib plasma and urine concentrations to toxicity, activity and clinical and molecular (i.e specific DNA polymorphisms and EGFR gene mutations) characteristics.
Methods: Pre-treated patients with advanced NSCLC consecutively treated with Erlotinib in Medical Oncology Unit of Parma from 2008 to 2010 were enrolled. Relative biological materials (blood, urine and cytological/tissue specimens) were collected. Erlotinib levels in spot serum and urine samples of all the patients after 7 (T1) and 30 (T2) days of treatment were quantified by LC-MS/MS analysis, carried out on an AB-Sciex API 4000

triple quadrupole mass spectrometer. Moreover, the metabolic phenotype of the main enzymes involved in Erlotinib metabolism (CYP3A4, CYP1A2 and CYP1A1), by the determination of the 6β-hydroxycortisol/cortisol ratio, and EGFR gene status were determined.
Results: 56 patients with stage IV NSCLC who received Erlotinib (orally 150 mg/day) in 2nd- or 3rd-line treatment were recruited. The main patient characteristics were: 21 (37%) males, with age mean 65.6 ± 9.20; 24 (43%) patients were non-smokers, 21 (37%) ex-smokers and 11 (20%) still smokers. 43 (78%) had adenocarcinoma, 6 (10%) squamous cell carcinoma and 7 (12%) not-otherwise specified NSCLC histotype. At T1 and in all the patients, Erlotinib levels, expressed as geometric means and geometric standard deviation, were 3.66 [2.17] μmol/l e 0.39 [3.07] μmol/mol creat in serum and urinary samples, respectively. At T2 the serum and urine amounts were significantly lower, 2.02 [4.05] μmol/l e 0.23 [4.47] μmol/mol creat, respectively. Serum and urinary drug concentrations were significant correlated both at T1 (r Pearson = 0.317, $p = 0.017$) and at T2 (r Pearson = 0.659, $p < 0.0001$). Patients who showed Grade 3-4 toxicity, received a dose reduction (from 150 to 100 mg/day) after T1. Higher Erlotinib levels were detected in patients with drug reduction, both in serum and urinary samples, and at each sampling times. Even if the urinary 6β-hydroxycortisol/cortisol ratio, metabolic phenotype of CYP3A4 activity, was not statistically different at T1 and T2, it was interesting to note that a negative correlation between serum Erlotinib levels and the 6β-hydroxycortisol/cortisol ratio was observed, only in the patients with dose reduction. In particular, at T1 the Pearson correlation coefficient was - 0.67 ($p = 0.012$) and at T2 was -0.76 ($p = 0.011$), respectively.
Conclusion: Our preliminary findings suggest that the pharmacokinetic and the metabolism of Erlotinib may be involved in its toxicity. The correlations with activity and clinical/molecular characteristics will be presented at the meeting.
Keywords: pharmacokinetic, pharmacogenomic, erlotinib, NSCLC

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.261 ERBB3 EXPRESSION ASSESSED BY IMMUNOHISTOCHEMISTRY (IHC) IN NON-SMALL CELL LUNG CANCER (NSCLC) TUMORS WITH EGFR MUTATION, BEFORE EGFR-TYROSINE-KINASE INHIBITOR (EGFR-TKI) EXPOSURE

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Background: Although most NSCLC patients (p) with EGFR mutation initially respond to EGFR-TKIs, the vast majority of these tumors ultimately become resistant to this treatment. One of the resistance mechanisms is the MET amplification by activating ErbB3 signaling. The aim of this study is to determine baseline ErbB3 expression in EGFR-mutated tumors before EGFR-TKI exposure.
Methods: We assessed ErbB3 expression by IHC in the pre-treatment samples from p with activating EGFR mutation screened in our center; expression was graded by two independent observers and tumors with a 2+/3+ score were classified as "high expression".
Results: 31 p with EGFR mutation were identified: median age 63 yrs, 25 female, 15 PS 0, 21 never-smoker, 30 ADC/ 1 NOS, 14 del exon 19/ 17 L858R exon 21, 18 stage IIIB-IV. 22 p received erlotinib for advanced disease, 16 as 1st line and 6 as 2nd line. Survival outcomes for p receiving erlotinib were: median progression-free survival (PFS) 9 months (mo) and median overall survival (OS) 26 mo. Survival outcomes were similar in patients receiving erlotinib as 1st line or as 2nd line. In 21 of 31 EGFR-mutated p, determination of ErbB3 expression was feasible. High ErbB3 membranous and cytoplasmic expression was found in 9 (29%), and 11 (35%) samples, respectively, with 6 (19%) of samples having high expression at both sites. No correlation was found between ErbB3 expression and age, sex, PS, smoking history, type of mutation or stage.

When we analyzed the group of 14 p with advanced disease treated with erlotinib for whom we also had the ErbB3 expression determination, we found no association between ErbB3 expression and PFS or OS.
Conclusion: In our experience, high ErbB3 expression assessed by IHC in EGFR-mutated tumors previous to EGFR-TKI exposure is frequent. ErbB3 warrants further study in pre-treatment biopsies from EGFR-mutated tumors to clarify its role and its potential use as therapeutic target.
Keywords: EGFR mutation, ErbB3

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.262 USEFULNESS OF SERUM CARCINOEMBRYONIC ANTIGEN (CEA) MONITORING TO DEFINE RESPONSE OR PROGRESSION TO CHEMOTHERAPY AND ITS CORRELATION WITH SURVIVAL IN PATIENTS WITH ADVANCED NON SMALL-CELL LUNG CANCER: A PROSPECTIVE COHORT STUDY

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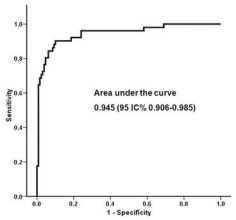
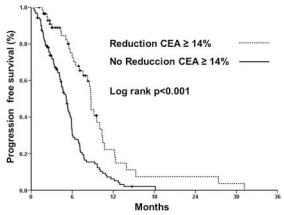
Background: Nowadays, there are no satisfactory markers to predict objective response to chemotherapy in Non Small-Cell Lung Cancer (NSCLC). Carcinoembryonic antigen (CEA) is an oncofetal protein attached to the epithelial-cell apical membrane via its c-terminal glycosyphospatidylinositol anchor; it is often over-expressed in NSCLC. High serum CEA levels are an independent prognostic factor for recurrence and survival in patients with NSCLC. Its role as a predictive marker has not been widely characterized.
Methods: A prospective evaluation of the relationship between changes in serum CEA levels with response measured by RECIST in patients with advanced NSCLC receiving only first or second line chemotherapy was performed. CEA levels were measured at baseline and after every two treatment cycles; comparison with objective response and its correlation to both progression free-survival (PFS) and overall survival (OS) was made. Protocol was approved by Institutional Boards.
Results: 183 (42.9%) of 426 patients had a baseline CEA serum level >10ng/ml (Median 60 ng/ml; range 10-7,440ng/ml). Treatment was platinum-based chemotherapy in 123 (67.2%) patients, single agent chemotherapy in 48 (26.2) and a tyrosine kinase inhibitor (TKI) in 12 patients (6.6%).
The mean follow-up time was 11.8 ±8.4 months. Objective global response, stable disease and disease progression were 28.3, 49.4 and 22.2%; respectively. Patients with global response had a reduction of CEA levels of 55.6% approximately (95%CI 64.3 to 46.8); while patients with stable disease or progressive disease had an increase of 9.4% (95%CI 1.5 to 17.3) and 87.5% (95%CI 60.9-114); respectively (p<0.001). The ROC curve analysis for the changes in CEA levels in responsive patients, had an area under the curve (AUC) of 0.945 (95%CI 0.91-.0.99) Sensitivity and specificity were of 90.2 and 89.9%, respectively, for a CEA level reduction of 14% or greater. AUC in progressive disease was 0.911 (95%CI 0.86-.0.961) with sensitivity and specificity of 85 and 15% - respectively - for a CEA level increase of 18% from baseline. PFS was longer in patients with a 14% reduction in CEA (8.7 months [CI 95% 8.4-9] vs 5.1 months [4.5-5.8], p<0.001). Neither reduction of CEA (p=0.48) nor objective response measured by RECIST (p=0.28) were predictive of OS.





Conclusion: A CEA level reduction is both a sensitive and specific marker of objective response; as well as a sensitive marker for progression to chemotherapy in advanced NSCLC. A decrease of 14% in CEA levels is associated to better PFS but not OS in advanced NSCLC.
Keywords: NSCLC, carcinoembryonic antigen, Response, progression free survival

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.263 NY-ESO-1 AS A PREDICTIVE MARKER IN STAGE 3A PATIENTS UNDERGOING NEOADJUVANT CHEMOTHERAPY FOR NON SMALL CELL LUNG CANCER (NSCLC)

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Background: The use of neoadjuvant chemotherapy in Stage 3A NSCLC is controversial with trials consistently failing to demonstrate a significant benefit. The ability to identify patients with chemoresponsive disease should aid clinical trial design and outcome. Cancer-Testis antigens (CTAg), such as MAGE A3, are currently being investigated as immunotherapeutic targets in the adjuvant setting. CTAgs are expressed in over 50% of both squamous cell and adenocarcinomas but restricted to testis in normal tissues. Since CTAgs have been proposed as markers of drug-resistant stem-like cells, we investigated the relationship between their expression and chemosensitivity.
Methods: Stage 3A patients treated with neoadjuvant chemotherapy at the Austin Hospital (AH), Melbourne and Weill Cornell Medical College (WCMC) New York were investigated. Preoperative mediastinal lymphadenectomy tissues were stained for a panel of CTAgs including NY-ESO-1, MAGE-A, MAGE-C1/CT7, GAGE and CT45 by immunohistochemistry. DNA was isolated from paraffin sections and subjected to mutation profiling using Sequenom's MassArray platform. Molecular results were correlated to baseline clinical characteristics, chemoresponsiveness (defined as pathological down-staging of TNM status), progression free and overall survival (OS).
Results: 95 patients (WCMC: 70, AH: 25) were studied. Staining for one or more CTAgs was positive in 50% of samples regardless of histology. NY-ESO-1 was expressed in 32 (33%) samples. DNA was successfully isolated from 88 samples. Mutations were seen predominantly in the EGFR (5/95) and KRAS (10/95) genes, although P53, BRAF and NRAS mutations were also seen. CTAg expression occurred independent to KRAS mutant tumors. NY-ESO-1 expression occurred independent to EGFR and KRAS mutations and was significantly associated with chemosensitivity in both datasets (Chi square p=0.010). Improved OS was only seen in the AH dataset (HR 0.36; 95% CI 0.14-0.96, p=0.04).
Conclusion: Expression of NY-ESO-1 predicts response to neoadjuvant chemotherapy in stage 3A NSCLC. Expression was independent to common mutations and in both adenocarcinoma and squamous cell carcinoma, suggesting that these antigens may represent molecules in alternate oncogenic pathways. Given the immunogenicity of these antigens, chemotherapy induced cellular lysis may have triggered an immunological response to the tumor. Mechanisms for these findings are being investigated in the pre and post-operative sera taken from these patients.
Keywords: NY-ESO-1, CT antigens, neoadjuvant chemotherapy, chemosensitivity

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.264 UNIQUE BRCA1, ERCC1 AND TYMS MRNA PROFILES MAY BE RELATED TO NSCLC PATIENT OUTCOME ACCORDING TO DISEASE STAGE.

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Background: BRCA1, ERCC1 and TYMS expression has been individually associated with patient outcome upon single chemotherapeutic agents; the fact is, however, that these agents are

usually given in combination. The aim of this study was to (a) understand variations in the expression of BRCA1, ERCC1 and TYMS in tumors in comparison to the non-cancerous lung, and (b) to develop mRNA expression profiles that might be applicable for the assessment of NSCLC patients in all stages of disease.
Methods: Relative mRNA expression of BRCA1, ERCC1 and TYMS was evaluated with qRT-PCR in a group of matched NSCLC tumor/non-cancerous lung samples (N=35) prepared from formalin-fixed paraffin-embedded tissues (FFPE), (test group 1). Samples were characterized as expressing normal (within a range of relative quantification [RQ] values allowing for a 10-fold difference of gene expression in non-cancerous lung samples) or deviating from normal transcript levels (RQ values outside this range) of BRCA1, ERCC1, RRM1 and TYMS. This classification of gene expression was considered necessary because in the majority of cases all genes deviating from normal appeared upregulated; the same classification was then applied on 232 FFPE samples from routinely processed NSCLC tissues (test group 2, to validate gene expression patterns in tumor vs non-cancerous tissues). Out of these, registered clinical data existed for 155 patients who had been treated in the adjuvant (N=39, 36 treated with platinum/taxane combinations), neoadjuvant (N=11) and chemo-naïve 1st line (N=105, 40 treated with platinum/taxane combinations) settings (clinical study group, to evaluate the effect of gene expression on patient outcome).
Results: ERCC1 expression deviated from normal in 30.2%, TYMS in 51.3% and BRCA1 in 83.3% of NSCLC tissues; these results from test group 2 applied with comparable percentages to all groups employed in this study. Profiling of all three genes revealed a favorable effect of deviating BRCA1 / normal ERCC1 / deviating TYMS in 1st line treated patients (log-rank p=0.019 [PFS] and p=0.044 [OS]); the same profile was, however, strongly associated with unfavorable outcome of patients treated in the adjuvant setting (log-rank p=0.002 [DFS] and p<0.001 [OS]). This profile was not drug- or regimen-specific. When reducing the profile to two genes, normal ERCC1 / deviating TYMS, a profile observed in 31% of the 1st line treated patients, was strongly associated with prolonged PFS and OS in this patient group irrespectively of treatment regimen (log-rank p=0.001 and p=0.016, respectively); for this profile, the same favorable effect was observed in the patient group treated with platinum/taxane combinations (PFS, p=0.001; OS, p=0.033). However, in the adjuvant setting, where practically all patients had received platinum/taxanes, the same profile was again associated with shorter DFS and OS (p=0.021 and p=0.008, respectively).
Conclusion: This study shows that, when assessed in combination, BRCA1/ERCC1/TYMS mRNA expression in tumors, as compared to non-cancerous lung tissues, is related to NSCLC patient outcome and to the effect of platinum/taxane treatment, in the case of ERCC1/TYMS. The impact of such profiles seems to be disease stage specific, since it appears inversed in the adjuvant and in the 1st line setting, even for the same chemotherapeutic combination.
Keywords: platinum, taxanes, gene expression profiling, NSCLC

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.265 IN VIVO ISOLATION OF CIRCULATING LUNG CANCER CELLS - A PRELIMINARY REPORT -

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Background: Circulating tumor cells (CTCs) in the bloodstream of lung cancer patients provide a source for early detection, prognosis, and therapy monitoring. Currently, CTCs are mostly isolated in vitro from small volumes of patient blood samples. In order to increase the sensitivity of the CTCs detection in the peripheral blood GILUPI has developed a novel in vivo method, the functionalized and structured medical wire (FSMW) for an in vivo application, which enables the capture of CTCs from the patient´s blood stream with a higher sensitivity and efficacy than existing methods. Enumeration and characterization of those CTC will serve to improve and monitor clinical cancer early detection and treatment.
Methods: The interaction of target CTC with the FSMW is mediated by an antibody directed against the epithelial cell adhesion molecule (EpCAM).

CTCs were isolated from non small lung cancer patients (n=40). In order to catch CTCs, the medical wire is inserted in a patient's vein for thirty minutes. An identification of epithelial origin of bound to the FSMW cells was performed by immunocytochemical staining against commonly used tumor markers of epithelial origin (cytokeratin, EGFR) as well as for negative selection with an CD45 antigen.
Results: In clinical studies, we successfully isolated EpCAM-positive tumor cells in the peripheral blood originating from non small lung cancer patients. First clinical results from 40 lung cancer patients indicate a sensitivity of 80% and a higher CTC capturing rate compared to existing in vitro methods. We could also confirm very good biocompatibility of the FSMW and did not report any side effects.
Conclusion: In vivo detection of the CTCs provides higher sensitivity, is safe for the patients and in an elaborated protocol specific for cells of epithelial origin. Subsequent the FSMW technology for isolating circulating tumor cells (CTCs) will be evaluated as an upstream circulating tumor cell (CTC) enrichment method for subsequent downstream analysis of tumor cells. In collaboration with Bayer Healthcare, Prometheus developed, a proximity mediated immune-assay platform, CEER (Collaborative Enzyme Enhanced Reactive ImmunoAssay) which provides valuable insight into the tumor cells. A clinical trial with downstream CEER analysis of CTCs obtained in vivo from 12 cancer patients using FSMW was initiated.
Keywords: NSCLC, circulating tumor cells

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.266 ATM DEFICIENCY IS ASSOCIATED WITH WORSE OUTCOME IN RESECTED NON-SMALL CELL LUNG CANCER

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Background: ATM, a serine/threonine protein kinase and a member of the phosphatidyl inositol-3 kinase like kinase family, is activated in response to DNA double strand breaks (DSBs). It phosphorylates multiple downstream proteins involved in cell cycle checkpoint arrest, DNA repair, and apoptosis. Aberrant ATM function has been implicated in several malignancies including lung cancer. In an analysis of listed mutations in 500 human protein kinases in 169 primary tumors and 40 cell lines, ATM mutations emerged at number 3 in terms of frequency, with a large proportion being found in lung cancers. However ATM's role and influence on outcome in NSCLC has not been extensively explored. We set out to assess the frequency with which ATM deficiency occurs in NSCLC and correlate such deficiency with outcome.
Methods: After ethical approval was obtained, demographic details, clinical variables and outcome data were gathered on patients with resected NSCLC at the Tom Baker Cancer Centre (TBCC) between 2003 to 2006 using the Glans-Look lung cancer database. Formalin-fixed paraffin embedded resected NSCLC tumors were obtained and tissue micro arrays (TMAs) generated. Expression was analyzed by quantitative immunofluorescent histochemistry using a rabbit anti-ATM monoclonal antibody (Epitomics) and the HistoRx AQUA® platform. ATM expression was quantified in both pan-cytokeratin positive tumor cells, as well as vimentin positive tumor-associated stromal cells. ATM proficient (BT) and deficient (UPN2) cell lines were used as controls. ATM deficiency was determined by assessing the ratio of maximum ATM expression in the malignant component with that seen in the stromal component. A cutpoint to identify two groups from the ATM maximum expression ratio was found using a method based on the log rank statistic. AQUA scores were correlated with clinical outcome using the Kaplan-Meier method, multivariate analysis and Spearman's rank correlation.
Results: 165 cases of resected NSCLC (113 stage I, 52 stage II, 16 stage III) were identified and their tumors incorporated into TMAs. Histology distribution, gender make up and median overall survival of the cohort were compatible with historical controls. The cutpoint for ATM tumour/stromal expression ratio was identified as 0.71. Patients with a low ATM expression ratio had a poorer progression free survival (P=0.004) and worse overall survival (P=0.0056) compared with those with a high ratio. Further analysis showed that

this effect was driven by the stage II and III patients with low ATM expression (HR: 4.86, 95% CI: 2.16 to 10.95, P=0.027) with no effect seen in the stage I cases.
Conclusion: Reduced ATM expression is associated with worse outcome in resected stage II and III NSCLC. Since many therapeutic interventions used in NSCLC rely on DNA damage for their effect, ATM deficiency is likely to influence response to specific cytotoxic and targeted agents. We recently demonstrated that loss of ATM function in mantle cell lymphoma sensitizes tumors to PARP-1 inhibition. Taken together, our results suggest that ATM deficiency in NSCLC may be a predictive as well as a prognostic marker.
Keywords: ATM, DNA repair, resected non small cell lung cancer, Prognosis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.267 PROGNOSTIC VALUE OF KI67 AND FDG-PET UPTAKE IN EARLY RECURRENCE OF NON-SMALL CELL LUNG CANCER AFTER COMPLETE RESECTION.

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Background: Treatment stratification in NSCLC is based on staging, which has been recently revised. Following current treatment guidelines half of the patients will have disease recurrence within 5 years after complete resection. This highlights the necessity for identifying tumour specific factors to identify patients at risk. Several heterogeneous studies have been reporting the prognostic value of both FDG-PET CT and Ki67 expression. Few studies however, describe FDG-PET acquisition based on standardized protocol and / or correct for glucose levels. The aim of this study was to determine whether these factors could be of additional prognostic value for early recurrence and survival, in primarily surgical treated NSCLC, in the context of TNM 7th edition.
Methods: Retrospective analysis was performed on a prospective database of patients, undergoing curative resection of NSCLC, from November 2006-November 2008. All patients underwent complete (pre)surgical staging including FDG-PET acquisition based on Netherlands protocol for multi-center trial standardization (NEDPAS). Immuno-histochemistry for Ki67 and PAS staining was performed following international guidelines. Patients with a history of malignancy, (neo) adjuvant treatment and/or diabetes were excluded. Postoperative staging was performed using TNM 7th edition. Follow up 24 months.
Results: A total of 35 patients met inclusion criteria for PET, 32 for pathological evaluation. Stage IA (n=23/21), 1B (n=5), 2A (n=3), 2B (n=3) and 3A (n=1). Disease recurrence was determined within 2 years in 5/35 patients, 3 disease related deaths during follow up. Both staging and FDG uptake were of significant prognostic value (resp. p=0,034 and p=0,021) for disease recurrence and disease related death. Multivariate non-significant (resp. p=0,155 and 0,151). Mean GC-SUVmax is different for postoperative determined stage I-II (p=0,006). FDG-uptake is suitable to identify patients at risk for recurrent disease (p=0,001) and of prognostic value for poor survival (p=0,004). Ki67 and PAS expression showed no significant correlation with disease recurrence and/or poor survival. We found no significant correlation for Ki67, PAS and FDG uptake.
Conclusion: PET is a useful tool to identify patients at risk of early disease recurrence and death within 2 years after complete resection of early stage NSCLC in addition to recently revised staging method. Prospective trials, performing FDG-PET following standardized protocol, are needed to identify clinically useful cut off values of GC-SUVmax, in order to produce stratification models applicable in future guidelines.
Keywords: FDG uptake, Early Stage NSCLC, curative resected

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.268 FIELD OF CANCERIZATION MOLECULAR PROFILING IN EARLY STAGE NSCLC PATIENTS TOWARDS DEVELOPMENT OF BIOMARKERS FOR PERSONALIZED PREVENTION

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Background: Increasing our understanding of lung cancer pathogenesis will aid in the identification of early stage (ES) non-small cell lung cancer (NSCLC) patients at higher risk for recurrence or second primary tumor (SPT) development which in turn is vital to personalizing prevention and therapy. We sought to perform global gene expression analysis of the field of cancerization in ever-smoker ES NSCLC patients to better understand lung cancer pathogenesis and predict recurrence or SPT development.

Methods: Patients on the prospective Vanguard study had definitively treated ES (I/II) NSCLC and were current or former smokers. Patients had bronchoscopies with brushings obtained from the main carina (MC), airways adjacent (ADJ) to the previously resected tumor and from airways distant from the tumor in the ipsilateral (NON-ADJ) and contralateral (CONTRA) lung at baseline, 12, 24 and 36 months following resective surgery. Nineteen patients were selected for the study based on airway sampling of at least five different regions per time point and continuously up to 24 or 36 months (391 airway samples from nineteen patients). Gene expression profiling of total RNA isolated from bronchial brushings was performed using the Affymetrix Human Gene 1.0 ST platform. Analysis began by construction of a mixed-effects model that incorporated information on the site and time (continuous) the bronchial brushing was obtained as fixed effects. Time and site-dependent field of cancerization differential expression profiles were identified based on a false discovery rate (FDR) cut-off of 5% and 1% based on p-value distributions, respectively, studied by hierarchical clustering and functionally analyzed using network analysis.

Results: 1395 genes were determined to be differentially expressed with time in the cancerization fields. Hierarchical clustering analysis using these genes demonstrated that samples (n=391) were divided into two clusters or branches which were significantly unbalanced with respect to time with the majority of the baseline and 36 months samples separated ($p<0.001$ of the Fisher's Exact test). Moreover, functional analysis of the genes showed that a nuclear factor-kB (NF-kB)-mediated gene-network was most significantly elevated ($p<0.001$) with time. 1165 gene features were differentially expressed by site. Two-dimensional clustering of these genes and samples showed distinct classes of differential expression and revealed two main sample clusters with significant separation of ADJ samples from MCs and non-adjacent CONTRA airway samples ($p=0.003$). Pathways analysis of the genes revealed that gene-networks mediated by NF-kB, PI3K and ERK1/2 were significantly elevated ($p<0.001$) in function in ADJ airway samples. Furthermore, hierarchical clustering analysis of patients (n=19) based on differences of expression (ADJ/NON-ADJ) of genes differentially expressed by paired t-tests between ADJ and NON-ADJ samples revealed two main clusters with all relapses located in one branch suggesting associations between field of cancerization expression profiles and lung cancer relapse.

Conclusion: Our findings highlight expression signatures and pathways in a "cancerization field" that may drive lung cancer pathogenesis and be associated with recurrence or SPT development in ES NSCLC patients and thus useful for derivation of biomarkers to guide personalized prevention strategies. Supported by DoD grants W81XWH-04-1-0142 and W81XWH-10-1-1007.

Keywords: Prevention, gene expression profiling, NSCLC, pathogenesis

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.269 EXHALED MICRORNAS AS POTENTIAL BIOMARKERS IN LUNG CANCER

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Background: There is a need for non-invasive airway-based biomarkers in lung carcinogenesis for both risk assessment of the ex-smoker, and earlier diagnosis. MicroRNAs are small, stable, noncoding RNAs that function in gene regulation. Recent studies have revealed that microRNAs play important regulatory roles in carcinogenesis. Exhaled breath condensate (EBC) contains airway lining fluid molecules, including nucleic acids, presumably inpart from epithelial cellular origins, as we've previously reported for DNA methylation. Here we pilot the detection of microRNAs in EBC from lung cancer patients and controls.
Methods: MicroRNA expression profiling using RNA-specific RT-qPCR was performed in EBC from 29 subjects, choosing literature-derived microRNAs segregating with case-control status, combined with an ongoing discovery effort we have commenced using microRNA-seq on lung tumors and surrounding non-tumor tissue. As of abstract deadline, the top three tumor-non-tumor differentiating microRNAs (miR-21, 126, and 200c) were chosen by consensus between the literature and our own discovery data. The qPCR primers were designed using our previously published RNA-specific realtime RT-PCR technique. All samples were run with positive and negative controls.
Results: We have detected varying combinations of microRNAs in EBC for all three microRNAs (miR-21, 126, and 200c) in most (>16 each) subjects. Case-control comparisons have not yet been made, pending generation of a more complete microRNA panel, and sampling from higher numbers of subjects.
Conclusion: Technically, we are able to detect microRNAs in the breath. We will validate this evolving miR panel both anatomically, as to airway topographic site of origin, and to the cells of origin, using banked lung specimens from these same donors. This potential biomarker class will be correlated to case-control phenotype. Once validated, our goal is to apply this non-invasive biomarker approach to lung cancer risk assessment, and/or early detection of lung cancer itself. Supported by NCI Grants CA 1RC1145422; 1K24139054; 1R21 CA 121068.
Keywords: MicroRNAs, Early Detection, risk assessment, exhaled breath

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.270 BIOMARKER PATTERN IN NEVER SMOKER PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC).

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Background: It is recognized that tumor biomarker (BM) expression plays an important role in personalized therapy in cancer patients (pts). Never smoker NSCLC pts represent 15% of all NSCLC, and their prognosis differs from former or current smokers. Two gene mutations are frequently seen in this population: EGFR and EML4/ALK mutations. These gene abnormalities are suitable for targeted therapy. However, their association with other potential BMs has not been well elucidated.
Methods: Tumor samples from 80 advanced NSCLC pts were analyzed for BM expression; 25 were never smokers. BMs were tested by using ResponseDx test: RNA expression of ERCC1, TS, and RRM1 was analyzed by RT-PCR and PCR analysis of DNA was used to determine K-ras, EGFR, and EML4/ALK mutation status.
Results: 25 pts out of 80 (31%) were never smokers; median age was 61 (range 40-79 years), 16 pts were female; 15 pts (60%) were Hispanic, 7 pts Caucasian, 2 pts Asian, and 1 pt African American. In 10 cases (40%), there was either no enough tissue

to develop the BM panel or tissue available at all. Relatively, Caucasian had a higher incidence of EGFR mutation (5 [71%] Caucasian and 4 Hispanic). Eleven pts (44%) had EGFR mutation, 1 pt had EML4/ALK, and 1 pt K-ras mutation. High EGFR expression correlates in 10 pts (91%) with EGFR mutation; EGFR mutations were found in 7 Adeno, 2 BAC, 1 large cell, and 1 undetermined. Most of the EGFR mutated pts (n=7) had low ERCC1 and RRM1 levels; 3 pts had high level expressions of these BMs. TS expression in EGRF mutated pts was equal (4 pts with high- and low-level each; 3 pts had no enough tissue for analysis). Both patients K-ras and EML4/ALK mutated had high levels of ERCC1, RRM1 and TS.

Conclusion: This report includes only never smoker. Our group continues screening pts for EGFR and other BMs as we have a special interest in analyzing these BMs in the Hispanic population. Although our cohort is small, we found similar patterns of BM expression (ERCC1, RRM1, TS) and a histology-preferred type in those pts who had EGFR mutated as it has been described by others (Gandara et al. ASCO 2010). Both patients who had poor prognosis by gene mutation analysis also expressed high levels of ERCC1, RRM1 and TS which may confer resistance to different chemotherapeutic agents. This cohort of pts is part of a larger study group where we were able to find that only ERCC1 and RRM1 indicate association with ethnicity. Hence, our group will continue enriching this important biologic data in NSCLC.

Keywords: Lung cancer, biomarker, ethnicity, never smoker

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.271 A MULTI-ANALYTE SERUM PANEL CAPABLE OF STRATIFYING NODE-NEGATIVE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS BASED ON RECURRENCE-FREE SURVIVAL

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Background: Lung cancer is the leading cause of cancer mortality worldwide despite efforts to enhance early detection and improvements in therapeutic options. The recent National Lung Screening Trial results, which preliminarily propose a 20% mortality reduction using CT imaging to screen patients for NSCLC, are promising but cannot differentiate aggressive from more indolent early-stage tumors. Surgery alone is curative for 60–70% of the pathologic stage I NSCLC patients. Molecular diagnostics which could identify stage I patients who have a high chance of tumor recurrence would have practical implications for developing node negative adjuvant trials. The objective of this study was to evaluate potential relationships between the preoperative levels of selected serum biomarkers with recurrence-free survival and overall survival in node negative NSCLC patients.

Methods: Immunobead assays based on the Luminex platform were used to measure pre-treatment serum levels of 74 circulating immunomodulatory biomarkers, growth factors, and autoantibodies that we previously correlated with preoperative nodal status. Pre-treatment sera of 80 surgically-resected NSCLC patients treated with at least 2 years clinical follow-up data were evaluated. 49 patients had no nodal disease ($T_{1\text{-}4}N_0M_0$), whereas 31 had progression to the locoregional lymph nodes ($T_{1\text{-}4}N_{1\text{-}3}M_0$). Mann-Whitney rank-sum tests were used to assess difference in biomarker concentrations with respect to sex, race, smoking history, and histology. For each biomarker, the difference in recurrence-free survivals were assessed by the log-rank PH test, and Kaplan-Meier estimates of recurrence-free survival curves were obtained using the R statistical software package.

Results: A Kaplan-Meier evaluation of recurrence-free survival revealed 11 serum biomarkers which were related to survival ($p \leq 0.05$). Using the Random Forest algorithm, we performed a multivariate biomarker selection analysis of these 11 biomarkers to define a classification scheme of 4 biomarkers, consisting of: tissue inhibitor of metalloproteinases-1 (TIMP-1), osteopontin, CA15-3, and an autoantibody

directed against phosphoglycerate mutase (PGAM). Performance of this panel to predict recurrence free survival in node negative patients treated by surgery revealed a 12% overall misclassification rate.
Conclusion: Here we report the development of a 4-target serum panel for prognosticating nodal involvement of early stage NSCLC with the potential to predict "micrometastatic" disease previously undetected by standard imaging and pathology. Further refinement of this panel has potential to better define patients for adjuvant systemic therapy who would otherwise receive surgery alone.
Keywords: NSCLC, disease recurrence, serum biomarker, Stage I

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.272 SERUM PROTEIN LEVELS MAY BE USEFUL IN SELECTING TREATMENT WITH AN EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR (EGFR TKI) VERSUS CHEMOTHERAPY IN PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS.

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Background: A phase III trial comparing gefitinib to docetaxel in previously treated stage IV/IIIB NSCLC patients showed no significant differences in progression-free survival (PFS) or overall survival (OS). Subset analyses based on clinical characteristics and molecular analyses (<30% patients had analyzable samples) failed to show significant differences in PFS or OS with the exception of superior PFS in gefitinib treated patients whose tumors contained EGFR exon 19 and 21 mutations. Erlotinib, docetaxel, and pemetrexed are approved in the second line setting. EGFR mutations have predictive value for PFS in the first and second line settings, but there are no other reliable ways to select an EGFR-TKI versus cytotoxic agents. The objective of this study was to examine whether circulating upstream members of the EGFR signaling pathway correlate with clinical outcome in previously-treated advanced NSCLC patients.
Methods: Luminex-based immunoassays were used to evaluate pre-treatment serum levels of 7 circulating protein biomarkers implicated EGFR signaling by the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways database. All patients (n=102) were previously treated with platinum-based chemotherapy and grouped for this study according to treatment containing either erlotinib (n=73) or cytotoxic chemotherapy (n=30). Whole blood was collected before treatment initiation and processed to serum using standard phlebotomy techniques with full institutional IRB approval and with written patient consent. For each biomarker, the difference in progression-free- (PFS) and overall-survival (OS) was assessed by the log-rank test and Kaplan-Meier estimates using the R statistical software package. The p-values reported are two-sided with p-values ≤ 0.01, 0.01-0.05, and 0.05-0.10 reported as strongly-significant, significant and marginally-significant (respectively).
Results: High serum levels of EGF were found to significantly associated with a favorable OS (7.5 vs. 24.3 months; p=0.028) for all previously-treated patients examined, whereas high levels of the heparin-binding EGF (HB-EGF) isoform was found to be strongly significant for predicting a favorable PFS (1.32 vs. 3.44 months; p=0.0018) and OS (5.1 vs. 11.6 months; p=0.0011) in the chemotherapy group alone. Similarly, high levels of betacellulin and epiregulin were strongly significant for favorable outcome in chemotherapy treated patients; betacellulin – PFS (4.0 vs. 1.3 months, p=.0015); Epiregulin - PFS (1.78 vs. 3.91, p=0.0029) and OS (6.67 vs. 19.43, p<0.001). In contrast to these results, low serum levels of transforming growth factor-alpha (TGF-α) and amphiregulin were strongly associated with prolonged PFS (e.g. TGF-α: 2.66 vs. 1.02 months, p=0.00027) and OS (e.g. TGF-α: 9.57 vs. 3.42 months, p=0.0033) regardless of treatment type. In all patients low levels of soluble EGFR was strongly significantly associated with shortened PFS and OS.
Conclusion: Although further validation is required to substantiate our findings, this preliminary work

demonstrates that upstream members of the EGFR signaling pathway show great promise as serum biomarker panel to help individualize treatment selection (chemotherapy vs. erlotinib) in patients with advanced NSCLC that fail first line therapy. Our efforts are currently focused on further examinations of this and other biological pathways in relation to our goal of developing a serum biomarker panel to help individualize treatment selection for advanced NSCLC.

Keywords: EGFR, serum biomarker, NSCLC, patient stratification

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.273 DECREASE OF CIRCULATING TUMOR CELLS ASSOCIATES WITH RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER, BUT NOT WITH SMALL CELL LUNG CANCER

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Background: Circulating tumor cells (CTC) have been detected in peripheral blood (PB) of patients with several malignant diseases. CTC are implied in metastasis and relapse and may serve as diagnostic parameter. The association of CTC with patient outcome and treatment response in lung cancer is still unclear. In this pilot study we aimed to elucidate whether quantification of CTC is technically feasible in lung cancer patients, and whether changes in CTC counts correlate with response to systemic platinum-based chemotherapy. Furthermore, we examined whether histology (SCLC vs. NSCLC) or tumor stage influenced CTC counts.

Methods: We analyzed 16 consecutive, untreated lung cancer patients treated at our institution. PB was drawn 1 hour before platinum-based chemotherapy on days 1 and 22 of 21 day cycles. Clinical response to chemotherapy was assessed following RECIST. PB mononuclear cells were enriched using buoyant density gradient centrifugation. Following immunomagnetic negative selection with anti-CD15 and anti-CD45 antibody-beads, CTC were positively selected using the bead-coupled monoclonal antibody BerEP4, that is directed against the human epithelial antigen EpCAM. For quantitation of CTC, cytospins of CTC-enriched samples were analyzed by immunocytochemistry using a panel of cytokeratin (CK) antibodies.

Results: CTC were identified prior to chemotherapy in 15/16 patients (6/6 SCLC, 9/10 NSCLC). Following one course of chemotherapy, a second NSCLC patient converted to CTC negativity. Only one of 6 SCLC patients patient showed decreasing CTC counts following chemotherapy. This patient achieved a CR. Five of 6 SCLC patients achieved a PR, which was associated with a significant increase of CTC counts following treatment (p less than 0.05). Seven of 10 NSCLC patients (70%) achieved a PR. Clinical response was significantly associated with changes in CTC count after one course of chemotherapy (p=0.006; r=0.8).

Conclusion: Detection of CTC enriched by a combined negative/positive selection strategy and immunocytochemistry is feasible in lung cancer patients. Changes in CTC counts after one course of chemotherapy may be predictive of treatment response in NSCLC. Further studies are warranted.

Keywords: Lung cancer, circulating tumor cells, platinum-based chemotherapy

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.274 SERUM BIOMARKERS FOR ANGIOGENESIS HAVE VALUE FOR PROGNOSTICATING PROGRESSION-FREE AND OVERALL OUTCOMES IN ADVANCED NSCLC

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Background: Angiogenesis is a key component of the epithelial-to-mesenchymal transition (EMT) and is believed to be important in the development and progression of NSCLC. Combining bevacizumab with chemotherapy or erlotilnib has resulted in superior progression-free survival in three randomized studies, but overall survival was improved with bevacizumab in only one trial. It seems likely that bevacizumab has a modest biologic effect in NSCLC. Validation of a biomarker which would identify patients who are most likely to benefit from bevacizumab would have practical therapeutic and economic implications. Here, we examine a series of serum biomarkers implicated in the angiogenesis functional pathway in an effort to delineate the impact of these proteins on survival outcomes in advanced NSCLC patients.
Methods: Luminex-based immunoassays were used to evaluate pre-treatment serum levels of 12 circulating protein biomarkers implicated in the regulation of angiogenesis by the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways database. Pre-treatment sera were prospectively collected from advanced NSCLC patients with full institutional IRB approval and written patient consent. Treatment groups evaluated include: front line platinum-based chemotherapy (n=42), second line or greater platinum-based chemotherapy (n=31), or erlotinib (after failing previous platinum-based chemotherapy)(n=73). Disease progression was measured using RECIST criteria. For each biomarker, the difference in progression-free- (PFS) and overall-survival (OS) was assessed by the log-rank test and Kaplan-Meier estimates using the R statistical software package.
Results: Low levels of expression of VEGF, macrophage migration inhibitory factor (MIF), hepatocyte growth factor (HGF), transforming growth factor-alpha (TGF-α), and placenta growth factor (PIGF) were all strongly-significant with respect to improved PFS (log rank p=0.0142, p=0.021, p=0.0097, p=0.00004, p=0.033; respectively) and OS (log rank p=0.0125, p=0.034, p=0.00005, p=0.004; respectively). High expression of VEGF receptors 1-3 were also associated with improved PFS though only VEGF-R2 was significantly correlated on OS (10.55 vs. 2.43 months, p=0.000002). Despite its reported role in promoting angiogenesis in tumor progression, high levels of expression of platelet-derived growth factor-BB (PDGF-BB) were associated with improved PFS and OS (p=0.024 and p=0.023, respectively). The collective impact of pro-angiogenic matrix metalloproteinases (MMPs) remains less clear in this functional pathway, arguably confounded by parallel roles in other functional pathways that correlate with clinical outcome. An exploratory analysis comparing biomarkers in bevacizumab treated patients (n=25) versus patients that did not receive bevacizumab showed that increased VEGF in bevacizumab treated patients correlated with both prolonged PFS and OS (p=0.000957, p=0.036611, respectively) while increased levels of VEGF patients not treated with bevacizumab was associated with shortened PFS and OS survival (p=0.041223, p=0.009831, respectively). The only other biomarkers with significance for OS in bevacizumab treated patients were MMP-2, sVEGFR1 and sVEGFR3, with sVEGFR1 also correlating with longer PFS.
Conclusion: An examination of circulating biomarkers associated with the KEGG-defined angiogenesis functional pathway has yielded a range of serum biomarkers with apparent value for prognosticating outcome in advanced NSCLC. If serum were available from phase III bevacizumab trials, it might be reasonable to further evaluate/ validate these and other pathway members as a means to potentially identify NSCLC patients most likely to benefit from this treatment.
Keywords: angiogenesis, patient outcome, EMT, Serum Biomarkers

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.275 PREDICTING RECURRENCE IN EARLY STAGE, RESECTED NON-SMALL CELL LUNG CANCER USING MUTATIONAL AND METHYLATION BIOMARKERS

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Background: Despite appropriate surgical intervention, approximately 30%-40% of patients with node negative non-small-cell lung cancer (NSCLC) have recurrent disease. Although clincopathological criteria fail to identify those at higher risk of relapse, recent evidence suggests that molecular biomarkers, such as oncogenic mutations and DNA hypermethylation, may hold prognostic value. Our objective was to determine if mutations or promoter hypermethylation of candidate genes predict disease recurrence after curative resection.
Methods: Paraffin embedded, surgically resected specimens from patients with stage I NSCLC were utilized. Mutational analysis was performed on NSCLC adenocarcinomas (n=35) and squamous cell carcinomas (n=5). A high-throughput genotyping method (SEQUENOM MassARRAY) and a multi base extension (MBE) matrix-assisted laser desorption/ionization time-of–flight (MALDI-TOF) mass spectrometry were employed to study 322 known somatic mutations involving 23 genes. After genetic mutations were detected, identification and validation of mutations were analyzed in duplicate. For methylation analysis, single-stage, methylation-specific PCR for APC, CDH13, RASSF1A, and CDKN2A was performed on bisulfite treated DNA from paired primary tumor and mediastinal lymph node samples from NSCLC adenocarcinomas (n=35) squamous cell carcinomas (n=15) and was considered to have methylation concordance if a gene methylated in the tumor was also detected as methylated in the lymph node.
Results: Patients whose primary tumors had EGFR gene mutations had a longer survival time, while patients with KRAS mutations had a poorer outcome. P53 mutations were seen only in the non-recurrence group. Overall, patients with longer survival times had more mutations compared to those with shorter survival times. Patients with NSCLC other than squamous cell histology with methylation concordance of primary tumor and lymph nodes have 78% increased odds for recurrence within 5 years compared to patients that test negative (OR=1.78; 95% CI 0.45; 6.97, p=0.409). Importantly, this test detected those aggressive NSCLCs that recurred in the first 2 years with an odds of recurrence of 2.22 (95% CI 0.379; 13.18, p=0.379).

Frequency of oncogene mutations and methylation concordance between tumor and lymph node across human lung cancer samples (%)

Gene		Recurrence (years after surgery)		
		Within 2 years	Between 2 to 5 years	Non-recurrence within 5 years
EGFR	-		30.7 (4/13)	36.8 (7/19)
KRAS	-	25 (2/8)	7.6 (1/13)	15.7 (3/19)
P53	-		-	15.7 (3/19)
NRAS	-	12.5 (1/8)		
PIK3CA	-	-	15.3 (2/13)	-
FGFR	-	12.5 (1/8)	-	-
CTTNB	-	12.5 (1/8)	-	-
No mutations	-	75.0 (6/8)	61.0 (8/13)	42.0 (8/19)
Histology	Methylation Concordance	Within 2 years	Between 2 to 5 years	Non-recurrence within 5 years
	+	62.5% (5/8)	84% (11/13)	68.9% (6/14)
Non-SCC	-	37.5% (3/8)	46% (6/13)	61.5% (8/14)
	-	0% (0/8)	0% (0/2)	0% (0/4)
SCC	-	100% (8/8)	100% (2/2)	100% (4/4)

Conclusion: Mutational and epigenetic analysis of paraffin-embedded tumors from patients with stage I NSCLC may be prognostic of cancer recurrence. A larger cohort is needed to identify a specific genetic profile of clinical outcome. MSP analyses suggest a test which increases a patient's odds of recurrence but must be examined in a larger cohort. A prospective validation of these results will be needed prior to clinical use.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 – Prognostic and Predictive Markers Tuesday, 5 July 2011 12:15-14:00

P2.276 CHARACTERISATION OF CIRCULATING TUMOUR CELLS AND MICROEMBOLI IN LUNG CANCER PATIENTS: BEYOND THE NUMBERS.

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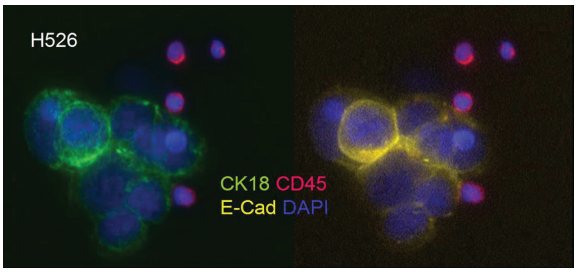
Background: Circulating tumour cells and circulating tumour microemboli (CTC/CTM) can be already detected at early stages of tumour progression in regional lymph nodes, peripheral blood, and bone marrow of cancer patients. CTCs in the peripheral blood have as yet unknown molecular characteristics and the clinical impact of detecting CTC/CTM is under intense debate.
Methods: We have utilised and developed several different technology platforms (Cell Search, ISET, Ariol Image analysis) in order to maximise our ability to detect and molecularly characterise CTCs/CTMs. We have successfully undertaken rare cell detection by all of these methods in addition

to fluorescence in situ hybridization (FISH) analysis, custom marker labelling and molecular characterisation by qtPCR. To further characterise the heterogeneous nature of these populations we have developed 4 colour mutiplex fluorescent staining techniques. Using these techniques we have successfully captured and enumerated both CTCs and CTMs. We have been able to stain cells for EMT, proliferation and tumour specific markers.



Results: The substantial data collected by this group suggest there is vast potential in CTC/CTM detection as a predictive/pharmacodynamic marker in early clinical trials. A particularly confounding problem is that invasive tumour cells often lose their epithelial antigens due to an epithelial to mesenchymal transition process. Considerable heterogeneity in the expression of EMT and other markers was observed within populations of CTC/CTM cells from individual patients. Furthermore, non-tumour epithelial cells were often also present in blood. Thus, it appears that a reliable diagnostic identification of CTC and CTM cannot be based simply on the expression of epithelial-specific transcripts or antigens.
Conclusion: All of these technologies have now become key applications in much of the clinical translational trial work undertaken by our group. Our multifaceted approach to rare cell detection and analysis enables us to further gain insight into possible mechanisms involved in metastasis. We are now routinely deploying these techniques in first into man trials of novel therapeutics agents.
Keywords: Circulating tumour cells, Biomarkers, Clinical Trials, EMT

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 - Imaging Tuesday, 5 July 2011 12:15-14:00

P2.277 DEVELOP AND VALIDATE CLINICAL PREDICTION MODEL TO ESTIMATE THE PROBABILITY OF MALIGNANCY IN SOLITARY PULMONARY NODULES FOR CHINESE PEOPLE

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Background: The Character of SPN were important for clinical decision-making and prognosis significance. But it was difficult and was a hot-spot for Clinicians. Mathematical model is based on the experience of Experimental Medicine, and is the advanced form of medical research. In judging the character of the SPN, the capability of mathematical model is similar to experienced clinicians . Studies on mathematical model for properties of SPN currently have been carried out abroad, but in China, there was not yet a mathematical model for Chinese people.So we collected data of Chinese people with SPN, Retrospective analysis informations and try to To evaluate the clinical factors affecting the probability of malignancy of solitary pulmonary nodules(SPN) with multivariate logistic regression analysis.Develop a clinical prediction model to estimate the probability of malignancy, and validate the value of the model.
Methods: from Jan 2000 to Sep 2009, 371 patients (197 male, 174 female) with SPN got definite pathological diagnosis in our institute. Clinical data of these patients included age,gender,course of disease,symptoms,history and quantity of Cigarette smoking, history of other tumor,Œ family history of tumor,site of tumor,diameter, calcification,specu lation,border,lobulation,traction of pleural,vascular convergence sign,cavity. To estimate the independent predictors of malignancy of SPN with multivariate analysis and then develop a . from Oct 2009 to Mar 2010, Other 62 patients with SPN got definite pathological diagnosis in our institute was used to validate value of this clinical prediction model, and compared our model with other two models.
Results: The median age of the patients was 57.1 years. Fifty three percent of the nodules were malignant, and forty six percent were benign. Logistic regression analysis show six clinical characteristics (age of patient(OR:1.073), diamete r(OR:1.966),border(OR:0.245),calcification(OR:0

.199),spiculation(OR:2.088)and the family history of tumor(OR:3.550) were independent predictors of malignancy in patients with SPN(P<0.05). The area under the ROC curve for our model (0.89; 50% CI 0.78 to 0.99) was higher than the other two foreign models(Sensitivity:92.5%,Specificity:81.8%,Pos itive predictive value:90.2%, Negative predictive value:85.7%).
Conclusion: Age of patient, diameter,border,calcif ication,spiculation and the family history of tumor were independent predictors of malignancy in patients with SPN. Our prediction model was more accurate than the other two foreign models, and was sufficiently to estimate the malignancy of patients with SPN.
Keywords: Prediction model, Solitary pulmonary nodule, Logistic regression analysis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 - Imaging Tuesday, 5 July 2011 12:15-14:00

P2.278 A CORRELATION STUDY ON POSITION AND VOLUME VARIATION OF PRIMARY LUNG CANCER DURING RESPIRATION BY 4D-CT.

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Background: By 4D-CT simulation ,the correlation of position movement of primary tumor with interested organs and the correlation of volume variation of primary tumors and lungs during different respiration phases for patients with lung cancer at free breath condition scanned could be investigated.
Methods: Based on simulation 4D-CT images which binned in 10 respiratory phases, 16 patients with lung cancer were scanned at free breath condition by simulation 4D-CT which connected to a respiration-monitoring system (RPM). A coordinate system was created based on image of T5 phase, which was registered by other images of 9 phases. Gross tumor volumes (GTV) and normal tissue structures (lungs, hilum of lungs, tracheal bifurcation, diaphragm top and skin markers) of 10 phases were contoured. The three dimensional position variation of GTVs centroid, hilum of lungs, tracheal bifurcation, diaphragm top, skin markers were measured and their correlation were analyzed, and the same for the volume variation of GTVs and lungs by 4D-CT images of 10 respiratory phases.
Results: Movement range of lung cancer in different lobe differed extinctly: 0.8mm–5.0mm in upper lobe, 5.7mm–5.9mm in middle lobe and 10.2mm–13.7mm in lower lobe. Movement range of lung cancer in three dimensional direction was different: Z-axis 4.31±4.34mmï¹¥Y-axis 2.19±1.04mmï¹¥X-axis 1.73±1.5mm. For individual patients, the range of maximum three-dimensional centroid movement was 0.75–13.65 mm for GTVs, 2.83–9.70 mm for tracheal bifurcation, 2.24–9.11 mm for hilum of lung, 6.21–25.40 mm for diaphragm top, and 0 –5.5 mm for skin markers. Mean volume of GTV was 20.90cm^3 range 20.25cm^3– 21.66 cm^3 ŒMean volume of lung was 2800.55cm^3 range 2657.58cm^3– 2968.54cm^3 . There was no statistical significance for volume variation of tumor and lung(r=0.23, p=0.52).
Conclusion: Based on 4D-CT, statistically significant differences of GTVs centroid movement were observed at different pulmonary lobes, and the differences of centroid movement in three dimensional directions were significant, but no significant correlation between three dimensional vector of GTVs and that of normal tissue structures or skin markers were observed. So individual 4D-CT measurement is necessary for definition of ITV margin for lung cancer.
Keywords: Cancer; non-small cell lung / radiotherapy, four-dimensional computed tomography, structures of interest

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.279 THE PLEURAL TAGGING ON HIGH RESOLUTION COMPUTED TOMOGRAPHY IN PREDICTING VISCERAL PLEURA INVOLVEMENT IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: A pleural tag is defined as a linear area of high attenuation surrounded by aerated lung, originating from the edge of the mass and extending peripherally to contact the pleural surface. It could be seen both in benign and malignant diseases. According to the 7th edition of the TNM classification for lung cancer from the IASLC Staging Project, pleural involvement should be confirmed and documented since the diagnosis of pleural invasion would influence the T staging and subsequent treatment strategy. The purpose of this study is to correlate the pleural tagging on high resolution computed tomography (HRCT) of chest with the operative findings, and histopathology in non-small cell lung cancer (NSCLC).
Methods: We analyzed 102 consecutive adult patients with NSCLC and received thoracotomy between January 2008 and October 2010 from the medical record registry and cross index system of a referral teaching hospital. HRCT before operation were interpreted by 2 experienced pulmonologists to identify tumors with pleural tag sign. Operative findings were reconfirmed by the chest surgeon. Pleural invasion was defined by Elastica-Van Gieson stain according to the criteria of IASLC and reviewed by a lung pathologist. Associations between the imaging and pathological findings were examined using a chi-square test. The correlation of operation finding and true pathologic pleural involvement were examined using Pearson's correlation. A p-value of less than 0.05 denotes a statistically significant difference.
Results: There are 43 NSCLC patients identified to have pleural tag sign. Six patients were excluded due to multiple nodules in the lung. Pathologically pleural involvement was found in 16 of 37 patients (43.2%). Tumor size is the only image predictive factor to correlate the pleural tagging and true pleural invasion with a mean tumor size of 38 mm ± 13 mm in invasion group and 23 mm ± 9 mm in noninvasion group (P< 0.001). Other factors including the mean tag length, location, cell type, and gender did not show significant difference between invasion and non-invasion groups. The CT pattern of tumor such as ground-glass opacity or solid type was not informative. Using tumor size of 22 mm as a cut level, the sensitivity of pleural tag sign was 93% and specificity was 52%, the positive predictive value of pleural tag sign was 60% and negative predictive values was 91%. Pleural involvement reported by chest surgeon during operation had no correlation with true pathologic pleural involvement.
Conclusion: Tumor with a diameter smaller than 22 mm and pleural tagging on HRCT is less likely to have true visceral pleura involvement.
Keywords: Lung Cancer Staging, Pleural tag sign, Elastica-Van Gieson stain, High resolution computed tomography

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P2.280 USEFULNESS OF PREOPERATIVE 3D-CT ANGIOGRAPHY FOR PRIMARY LUNG CANCER

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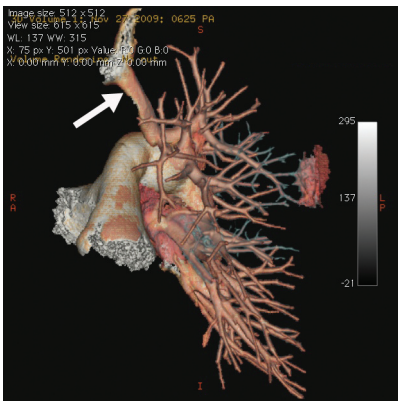
Background: In recent years, a breakthrough in diagnostic technology in radiographical image is superimpressive. Three dimensional computed tomography (3D-CT) has often been used as a useful method of investigation before surgery. So 3D-CT enables surgeons to be able to operate more safety. In our hospital, 64-row multi-detector computed tomography (MDCT) was first introduced in November 2009. This study investigated utility of preoperative 3D-CT for primary lung cancer.
Methods: Thirty-eight patients who underwent either a lobectomy or a segmentectomy for lung cancer between January 2009 and December 2010 at Ayabe City Hospital were included in this study. Video assisted thoracic surgery (VATS) was performed in all 38 patients. Fourteen of all patients between January and October 2009 had been examined by CT (Asteion Multi 4-row, 0.75 s/rot, Toshiba), and an iodinated contrast medium had been administered intravenously by a mechanical injector into their upper limbs (Group A). The remaining twenty-four patients between November 2009 and December 2010 had been examined by CT (Light Speed VCT 64-row, 0.4 s/rot, GE Healthcare), and an iodinated contrast medium had been administered intravenously by a mechanical injector into their

upper limbs (Group B). In all cases of group B coronal, sagittal and 3D-CT angiography images were constructed. One surgeon performed all operations, and analyzed these images.



Results: There was no statistically significant difference of sex, respiratory functions, operative duration, and duration of the chest tube placement between both groups. However, operative duration tended to be longer in the cases of group A than that of group B (291 vs 245 ; p=0.08). The amount of blood loss (p=0.02) and the length of postoperative hospital stay (p=0.04) was less in group B than in group A. There was no postoperative death and there were no serious complications in both groups.
Conclusion: Coronal, sagittal and 3D- CT angiography images using MDCT quickly provides important preoperative information to surgeons and could play an important role in facilitating VATS lobectomy procedure more safety. We therefore recommend using these images for thoracic operations, especially before performing VATS lobectomy.
Keywords: VATS lobectomy, 3D-CT angiography, Lung cancer

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P2.281 EARLY POSITRON EMISSION TOMOGRAPHY (PET) SCAN AFTER ONE CYCLE OF NEOADJUVANT CHEMOTHERAPY FOR NON-SMALL-CELL LUNG CANCER(NSCLC): A PILOT TRIAL.

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Background: Chemotherapy has become an important component of the therapy of stages II and IIIA NSCLC, treated with surgery. FDG-PET scan may have prognostic or predictive value after one cycle of induction chemotherapy.
Methods: Patients with stage IB to IIIB (T4 considered operable at our institution) NSCLC were treated with 3 cycles of neoadjuvant chemotherapy using cisplatin and pemetrexed. Between days 18 and 21 after the first cycle of chemotherapy, patients underwent FDG-PET scan. Investigators caring for patients were blinded to results unless they showed progression. FDG-PET response was defined as decrease of the SUV of the dominant lesion ≥ 20%.
Results: Between 10/05 and 02/10, 25 patients were enrolled. One patient was excluded from the efficacy analysis because she had a carcinoid tumor (despite two independent reviews indicating NSCLC in the initial biopsy). Fifty two percent were female, 88% white, and median age was 62 years. Histology was divided into squamous cell 12%, NOS 16%, large cell 4% and adenocarcinoma 66%. Stage distribution was: 16% IB, 4% IIB and 79% IIIA (58% confirmed by mediastinoscopy). Treatment was well tolerated and only one patient had a grade 4 toxicity. Three patients did not have surgery: one had a stroke, one had disease progression and one had a drop in performance status. The median follow-up of surviving patients is 30 months. The 4 year PFS and OS for the entire population were 52 and 68%, respectively . Nineteen patients had a baseline FDG-PET scan and a day 18-21 available for comparison. Eleven patients (57%) were considered responders on day 18-21 FDG-PET scan. Responders had an OS at 3 years of 45% , while the percentage for non-responders was 88% (P= 0.45). Between years 2 and 4 of follow-up, both the PFS and OS curves for non-responders were consistently above the curves for responders.
Conclusion: The outcome of patients in this trial was better than predicted based on the initial staging. Treatment with cisplatin and pemetrexed was well tolerated in the neoadjuvant setting. This pilot trial showed no evidence that a PET scan after one cycle of chemotherapy can predict the outcome

of patients with NSCLC treated with neoadjuvant chemotherapy.
Keywords: neoadjuvant, Chemotherapy

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.282 ASSESSMENT OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER USING 18F-FDG PET/CT: SUVMAX VS METABOLIC TUMOR VOLUME

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Background: We aimed to evaluate metabolic tumor volume (MTV) compared to SUVmax measurement as markers of histopathological response to neoadjuvant chemotherapy in locally advanced NSCLC.
Methods: Twenty-two patients (18 men; median age:64 years) with locally advanced NSCLC received neoadjuvant platinum-based chemotherapy and, if considered resectable, proceeded to surgery (14/22). Patients had FDG-PET/CT scans before and after 3 cycles of chemotherapy. SUVmax and MTV (40%-SUVmax and adaptive-threshold methods) of the primary tumor was recorded (DOSIsoft Software). SUVmax was graded using EORTC criteria. Pathological response was defined as: non-responders, partial responders (>10% residual tumor cells) and pathological responders (<10% residual tumor cells). Inflammatory cell presence within the tumor was graded as low, moderate or high. Changes in SUVmax and MTV were correlated with pathological response (Wilcoxon test).
Results: There were 8 partial responders, 3 pathological responders 3 non responders. The median decrease of tumor SUVmax was higher in pathological responders than non and partial responders (79% vs 24%, p=0.086). A median percentage decrease in MTV was more significant in pathological responders (84% vs 54% for fixed threshold, p=0.035; 90% vs 47% for adaptive-threshold method, p=0.043). In partial pathological responders, EORTC criteria misclassified 4/8 patients as stable or progressive disease. In these 4 patients, MTV decreased (median percentage decrease: 59% for fixed threshold method, 40% for adaptive-threshold method) and inflammatory cell accumulation was noted within the tumor: moderate (n=3) or low (n=1).
Conclusion: SUVmax measurement seems to be insufficient as a criteria of assessment of the therapeutic response, probably because of post-chemotherapy inflammatory changes. MTV could be a complementary parameter in the assessment of pathological response after neoadjuvant chemotherapy in NSCLC.
Keywords: metabolic tumor volume, neoadjuvant chemotherapy, Non-Small-Cell Lung Cancer

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P2.283 CAN METABOLIC IMAGING OBVIATE THE NEED FOR MEDIASTINOSCOPY IN NON-SMALL CELL LUNG CANCER IN A TUBERCULOUS-ENDEMIC COUNTRY?

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Background: Metabolic imaging with 18-F Fluoro Deoxy Glucose (FDG)Positron Emission Tomography-Computed Tomography (PET-CT) scanning has revolutionized the preoperative diagnostic workup in patients with localized non-small call lung cancer (NSCLC). In addition to diagnosing occult distant metastases, PET-CT scanning has been advocated as an important diagnostic tool for accurate diagnosis of mediastinal lymph node involvement. Tuberculosis is a known confounder and can detract from the utility of PET-CT especially in endemic countries. Very few studies have compared the accuracy of mediastinal lymph node involvement by PET-CT scanning with mediastinoscopy against the gold standard of histopathology in a tuberculous endemic country.
Methods: We retrospectively reviewed patients with non-small cell lung cancer who underwent mediastinoscopy or systematic mediastinal lymph

node dissection after an 18-F FDG PET-CT scan. Patients who underwent PET-CT but did not have histopathological evaluation of the mediastinal lymph nodes were excluded. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) and accuracy of PET-CT scanning was compared with that of mediastinoscopy and formal mediastinal lymph node dissection. False positive lymph nodes on PET-CT were examined for involvement by tuberculosis.
Results: Seventy three consecutive patients who had an 18-F FDG PET-CT scan prior to mediastinoscopy were evaluated. Twenty two of 73 (30.1%) patients had mediastinal lymph node involvement on histopathology. The sensitivity, specificity, PPV, NPV and accuracy of 18-F FDG PET-CT scanning vs mediastinoscopy was 77.3 vs 80%, 72.5 vs 100%, 54.8 vs 100% and 88.1 vs 92.9% respectively. False positivity with PET-CT scanning was seen much more with reactive inflammatory (79%) than tuberculous (21%) lymphadenopathy. Station-wise evaluation of 359 lymph node stations yielded similar results.
Conclusion: PET-CT scanning might obviate the need for mediastinoscopy in patients with no FDG uptake in mediastinal lymph nodes but has a high false positivity. Surprisingly, non-specific inflammatory pathology was a bigger confounder than tuberculosis even in an endemic country like ours. Further studies are required to identify PET-CT uptake characteristics which could reliably distinguish inflammatory from metastatic involvement of mediastinal lymph nodes.
Keywords: Lung cancer, Metabolic imaging, PET-CT

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P2.284 IS HIGH PRE-TREATMENT FDG UPTAKE IN CERTAIN REGIONS OF THE NORMAL LUNG CORRELATED TO THE DEVELOPMENT OF RADIATION INDUCED LUNG TOXICITY AFTER RADIOTHERAPY? AN IN-SILICO TRIAL WITH A NOVEL APPROACH: THE "VIRTUAL PATIENT": FUSING DATA FROM MULTIPLE LUNG CANCER PATIENTS INTO A COMMON SPATIAL REFERENCE

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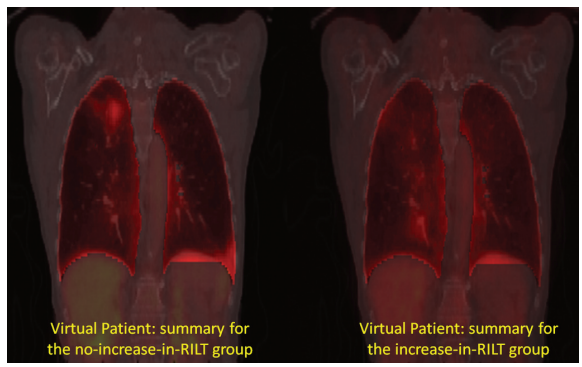
Background: Pre-treatment FDG uptake levels in the lungs are prognostic for radiation induced lung toxicity (RILT) in NSCLC patients. In this study, we investigated if FDG uptake in specific normal-lung regions is correlated to the development of RILT after radiotherapy. To this end, we use a novel approach based on non-rigid registration for transforming and fusing data from multiple lung cancer patients into a common spatial reference ("Virtual Patient") in order to perform spatial-based statistics. This allows us to study the effects of radiotherapy by comparing CT, PET and dose distribution for multiple patients having of not having a complication.
Methods: An intensity-based affine alignment followed by a log-domain phase-based non-rigid registration were applied, producing for each patient a deformation field representing the transformation from the reference to the patient. For each patient, the tumor was delineated and ignored. In this study we considered two distinct locations: the lower and the middle/upper lung lobes. The lobes were delineated only on the reference patient. We performed non-rigid registration of patients to map corresponding lung regions between them. To achieve higher-quality deformation, the virtual patient was chosen such that the amount of deformation needed to deform to the other patients is smallest. For this study we included 20 patients with relatively high mean SUV uptake value, 10 with increased RILT score during treatment (change in dyspnea grade > =1) and 10 without an increase.
Results:



CT and PET images were successfully deformed

towards the reference "virtual patient" (see Figure 1) using the deformation fields resulting from registration. Patients with higher FDG uptake in the lower lung lobes prior to radiation treatment were found to be more likely to develop RILT. The mean SUV level for the lower lung lobes of the virtual patient was 0.90(±0.06) for the group whose RILT score increased, and 0.73(±0.05) for the no-increase-in-RILT group.

Conclusion: Our conclusion is twofold: a) These results showed that non-rigid registration was able to match accurately the lung contours of the reference with the lung contours of the patients; b) Thanks to the novel, virtual-patient approach we showed that location of the pre-treatment FDG uptake in the lungs is an indicator for a potential development of dyspnea after radiation treatment of NSCLC patients. The result suggests treatment planning may be improved if certain anatomic sub-regions are avoided. These results should be confirmed in a larger dataset.

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P2.285 DIAGNOSTIC PERFORMANCE OF INTEGRATED POSITRON EMISSION TOMOGRAPHY/COMPUTER TOMOGRAPHY FOR MEDIASTINAL LYMPH NODES STAGING IN NON-SMALL CELL LUNG CANCER: A BIVARIATE SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Accurate clinical staging of mediastinal lymph nodes (MLN) for patients with non-small cell lung cancer (NSCLC) is important in determining therapeutic options and prognoses. Integrated positron emission tomography and computed tomography (PET/CT) scanning is becoming widely used for MLN staging in patients with non-small cell lung cancer. We performed a bivariate meta-analysis to determine the pooled sensitivity and specificity of this imaging modality.

Methods: The PUBMED/MEDLINE, EMBASE and SPRINGERLINK databases were searched for the related articles on PET/CT for MLN staging in patients with NSCLC. Sensitivity and specificity were calculated for every study. Hierarchical summary receiver operating characteristic curves were used to summarize overall test performance, and study quality was assessed. Potential between-study heterogeneity was explored by subgroup analysis.

Results: Fourteen of 320 initially identified reports were included in the meta-analysis. When we did not consider the analysis unite, the pooled weighted sensitivity (SEN) and specificity (SPE) were 0.73(95%CI 0.65~0.79) and 0.92(95% CI 0.88~0.94), respectively. In patient-based data analysis, the pooled weighted SEN was 0.76(95%CI 0.65~0.84) and the pooled weighted SPE was 0.88(95%CI 0.82~0.92). In node-based data analysis, the pooled SEN was 0.68(95%CI 0.56~0.78) and the pooled SPE was 0.95(95%CI 0.91~0.97).

Conclusion: Integrated PET/CT is an accurate noninvasive imaging test and has excellent diagnostic performance, and specificity for MLN staging in patients with NSCLC.

Keywords: integrated positron emission tomography and computed tomography, mediastinal lymph nodes staging, Non-small cell lung cancer, meta-analysis

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P2.286 AUTOMATIC IMAGE REGISTRATION OF LUNG CT WITH SYNCHRONOUSLY ACQUIRED HYPERPOLARIZED HELIUM-3 MRI AND PROTON MRI FOR PATIENTS WITH NSCLC

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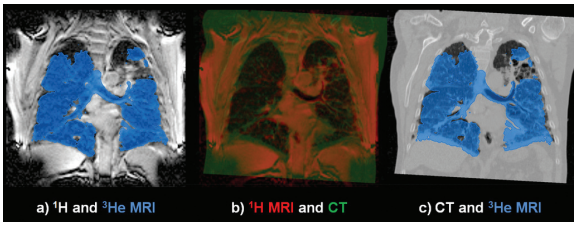
Background: Same breath-hold hyperpolarized ^{3}He MRI and ^{1}H MRI lung image acquisition has recently

been developed [1]. The aim of this study was to test the feasibility of synchronous ^{1}H-^{3}He MRI acquisition in lung cancer patients and to register the MRI to radiotherapy planning CT.
Methods: Before radiotherapy, 4 patients underwent MRI. ^{3}He gas was polarized on site and ventilation images were acquired during a single breath-hold of 1L ^{3}He / N_2 mix. With patients in the treatment position, ^{3}He MRI was acquired on a 3T system fitted with a second radiofrequency amplifier using prototype transmit–receive (T-R) coils. During the same breath-hold, the coil was detuned during ^{1}H transmit and ^{1}H T–R was performed with the scanner's ^{1}H body coil, which itself was actively detuned during ^{3}He T–R [1]. On the same day, radiotherapy planning CT was acquired using an inspiration breath-hold technique to simulate the MRI breath-hold [2]. The required ^{3}He MRI to CT image registration was performed in two automatic steps. Firstly, ^{1}H MRI was rigidly registered to planning CT using mutual information. Secondly, as ^{3}He and ^{1}H MRI are acquired in a single breath-hold the calculated transformation for ^{1}H MRI to CT was directly applicable to ^{3}He MRI.
Results: The 4 patients completed the imaging procedure and held their breath sufficiently for all sets of images to be acquired without any detrimental clinical effects. All ventilation images were successfully fused with radiotherapy planning CT. The registration procedure is demonstrated in Fig 1. a) ^{3}He MRI (blue) and ^{1}H MRI are inherently registered due to the single breath-hold acquisition sequence. b) ^{1}H MRI (red) is registered to the radiotherapy planning CT (green). c) The same image transformation is applied to the ^{3}He MRI to generate the registered ventilation and CT images.



Conclusion: This preliminary work demonstrates that synchronous acquisition of ^{3}He and ^{1}H lung MRI is possible for NSCLC patients, and that the ventilation images can be registered to CT via mutual information of the ^{1}H MRI. The automatic method of registration may be a useful supplementary tool for the planning and evaluation of lung cancer radiotherapy and its side effects [3,4]. [1] Wild JM et al. NMR Biomed (DOI: 10.1002/nbm.1565), 2010 [2] Ireland RH et al. Phys Med Biol 53(21):6055-6063, 2008 [3] Ireland RH et al. Int J Radiat Oncol Biol Phys 68(1):273-281, 2007 [4] Ireland RH et al. Radiother Oncol 97(2):244-248, 2010
Keywords: Radiotherapy Planning, NSCLC, Hyperpolised Helium MRI, Proton MRI

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P2.287 ERLOTINIB ACCUMULATION IN BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER -VISUALIZATION BY PET IN A PATIENT HARBORING A MUTATION IN THE EPIDERMAL GROWTH FACTOR RECEPTOR

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Background: Drugs directed towards the epidermal growth factor receptor (EGFR), such as erlotinib (Tarceva®) and gefitinib (Iressa®), are used for the treatment of patients with advanced non-small cell lung cancer (NSCLC), including patients with brain metastases. However, whether erlotinib actually enters into brain metastases has not been adequately elucidated. In this study, we investigated the accumulation of [^{11}C]-erlotinib by positron emission tomography (PET) and magnetic resonance imaging (MRI).
Methods: A 32-year-old patient with NSCLC and multiple brain metastases was treated with first-line erlotinib. EGFR mutations were determined by analyzing a fine-needle lung tumor biopsy taken prior to treatment. A PET scan of the brain with [^{11}C]-erlotinib was performed during treatment, and a MRI of the head and a computed tomography (CT) of the chest were performed pre- and posttreatment.
Results: The primary lung tumor displayed an erlotinib-sensitizing exon 19 deletion in the EGFR gene and [^{11}C]-erlotinib PET showed accumulation in the brain metastases. Post-treatment MRI and CT

demonstrated regression of both the brain metastases and the primary lung tumor.
Conclusion: Our data demonstrated that erlotinib accumulated in brain metastases in a NSCLC patient who responded to the treatment.
Keywords: NSCLC, EGFR mutation, erlotinib, PET

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P2.288 EXCEPTIONAL LONG-TERM SURVIVAL FOR PATIENTS WITH UNRESECTABLE NON-SMALL CELL LUNG CANCER TREATED WITH RADICAL RADIATION THERAPY ON A PROSPECTIVE CLINICAL TRIAL OF FDG-PET/CT SCANNING FOR STAGING AND TREATMENT PLANNING

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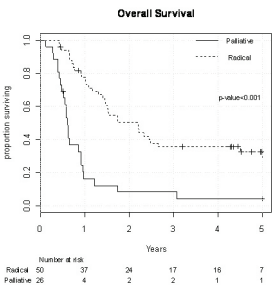
Background: We recently reported that combined FDG-PET/CT profoundly influences patient selection and radiation therapy (RT) planning in patients with non-small cell lung cancer (NSCLC) considered suitable for radical chemoRT/RT after conventional staging (CS). In this report, for the first time, we document survival of patients treated on that study.
Methods: Consecutive consenting candidates for radical RT with stage I-IIIB NSCLC who had undergone CS were enrolled. Those who remained candidates for radical RT after CS underwent a dedicated PET/CT scan in the RT planning position for both staging and RT target volume definition (according to a detailed visual protocol). We aimed to recruit 50 patients who could safely undergo radical chemoradiation to 60 Gy in 30 fractions over 6 weeks after PET/CT imaging and planning. It was expected that > 50 patients would need to be enrolled because of stage migration after PET/CT. Patients who had a previous PET/CT >30 days previously or performed in a position unsuitable for RT planning had a further PET/CT scan. After PET/CT, patients still eligible received radical RT/chemoRT and patients with PET-detected advanced disease received palliative therapies. Survival for both groups was recorded from the PET/CT scan date.
Results: We recruited 76 eligible patients, of whom 50 were deemed suitable for RT to 60 Gy after PET/CT imaging and 26 (34%) received palliative therapies because of distant metastasis (n=12) or extensive locoregional disease seen on PET/CT (n=14). Approximately 1/3 of radical RT patients would have had a grade I geographic miss (FDG-avid tumor outside PTV) if RT was planned without PET. Overall survival (OS) for all 76 patients was 56.8% (46.5% - 69.3%) at one year and 24.9% (16.7% - 37.2%) at 4 years respectively. OS for the 50 patients treated radically was 77.5% (66.6% - 90.2%) and 35.6% (24.3% - 52.1%) at one and four years respectively. OS for the 26 patients treated palliatively was significantly worse at 16.3% (6.7% - 39.8%) and 4.1% (0.6% - 27.7%) at one and four years respectively (P<0.001).



Conclusion: Without PET/CT, all patients would have received radical RT. Although >1/3 received palliative therapies, survival for the entire cohort comprising both radically and palliatively-treated patients was good. Survival for patients actually treated with radical chemoRT/RT after selection with PET/CT was exceptionally good, suggesting a possible survival benefit from timely PET/CT-based patient selection and RT planning.
Keywords: Non-small cell lung cancer, Positron Emission tomography, Radiation Therapy, Chemotherapy

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P2.289 METASTATIC PERICARDIAL INVOLVEMENT AS THE FIRST SIGN OF NEOPLASTIC DISEASE – DIAGNOSTIC SIGNIFICANCE OF MEDIASTINAL LYMPH NODES ENLARGEMENT ON CHEST CT AND INCREASED TUMOR MARKERS CONCENTRATION IN PERICARDIAL FLUID.

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Background: Large pericardial effusion (pe) is a life threatening pathology requiring prompt diagnosis and effective local treatment. Malignancy and especially lung cancer, is one of the leading causes. The aim of the present study was to find the optimal diagnostic algorithm for assessing the probability of neoplastic pericardial involvement.

Methods: 146 patients (pts) treated in the National Institute of Tuberculosis and Lung Diseases with pericardiocenthesis or pericardioscopy in the period of 1989-2006 entered the study. Neoplastic pericardial effusion (npe) was recognized in 66 pts, based on positive pe cytology and/or neoplastic pericardial infiltration in pericardial biopsy specimen. Primary site of disease was: lung – in 46 pts, breast – in 10, mesothelioma – in 3, others – in 7 pts. Benign pericardial effusion (bpe) was recognized in 80 pts with negative results of pe cytology and/or pericardial biopsy specimen, and no signs of neoplastic disease at the time of hospitalization and during 12 months of subsequent observation time. Chest CT scan was performed with Somatom Sensation 16, tumor markers (Cyfra 21-1 and CEA) concentrations in pf were measured with Elecsys- Roche assay.

Results: Mediastinal lymph nodes enlargement (short axis>1 cm) was observed in 93% of pts with npe and in 30% of pts with bpe ($p<0.00001$). Median Cyfra 21-1 values in npe and in bpe were 62,9 ng/ml and 13,4 ng/ml respectively ($p<0.0001$). Median CEA values in npe and in bpe were 22,9 ng/ml and 0,9 ng/ml respectively ($p<0.0001$). Optimal cut off values calculated by ROC analysis were: 95 ng/ml for Cyfra 21-1 and 5 ng/ml for CEA. Diagnostic utility of examined variables is presented below. Parameter Sensitivity Specificity PPV NPV Lymphadenopathy 0.93 0.7 0.66 0.94 Cyfra 21-1>95 ng/ml 0.64 0.95 0.93 0.71 CEA >5 ng/ml 0.63 0.94 0.91 0.71

Conclusion: Mediastinal lymph nodes enlargement and increased Cyfra 21-1> 95 ng/ml and CEA > 5 ng/ml in pe are of high diagnostic significance in assessing the probability of npe. The diagnostic algorithm combining these variables is presently under evaluation.

Keywords: pericardial effusion, Lung cancer, mediastinal lymphadenopathy, tumor markers

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P2.290 DUAL-ENERGY CT IN THE PATIENTS TREATED WITH ANTI-ANGIOGENIC AGENT FOR NON-SMALL CELL LUNG CANCER: A NEW METHOD OF MONITORING TREATMENT?

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Background: Regarding to anti-angiogenic treatment of non–small-cell lung cancer (NSCLC), intratumoral hemorrhage related to the anti-angiogenic action of the drug can lead to increase in size of the tumor and be misinterpreted to progressive disease. Recent a few studies showed the iodine component in lung nodules is measurable on iodine enhanced image of dual-energy CT (DECT)

and is comparable to the real value of the degree of enhancement. This study aimed to determine the clinical feasibility of dual-energy CT in the evaluation of response after anti-angiogenic therapy of NSCLC.

Methods: Ten NSCLC patients treated with bevacizumab underwent CT scans were obtained before and 3 minutes after contrast material injection by using a scanner with a dual-energy technique. Image sets that included nonenhanced weighted average, enhanced weighted average, virtual nonenhanced (VNC), and iodine-enhanced images were reconstructed. CT numbers of NSCLCs on virtual nonenhanced and nonenhanced weighted average images were compared, and CT numbers on iodine-enhanced image and the degree of enhancement on average images (subtraction of CT number of a tumor on a nonenhanced weighted average image from its CT number on an enhanced weighted average image) were compared.

Results: CT numbers showed no significant difference between virtual nonenhanced and nonenhanced weighted average images (37.7 ± 6.5 vs. 40.4 ± 6.3, respectively, P = .195, Wilcoxon test). CT numbers between iodine enhanced image and the degree of enhancement also showed no significant difference (33.7 ± 24.4 vs. 35.4 ± 24.6, respectively, P = .652).

Conclusion: Dual-energy CT may serve as useful tool for response evaluation after anti-angiogenic treatment in NSCLC, providing the degree of enhancement of NSCLC without additional radiation dose.

Keywords: non–small-cell lung cancer, Response evaluation, antiangiogenic therapy, dual-energy CT technique

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P2.291 EVALUATION OF FLT-PET AS EARLY PREDICTOR OF RESPONSE TO RADICAL RT IN PATIENT WITH NON-SMALL CELL LUNG CANCER

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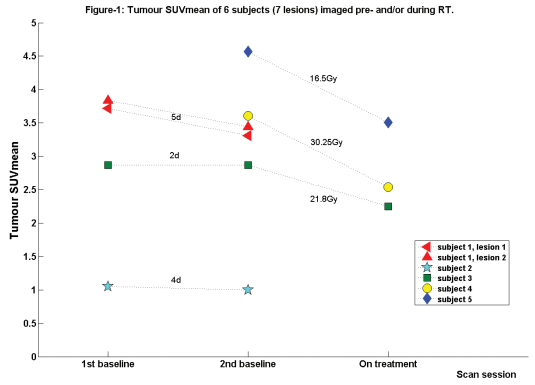
Background: [F-18]Fluorothymidine (FLT), a radiotracer probing proliferation, holds promise as an early response biomarker. There is limited literature on FLT PET in the evaluation of response to radical RT for lung cancer (Everitt 2009, Vera 2011). Most patients studied received concurrent chemo-RT, rather than RT alone. Questions also remain about the baseline variation and optimal methodology for tumour delineation and analysis.

Methods: FLT-PET imaging is performed in patients with non-small cell lung cancer (NSCLC) scheduled for radical RT twice at baseline (scan 1 and 2) with the objective to assess reproducibility and after 3-10 fractions of treatment (scan 3), to assess early response. All patients consent to an ethically approved protocol also including serial blood sampling for analysis of circulating biomarkers of cell death (M30/65), aiming to recruit at least 12 patients. Data are dynamically acquired for 60min on the TrueV PET/CT scanner. 45-60 minute images are reconstructed using 3D-OSEM, smoothed with a 4mm Gaussian filter. Tumours are manually delineated on PET-CT images by two thoracic radiology experts and functional volumes are defined using a region-growing fixed-threshold algorithm set at 41% of SUVmax. SUV reproducibility is measured as (SUV2-SUV1)/(SUV1+SUV2)*200. RT response is calculated as % change relative to single or average baseline value.

Results: To date, six patients undergoing radical RT (5 sequential after chemotherapy, 1 RT alone) had a total of 12 scans: All were male, aged 66-77 years with inoperable Stage II/III NSCLC treated with an accelerated RT regimen of 55Gy in 20 fractions. Two patients underwent scans 1 and 2, two had scans 1 and 3, one completed scans 1, 2 and 3 and one had scan 1 only (not reported). Pre-treatment scans were done within 2-5 days and on-treatment scans 7-16 days after RT initiation. Average tumour SUVmean reproducibility was 7.3%. After 6, 8 and 11 2.75Gy fractions, tumour SUVmean decreased by 23%, 21% and 30% respectively. SUVmax reproducibility and response were similar.



Conclusion: In agreement to previous studies (de Langen, 2009), our preliminary results demonstrate little baseline variation suggesting that one baseline scan is sufficient for comparison to an on- or post-treatment scan. To date, we observed less average decrease in primary tumour uptake (SUVmax, 26.6%, SUVmean 24.8%) compared to previous reports using comparable RT dose but with concomitant chemotherapy (SUVmax >40%) (Everitt, 2009). Recruitment is ongoing and results from analysis of blood borne cell death biomarkers in addition to updated results on FLT-PET will be reported.

Keywords: [F-18]Fluorothymidine PET, Non-small cell lung cancer, Radiotherapy

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P2.292 VALIDATION OF EXISTING CLINICAL PREDICTION MODELS FOR PATIENTS WITH SOLITARY PULMONARY NODULES (SPN) MANAGED BY A LUNG MULTI-DISCIPLINARY TEAM (MDT).

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Background: The management of patients with SPNs depends critically on the pre-test probability of malignancy. There are currently two clinical predictions models for SPNs based on data from North America. However, there is no published evidence that these models have been validated in the UK population, in particular in patients who are managed by a Lung MDT Objective: To validate two existing clinical prediction models in patients with SPNs managed by the Lung MDT at a large teaching hospital in Northern England

Methods: 175 patients (age range 32-92 years, 91 females) with SPNs measuring 8–30 mm managed by the Lung MDT over a 3 year period (1st January 2007 - 31st December 2009) were identified retrospectively through the institutional Lung Cancer database. Data on age, smoking, cancer history, nodule size, location, spiculation, and final diagnosis were collected. Each patient's final diagnosis was compared with the probability of malignancy predicted by two models: one developed at the Mayo Clinic and the other developed from patients enrolled in a Veteran Affairs (VA) Cooperative Study. The accuracy of each model was assessed by calculating areas under the receiver operating characteristic (ROC) curve and the models were calibrated by comparing predicted and observed rates of malignancy

Results: The area under the ROC curve for the Mayo Clinic model (0.832; 95% CI 0.753-0.911) was higher than that of the VA model (0.739; 95% CI 0.641-0.838) but this difference was not statistically significant. Calibration curves showed that both models slightly underestimated the probability of malignancy for patients across all deciles of predicted probabilities, except for those with highest probability of malignancy, where the VA model slightly overestimated the probability of malignancy

Conclusion: The two existing prediction models are sufficiently accurate to guide decisions about management of patients with SPNs managed by the Lung MDT at a large teaching hospital in the UK

Keywords: Solitary pulmonary nodule, Cancer, Prediction model, CT

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.293 CORRELATION OF THE STANDARDIZED UPTAKE VALUE IN FDG-PET WITH THE BIOLOGICAL MARKER IN LUNG ADENOCARCINOMA LESS THAN 3CM

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Background: Fluorodeoxyglucose positron emission tomography (FDG-PET) has become an important tool for the diagnosis and the staging of non-small cell lung cancer. FDG-PET maximal standardized uptake values (SUV_{max}) of primary lesion have been shown to have the correlation with some clinicopathological factors, but its biological mechanism is unclear.
Methods: We conducted a retrospective review of 60 patients who underwent preoperative FDG-PET and complete resection of lung adenocarcinoma less than 3cm. Immunohistochemical study for cyclooxygenase-2 (Cox-2), Ki-67, vascular endothelial growth factor (VEGF), thyroid transcription factor-1(TTF-1), phosphorylated epidermal growth factor receptor (pEGFR), insulin-like growth factor 1 receptor (IGFR), and platelet-derived growth factor receptor α (PDGFRα) was performed, and the correlation between the expression of these biological markers and SUV_{max} was evaluated.
Results: A significant correlation was observed between the SUV_{max} and Cox-2, Ki-67, and VEGF expression. Cases which expressed the growth factor receptors tended to have higher SUV_{max}, but it's not significant. The expression of Cox-2 was significantly associated with Ki-67 and VEGF expression, and the expression of VEGF was significantly associated with Cox-2, Ki-67, PDGFRα, and TTF-1 expression. EGFR mutation did not correlate with SUV_{max}.
Conclusion: The expression of Cox-2, Ki-67 and VEGF is associated with the SUV_{max} in lung adenocarcinoma less than 3cm. These results showed that the SUV_{max} might reflect the cellular proliferation and aggressiveness even in the small lung adenocarcinoma.
Keywords: lung adenocarcinoma, FDG-PET, VEGF, COX2

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.294 A RADIOGRAPHIC AND PATHOLOGICAL ANALYSIS OF SMALL LUNG ADENOCARCINOMAS WITH AIR-CONTAINING TYPE LESIONS BY USING COMPUTED TOMOGRAPHY

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Background: Cases of solitary small noninvasive peripheral lung tumors (adenocarcinoma in situ, AIS) with a 100% 5-year survival and minimally invasive adenocarcinoma (MIA, invasion diameter <= 5 mm) with approximately 100% 5-year survival have been reported. Based on thin-section computed tomography (TS-CT) findings, small lung adenocarcinomas are classified as either air-containing or solid-density type. Therefore, we analyzed the relationship between air-containing type and International Association for the Study of Lung Cancer classification of lung adenocarcinoma.
Methods: Of 308 consecutive patients with 316 lesions who underwent surgical resection for peripheral lung adenocarcinomas (diameter, <=20 mm) between April 2004 and October 2010, the TS-CT findings and pathologic specimens of 137 patients with 142 air-containing lesions were reviewed.
By using TS-CT scan images, a tumor was classified as an "air-containing" type if the maximum diameter of tumor opacity on the mediastinal window image was less than or equal to half of that seen on the lung window image and as a "solid-density" type if the maximum diameter on the mediastinal window image was more than half of that on the lung window image. "Disappearance rate" was defined as the percentage loss in the mediastinal window. Then, the invasion diameter of air-containing type was measured. The correlation between TS-CT scan findings (air bronchogram, pulmonary vascular

convergent, pulmonary vascular involvement, indentation, notch, and disappearance rate) and pathological findings (subclassification) were investigated.
Results: Of the 142 air-containing lesions, 114 had AIS and 28 had MIA. The average diameter of tumor invasion in MIA was 2.3 mm (range, 0.5-5.0 mm). Invasive adenocarcinoma with invasion diameter of >5 mm, vascular invasion, and lymphatic invasion were not observed in air-containing lesions, and none of the patients has a recurrence. Both AIS and MIA showed air bronchogram, pulmonary vascular convergent, pulmonary vascular involvement, indentation, and notching. There was no significant difference in the correlation of TS-CT scan findings and the pathological findings.
Conclusion: Both AIS and MIA showed TS-CT findings of lung adenocarcinoma, such as air bronchogram, pulmonary vascular convergent, pulmonary vascular involvement, indentation, and notching; therefore, TS-CT findings made nothing for diagnostic imaging of AIS and MIA. Invasive adenocarcinoma with invasion diameter of >5 mm were not observed in air-containing type with diameters of <20 mm. In conclusion, small lung adenocarcinoma with air-containing type was AIS or MIA.
Keywords: minimally invasive adenocarcinoma, air-containing type, thin-section computed tomography, adenocarcinoma in situ

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P2.295 RADIOLOGICAL FEATURES OF ADVANCED NON-SMALL CELL LUNG CANCER WITH THE PRESENCE OF EGFR MUTATION COMPARED WITH THERAPEUTIC RESPONSE FOR TKIS

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Background: Primary tumor maximum standardized uptake value (SUV max) of FDG PET has been studied as a potential factor for overall survival or therapeutic responses in patients with non-small cell lung cancer (NSCLC). On the other hands, epidermal growth factor receptor (EGFR) mutation is the most important therapeutic predict factor to tyrosine kinase inhibitors (TKIs) in NSCLC, especially adenocarcinoma. The purpose of this study is to identify any particular imaging features on CT and SUV max of FDG-PET in patients with advanced NSCLC confirmed adenocarcinoma and known EGFR mutations, and to assess the relationship between the radiological features and the therapeutic response for EGFR TKIs.
Methods: Institutional review board approval was obtained for this retrospective study. For subsequent 49 patients with a histologic diagnosis of adenocarcinoma of advanced NSCLC and known EGFR mutation status between May and September 2009, lesion density (part-solid versus solid) on thin-section CT, SUV max of primary lesion and sites of metastases were assessed. And the imaging findings were compared with the therapeutic response (PD versus SD/PR).
Results: Thirty-one of the patients were female and eighteen were male. The majority of patients had stage IV disease. FDG-PET was performed in thirty-three patients. There were eight with part-solid and the other 41 with solid appearance of primary tumor on thin-section CT. The SUV max of primary tumor was ranged from 2.5 to 17.1 (mean; 9.3). Most of patients had multiple distant metastases, high frequent metastatic site were pleural dissemination, intrapulmonary and bone, respectively. 32 patients had exon 19 deletion type and 17 had L858R within exon 21 for EGFR mutation. Forty patients were administrated TKIs, gefitinib for 36 patients and erlotinib for four. The mean duration of these medication was 244 days, ranged from 20 to 689. Therapeutic responses were evaluated as PR in 24, SD in 10 and PD in 6. The SUV max of primary tumor was not correlated with the duration of oral TKIs (γ=-0.1266, p=0.5081 at Spearman's coefficient). And CT findings of primary tumor did not also have a correlation with the duration of oral TKIs (solid vs. part solid, p=0.1043 at t-test). Furthermore, the SUV max of primary tumor had no relationship for therapeutic effect (p=1.000). But liver metastases were significantly lower than pleural dissemination (p<0.001), intrapulmonary (p<0.001), brain (p=0.0022) and bone metastases (p<0.001), respectively.
Conclusion: There was no specific CT appearance of primary tumor in advanced lung adenocarcinoma

with the presence of an EGFR mutation, and no relationship between radiological features and tumor response for EGFR TKIs.

Keywords: Non small cell lung cancer, Adenocarcinoma, EGFR mutation, FDG PET

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P2.296 REPEATABILITY OF SERIAL 18F-FDG UPTAKE MEASUREMENTS IN TUMORS USING PET: A META-ANALYSIS

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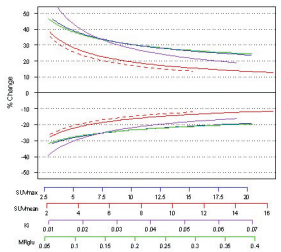
Background: Although guidelines are yet based on anatomic size measurements (RECIST) these criteria have limitations, particularly with newer anti-cancer therapies that stabilize disease. Metabolic response, assessed by PET, might add to size measurements. To discriminate true signal changes from noise the repeatability needs to be known.

Methods: A systematic literature search was performed to identify studies addressing ^{18}F-FDG repeatability in malignant tumors. For each of four PET uptake measures, SUV_{max}, SUV_{mean}, K_i and MR_{glu}, the level of agreement between test and retest values was assessed with the CR95. The relation between the test-retest ratio and the level of uptake and tumor volume was evaluated with generalized linear mixed effects models. Principle component transformation was used to compare the repeatability of the four different uptake measures.

Results: Seven repeatability studies were identified. Percentage repeatability was a function of the level of uptake (Figure). Therefore, a binary model was developed in which the absolute change between the test and retest scan was used for tumors with low uptake values and the percentage change for tumors with high uptake values (Table). Tumor volume did not affect SUV_{mean} repeatability, but K_i and MR_{glu} had poor repeatability at tumor volumes below 4.5 cm^3.



	Repeatability Threshold	Mean > Threshold % Change	Mean < Threshold Absolute Change
SUV_{max}	7.8	25%	-1.9
SUV_{mean}	4.7	20%	-0.94
K_i (mL/min/mL)	0.26	25%	-0.065
MR_{glu} (µmol/mL/min)	0.15	25%	-0.037

Conclusion: Good repeatability was found for all ^{18}F-FDG uptake measures with SUV_{mean} performing best. Because percentage repeatability was a function of the uptake level, we propose to use absolute- instead of percentage change for lesions with low uptake.

Keywords: 18F-FDG PET, Repeatability, Cancer

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P2.297 REDUCTION OF STANDARDIZED UPTAKE VALUE IN 18F-FDG PET MIGHT REVEAL THE SIMILAR SURVIVAL BENEFIT OF STABLE DISEASE AND PARTIAL RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN UNTREATED ADVANCED NON-SMALL CELL LUNG CANCER

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Background: ^{18}F- fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) appears

particularly valuable in stable disease (SD). This prospective study was undertaken to evaluate the impact of SD and partial response (PR) to platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC) on survival in terms of maximum standardized uptake value (SUV_{max}) reduction in ^{18}F-FDG PET after two cycles of chemotherapy.
Methods: Untreated patients with advanced NSCLC recommended to undergo platinum-based chemotherapy were eligible for this study. They did ^{18}F-FDG PET at the baseline and after two cycles of chemotherapy.
Results: 43 patients were enrolled from August 2003 to May 2007. Median progression-free survival (PFS) was 6.0 months (95%CI, 4.8 7.2) for 16 achieving SD and 6.2 months (95%CI, 4.3 8.1) for 18 achieving PR, p = 0.965. Median overall survival OS was 20.0 months (95%CI, 2.0 38.0) and 15.0 months (95%CI, 6.7 23.3) respectively, p = 0.194. PFS was significantly correlated with first-line response (p = 0.013), but OS was significantly correlated with first-line response (p = 0.009) and epidermal growth factor receptor tyrosine kinase inhibitors in the 2nd or 3rd-line setting (p = 0.010). Mean SUV_{max} at the baseline was significantly correlated with that after two cycles of chemotherapy for SD patients (r = 0.853, p = 0.000) and PR patients (r = 0.658, p = 0.003) respectively, and mean SUV_{max} reduction was of significant difference for SD patients (p = 0.014) and PR patients (p = 0.000) respectively.
Conclusion: A significant SUV_{max} reduction in ^{18}F-FDG PET might reveal the similar survival benefit of SD and PR to platinum-based chemotherapy in untreated advanced NSCLC.

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P2.298 EVALUATION OF PLEURAL EFFUSION IN PATIENTS WITH NONSMALL CELL LUNG CANCER USING FDG PET-CT

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Background: Pleural effusions frequently seen in patients with lung cancer. Many of them are malignant but some of them are benign, reactive fluid. Sometimes it can be difficult to differentiate types of effusion. FDG PET-Ct is an noninvasive imaging method which is widely used to staging lung cancer.
Methods: For two years period, 52 of patients histological proven nonsmall cell lung cancer patients with pleural effusion who were performed FDG PET-CT for staging prosedure lung cancer was evaluated
Results: Patients pleural fluid volume (Min-modarate-massive), FDG PET-CT findings, pleural fluid pathological and biochemical parameters (transudate/exudate) were determined. Results of FDG PET-CT findings were coraleted with pathologica diagnosis of pleural fluid or pleural biopsy. Senstivity, spesifity, accuracy, PPV and NPV of FDG PET_CT for detecting malignant pleural effusion were calculated.
Conclusion: FDG PET_CT may be useful in differantiation malignant or benign pleural effusion in patients with NSCLC
Keywords: pleural effusions, malignant/ benign, FDG PET_CT, Lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.299 CAN PET-CT BE A PROGNOSTIC FACTOR IN PATIENTS WITH NON-SMALL CELL LUNG CANCER?

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Background: Although advanced diagnostic and theraphautic development are achieved, lung cancer is the most leading cause of death in both gender around the world. The stage of tumor is stil the most important factor in determining the prognosis of lung cancer. Since even at the same stage, survival rates are different and additional factors are needed for determining the prognosis. In this study, in order to determine the role of FDG-PET([^{18}F]-fluoro-2-deoxy-D-glucose Positron Emission Tomography)

as a prognostic factor in patients with non-small cell lung cancer, the relationship between SUVmax (maximum Standardized Uptake Value) and histological and TMN characteristics of the tumor were evaluated.
Methods: The data of 77 lung cancer patients, pathologically diagnosed as NSCLC, admitted to the Department of Chest Disease, School of Medicine, University of Çukurova between June 2006 and August 2009 were retrospectively analyzed.The patients were followed up till August 2010.
Results: The mean age of the patients included into the study were 77 (5 female (6,5%) mean age was 57 years (range 32-81). Histological distribution of patients was as follows 34(44,2%) adenocarcinoma, 29(37,7%) squamous carcinoma, 14 (18,2%) undetermined NSCLC. While 24 (31,2%) patients were at stage I-III, 53 (68,8%) patients were at stage IV. We found no signficant correlation between SUV max value and TNM stages, N values, and histological types were detected. But, in case of tumor size, SUV max was found to be higher in tumors larger that 3 cm (n=57, 13,11 ± 6,46; p=0.02). No significant correlation between the SUV max value and the histological types of the tumor except in the undetermined group of NSCLC in which weak positive correlation with SUV max value was determined in this group when the cut off value of the SUV max was taken as 7 (n=14, p=0.052). Also, patients with SUV max greater than 7 were significantly more in the group having a tumor size greater than 3 cm (p=0.002). However none of the parameters including histological subtype, TNM stage, N value, and SUV max value of tumor were found to be correlated with the survival. On the other hand, by cox regression analyses, it was seen that each one milimeter increase of the tumor size, increases the percentage of death by 1,6%. (95% CI, 1.0011-1.0309) and tumor size was found to be statistically significantly correlated with the survival (p=0,049).
Conclusion: In our study, tumor size found to be the only significant determinate of the survival, patients with SUV max greater than 7 were significantly more in the group having a tumor size greater than 3 cm.But,no significant correlation was found between survival and histological subtype, TNM stage, N value, and SUV max value of tumor in NSCLC. We conclude that further prospective and multicentric studies with larger patients groups are needed to identify parameters effecting FDG uptake and the relation of SUV with prognosis in NSCLC.
Keywords: Prognosis, NSCLC, FDG PET

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P2.300 MULTICENTER EXPERT PANEL REVIEW OF FDG-PET/CT FOR RADIOTHERAPY PLANNING IN LOCALLY ADVANCED NSCLC: ADRESSING THE CHALLENGE OF INTER-OBSERVER VARIABILITY

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Background: To guarantee quality assurance in a randomized multicenter study on PET-based radiotherapy planning in locally advanced lung cancer (PET-Plan*), mediastinal and hilar lymph nodes (LN) of study patients are reviewed for visual FDG-positivity and anatomical localisation by an online panel of 9 experts via an electronic Case Report Form (eCRF; Alcedis, Giessen). During the review process, two blinded observers independently evaluate PET/CT datasets of each study patient. In case of discrepancies an additional review by a third non-blinded observer is performed. In order to minimize the interobserver variability within this panel, we initiated a harmonisation process to establish detailed criteria of PET-reading and reporting.

Methods: For the harmonisation process ten discrepantly reported study cases during the early (oder initial) stage of the panel were re-evaluated in a blinded manner by all panel members for FDG-positive lymph nodes and their anatomical localisation according to an atlas. As a result of this process detailed criteria for reading and reporting FDG-PET within the context of the study could be elaborated . These criteria were applied to image data of 13 non-study patients with 42 mediastinal lymph nodes, for which biopsy results were available.
Results: Before the harmonisation process, inter-observer variability among the observers was in the range of literature (kappa around 0,6 for detecting positive mediastinal and hilar lymph nodes in FDG-PET). Inter-observer agreement was particularly poor for the conjoint evaluation of hilar lymph nodes and of rarely affected lymph node stations. Therefore, the criteria for reading and reporting PET elaborated by the panel tackled the following issues: conjoint evaluation of nodal stations 1/ 2 and 10/11, positive reporting of node stations in direct neighborhood of the primary tumour, reporting only the primarily affected positive lymph node station in the case of a LN < 15 mm in equivocal anatomical location while positively reporting all affected stations in case of larger or bulky lymph nodes Furthermore, the pre-test probability is taken into account in cases of equivocal FDG-accumulation. In comparison to biopsy results, none of the tumor affected nodes was read negative by the panel in consensus, while a relevant but acceptable rate of nodes were reported falsely positive.
Conclusion: Despite a relevant inter-observer variability, whose improvement will be subject to further studies, there was an encouraging agreement of the expert panel concerning the detection of tumor affected nodes. This is an important finding in the context of the use of FDG-PET for radiotherapy planning, supporting the restriction of target volumes to FDG-positive lymph node regions only. *
Supported by Deutsche Krebshilfe
Keywords: Interobserver Variability, FDG-PET/ CT, Expert Panel

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P2.301 NON-INVASIVE BIOCONDUCTANCE MEASUREMENT AS ADJUNCTIVE DIAGNOSTIC TECHNIQUE OF LUNG CANCERS IN SUBJECTS WITH ABNORMAL CHEST CT.

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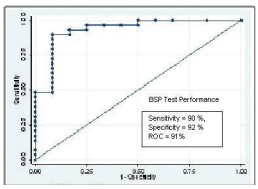
Background: Recent findings confirm utility of chest CT screening in reducing lung cancer (LC) mortality in high-risk populations. While the majority of CT-detected lung nodules (85 – 95%) are benign, a clinical decision is necessary. The bioelectrical properties of cancerous tissue vary significantly from benign tissue. We hypothesize that cutaneous bioconductance could help in distinguishing benign from malignant CT-detected chest lesions. Having an adjunctive diagnostic technology that's non-invasive and discriminates between the need for more ionizing radiation studies or biopsies versus observation would be valuable.
Methods: Forty-one subjects, 22 male, 19 female (ages 34-80) were evaluated for possible LC based on at least one suspicious radiological finding, a non-calcified nodule. Subjects were measured with the trans-thoracic Bioconductance Scan Platform (BSP). The BSP device collects measurements at several anatomical locations across the thorax and other sites providing conductivity data. Measurement sessions were completed prior to tissue diagnosis.
Results: 29 subjects had confirmed LC by pathology (26 NSCLC, 2 SCLC, 1 carcinoid) with mass sizes ranging from 0.4 cm to 14.6 cm, median 2.8 cm. 12 subjects had a benign outcome based on pathology (9) or by stable follow-up CT scans (3) at 2, 4 and 8 months. For each subject a composite score from the collected data was calculated and an optimal cut-point set for discriminating between the malignant and benign outcomes chosen. BSP data for malignant cases resulted in 26 true positives (including 2 with small masses of 0.8 cm) and 3 false negatives

(including the carcinoid case), for a 90% sensitivity. For 12 benign cases, 1 false positive and 11 true negatives yield a specificity of 92%. Thus, the overall ROC from BSP analysis was 91%.



Conclusion: A high-precision transthoracic BSP can non-invasively provide bioconductance measurements that are scored to have a strong association with an in-vivo thoracic malignancy. It's simple to perform, involves no ionizing radiation, and differs from other LC "biomarkers" by focusing strictly upon characterization of an already identified indeterminate lung mass. A technology that will provide adjunctive information to CT scanning to determine the most appropriate diagnostic pathway, either biopsy or further follow-up, would be an important advance for the clinician.

Keywords: Bioconductance, Adjunctive Diagnostic Technique, BSP - Bioconductance Scan Platform

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P2.302 THE DIAGNOSTIC ROLE OF DUAL PHASE F-18 FDG PET/CT IN CHARACTERIZATION OF SOLITARY PULMONARY NODULES

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Background: Our objective was to evaluate the diagnostic role of dual phase F-18 FDG PET/CT in the characterization of the solitary pulmonary nodules (SPN). We also compared the SUV variables adjusted to body surface area (BSA), lean body mass (LBM) and blood glucose level (GLC) in the terms of decision making in patients with SPN.

Methods: A total of 36 SPN in 36 patients (15 female; 21 male; age range, 32-83 years) were included in this retrospective study. The final diagnosis was confirmed by histopathologically or follow-up by CT. Two PET/CT scans were performed one (early) and two hours (delayed) after injection of F-18 FDG. SUV values (early and delayed SUVmax and SUVmean adjusted to body weight; SUVmax and SUVmean adjusted to BSA, LBM and GLC); retention index (RI); nodule to mediastinum (nodule activity/subcarinal roi activity) ratios (nod/med) were calculated. The sensitivity, specificity, negative (NPV) and positive predictive values (PPV) and accuracy of early and delayed F-18 FDG PET/CT (both visual and semiquantitative assessments) and low dose non-enhanced CT were calculated. ROC curves were obtained for each SUV parameter, nod/med ratio and RI. The threshold values were calculated in the terms of highest sensitivity and specificity points.

Results: Histopathological evaluations and follow up of the patients revealed 16 patients had malignant tumour whereas 20 patients had benign lesions. There was no statistical difference between malign and benign SPN patients in the terms of height, injection dose of F18 FDG, weight, blood glucose, BSA and LBM values. The median (min-max) SUVmax values were 1.5 (0.5-4.1) in benign group and 4 (1.3-38) in malign SPN group. Early and delayed SUVmax, SUVmean, BSA-SUVmax, BSA-SUVmean, LBM-SUVmax, LBM-SUVmean, GLC-SUVmax, GLC-SUVmean ve nod/med values were statistically higher in malign SPN group than benign group. The sensitivity, specificity, NPV, PPV and accuracy of low dose non-enhanced CT was 88%, 50% and 67% respectively. With the threshold value of early SUVmax as 2.5 and 3.05 that is obtained from our population using ROC curve, 94-75% sensitivity, 75-80% specificity and 83-78% accuracy were calculated respectively. With the same threshold values for delayed scan, 100-88% sensitivity, 75-85% specificity and 86-86% accuracy were obtained respectively. The delayed BSA-SUVmax and LBM-SUVmax had 100% sensitivity, 80% specificity in the determining SPN characterization.

Conclusion: The study showed that dual Phase PET/CT might increase the diagnostic potential of F-18 FDG PET in the characterization of SPN. BSA, LBM and glucose corrected SUV values did not have better diagnostic performance compared to routine

body weight adjusted SUVmax values. SUVmax as 2.5 for early images and SUVmax as 3.05 for delayed images were acceptable threshold values in the characterization of SPN by F-18 FDG PET/CT. In this particular study group, a threshold value cannot be determined for retention index, but higher retention index values may show higher malignant potential in solitary pulmonary nodules.
Keyword: F-18 FDG PET/CT, SUV, Solitary pulmonary nodule, dual phase PET/CT

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P2.303 A NOVEL APPROACH TO IMAGING AND TREATMENT OF BRONCHIAL CARCINOIDS - EXPERIENCE IN WESTERN AUSTRALIA

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Background: Treatment options in advanced-stage neuroendocrine tumors are limited. There is a promising new therapy in which radioactive atoms are attached to molecules that target and bind to neuroendocrine cancer cells. In Western Australia several patients with bronchogenic carcinoid tumours have received Lutetium-177 (Lu-177) Peptide Receptor Radionuclide Therapy (PRRT). Lu-177 tagged Octreotate (a somatostatin analogue) is combined with a radiosensitizing chemotherapy agent (Capecitabine). To identify eligible patients, imaging has been performed using 68Ga-1,4,7,10-tetraazacyclododecane-tetraacetic acid-D-Phe1,Tyr3-octreotate (DOTATATE), a novel selective somatostatin receptor PET ligand. Bronchial carcinoids typically have low glucose turnover, and 18F- FDG is thought to be of limited use in these patients. Compared with18F-FDG in the detection of pulmonary neuroendocrine tumors 68Ga-DOTATATE is more specific and has been shown to be superior in discriminating endobronchial tumor from distal collapsed lung.
Methods: Images were acquired 60 min after injection of 120MBq of 68Ga- DOTATATE. Imaging was performed using a dedicated GE Discovery ST camera combining a PET unit and a 16-slice CT unit; whole-body examinations (brain to mid thigh) were performed with the patient supine. The 68Ga-DOTATATE and 18F-FDG PET/CT studies were reviewed for areas of abnormally increased tracer uptake by an experienced nuclear medicine physician. Eligible patients were treated with a therapy activity of 7.9GBq 177Lu-octreotate administered with as a day patient at Fremantle Hospital with concomitant amino acid nephroprotection and tropisetron emesis prophylaxis. Whole body gamma imaging at 4hrs and 24hrs was performed.
Results: Since January 2010, X eligible patients with bronchial carcinoid have been identified with 68Ga-DOTATATE and treated with Lu-177 tagged Octreotate combined with Capecitabine. Our preliminary results are positive with a symptomatic improvement observed in most patients and possibly a survivial benefit. No serious side effects have been observed to date. FIGURE - 68Ga-DOTATATE PET/CT demonstrating uptake in right upper lobe bronchial carcinoid (UNABLE TO ATTACH FIGURE)
Conclusion: Early experience in Western Australia has confirmed 68Ga-DOTATATE is a good alternative to FDG18-PET/CT in imaging of bronchial carcinoids and assessment of suitability for treatment including 177Lu-octreotate with oral capecitabine. Initial results in our pilot group indicate symptomatic improvement and possibly a survival benefit.
Keywords: Neuroendocrine, PET/CT, Ga-DOTATATE

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P2.304 18F-FDG PET/CT SCAN AND ULTRASOUND GUIDED TRANS-BRONCHIAL/TRANS-TRACHEAL LYMPH NODE NEEDLE ASPIRATION (EBUS/EUS) IN RESTAGING OF LOCALLY-ADVANCED (LA) NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH INDUCTION CHEMOTHERAPY FOLLOWED BY 3-DIMENSIONAL-HYPOFRACTIONATED ACCELERATED RADIOTHERAPY (3D-HAR): OUR EXPERIENCE.

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Background: Accurate restaging in patients with LA-NSCLC treated with chemotherapy and radiotherapy plays an important role in determining the patient outcome, because it is well known that lymph node down staging after treatment completion is the most indicator of better survival in this setting. However invasive restaging after multimodality therapy may be very difficult. ^{18}F-FDG PET/CT scan is a non-invasive exam allows the monitoring of clinical result obtained by treatment. EBUS/EUS allows a cito- histological sample of mediastinal suspected masses and/or lymph nodes to distinguish benign flogosis to malignant involvement. We investigated the concordance of EBUS/EUS and ^{18}F-FDG PET/CT scan in mediastinal restaging.
Methods: We collected all clinical data about all consecutive patients with LA-NSCLC which performed a ^{18}F-FDG PET/CT scan before induction chemotherapy containing platin followed by 3D-HAR. At treatment completion patients performed a restaging with ^{18}F-FDG PET/CT scan and EBUS/EUS. We matched the ^{18}F-FDG PET/CT scan results with those reported by EBUS/EUS and cito- histological specimens.
Results: From May 2007 to December 2010, overall 12 consecutive patients have been analyzed: there were 10 (83%) males and 2 (17%) females, with a median age of 62 (range: 50 – 74) years. There were: 5 (42%) adenocarcinoma, 4 (33%) squamous cell carcinoma, 1 (8%) great cell carcinoma and finally 2 (17%) NSCLC not other specified. Pathological mediastinal lymph node involvement was reported in 6 (50%) patients. In 5(42 patients, pathological involvement was absent and in one case was not-diagnostic (8%) . Overall there were 11 (92%) stage IIIA and 1 (8%) stage IIIB disease with a left emithorax involvement in 6 (50%) patients, right emithorax involvement in 5 (42%) patients and finally unknown side in 1 (8%) patients. Overall positive EBUS/EUS procedures had similar positive ^{18}F-FDG PET/CT scan. However in 5 (42%) patients EBUS/EUS didn't show a lymph node involvement, as PET had pointed probably due to the false positive related to flogosis.
Conclusion: In LA-NSCLC treated with multimodality therapy, it seems reasonable to perform EBUS/EUS already done to complete the restaging with ^{18}F-FDG PET/CT scan in order to distinguish sensitive from resistant disease for the different prognosis in these two groups of patients. The major benefit of this modality is the possibility to distinguish flogosis to pathological involvement of mediastinum. Supported by GIPO.
Keywords: EBUS, EUS

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P2.305 POSITRON EMISSION TOMOGRAPHY CAN DETECT POSTOPERATIVE RECURRENCE OF THE LUNG CANCER ANTECEDENT TO THE ELEVATION OF SERUM CARCINOEMBRYONIC ANTIGEN

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Background: Lung cancer very often recurs even though curative surgical resection has performed. It is important to manage the patients with postoperative state for lung cancer, but it is still controversial. In this study, we show the usefulness for postoperative screening of lung cancer with positron emission tomography (PET) or PET-computed tomography (PET-CT).
Methods: Forty-eight patients who had shown postoperative relapse of lung cancer were enrolled in this study. They were 32 male and 16 female, and their mean age at surgery was 67.7 years. The pathological tumor stage at surgery was IA in 10 patients, IB in 19, IIA in 1, IIB in 8 and IIIA in 10. They received postoperative surveillance with serum carcinoembryonic antigen (CEA) and PET/PET-CT at 6, 12, 18, 24, 36, 48, 60 months after operation.
Results: Forty-three of 48 patients were pointed out the tumor relapse on scheduled screening, whereas the others were at unscheduled time.
The recurrent site was as follows; 18 of local recurrences (tumor relapse at surgical stump in 4 patients, intra-thoracic lymph node metastasis in 9 and pleural dissemination in 6), and 30 of distant metastases to lung (n=14), bone (n=7), brain (n=4),

liver (n=1) etc.). Recurrent tumors were mainly detected with PET or PET-CT. Only 4 cases elevated serum CEA level prior to detection of PET-CT imaging. Most of the patients whose relapsed tumor was detected by PET/PET-CT still showed normal serum CEA level. The patients without PET/PET-CT abnormalities recurred with pleural dissemination or brain metastasis.

		At recurrence CEA		
		negative*	positive*	
PET/PET-CT	negative	5	4	9
	positive	23	16	39
		28	20	

*CEA positive: over 5.0 ng/ml

Conclusion: Regular screening with PET/PET-CT could spend less time and cost. It could tell us not only possibility of recurrence like serum CEA level do, but also it's location and spread. Then we can treat patients immediately.
We herein show that detection of tumor recurrence by PET/PET-CT is earlier than by serum tumor marker examination. Whole-body PET/PET-CT and brain MRI are recommended for tumor screening. Postoperative PET/PET-CT screening could lead us earlier detection and treatment for recurrent tumor.
Keywords: outpatient, Non small cell lung cancer, Positron Emission tomography

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P2.306 PRELIMINARY STUDY ON THE CORRELATION BETWEEN TUMOR CHARACTERISTICS AND THE FLUORINE-18-FLUORODEOXYGLUCOSE UPTAKE VALUE, CONSIDERING THE VOLUME AND DENSITY OF LUNG TUMORS

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Background: Fluorine-18-fluorodeoxyglucose (FDG)–positron emission tomography (PET)/computed tomography (CT) has been recognized as a useful tool for characterizing pulmonary lesions. Furthermore, the maximum standardized uptake value (SUVmax) on FDG-PET/CT can help in prognosis of non-small cell lung cancer (NSCLC); however, the volume or density of these lesions must be known.

Methods: Between July 2010 and January 2011, 42 patients with primary and metastatic lung cancer underwent radical surgical resection of the lungs at Ehime University Hospital. The imaging sets of 34 of these patients undergoing FDG-PET/CT and multidetector CT at our institute were included in the present study. All patients underwent FDG-PET/CT with a GE Discovery 600 (GE Healthcare, Milwaukee, WI) for clinical indications. Images were analyzed using a GE Advantage Workstation VolumeShare 4 (GE Healthcare, Milwaukee, WI), capable of advanced image processing and manipulation. Modified average SUV was evaluated using the following formula: modified average SUV = average SUV/tumor volume × (CT number + 1000). We considered a lung tumor as an ellipsoid body and calculated the volume of these tumors using the following formula: $(4 \times \pi \times r1 \times r2 \times r3)/3$ (r1 is the width axis radius, r2 is the length axis radius, r3 is the height axis radius). Data were analyzed using Student's t test.
Results: In this patient population, 20 showed pathological Stage I NSCLC, 4 showed Stage II, 4 showed Stage III, and 6 showed lung metastases. Histological diagnosis revealed adenocarcinoma (ad) in 20, squamous cell carcinoma (sq) in 7, pleomorphic carcinoma in 1, and lung metastases in 6. The modified average SUV of pathological Stage I, II, III NSCLC, and lung metastasis was 0.96, 0.11, 1.61, and 3.17, respectively. The modified average SUV of pathological Stage I was significantly higher than that of Stage II ($p = 0.037$) and lower than that of metastasis ($p = 0.002$). However, the modified average SUV of pathological Stage II was significantly lower than that of metastasis ($p = 0.031$). Furthermore, the modified average SUV of ad, sq, and lung metastasis was 1.47, 1.04, and 3.17, respectively. No significant difference was observed between the modified average SUV of ad and sq ($p = 0.414$). However, the modified average SUV of ad was significantly lower than that of metastasis ($p = 0.001$).
Conclusion: SUV is calculated as a ratio of tissue radioactivity concentration at time and injected dose at the time of injection divided by body weight. Therefore, it is necessary to consider tumor volume and density in order to characterize malignant tumors. Studies with a larger number of patients and modalities to estimate tumor volume and density are required to acquire more information regarding tumors detected with FDG-PET/CT.
Keywords: Lung cancer, Positron Emission tomography

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P2.307 FUNCTIONAL IMAGING OF LUNG CANCER USING DUAL ENERGY CT: HOW DOES IODINE RELATED ATTENUATION CORRELATE WITH STANDARDIZED UPTAKE VLAUE OF 18FDG-PET-CT?

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Background: Functional imaging is a promising approach to improve the response assessment of lung cancer after therapy. Dual energy CT is a new CT technique which allows a selective visualization of intravenously injected iodinated contrast media as a surrogate for blood volume in tumor. The purpose of this study was to investigate the correlation between maximum standardized uptake value (SUV_{max}) of ^{18}FDG PET-CT and iodine-related attenuation (IRA) of dual energy CT in patients with lung cancer.
Methods: In a retrospective study 37 patients with lung cancer (27 NSCLC, 10 SCLC, 86 PET-CT positive thoracic lymph nodes (LN)) who underwent both ^{18}FDG PET-CT and DECT were analyzed. While the mean study intervals between ^{18}FDG PET-CT and DECT was 27±31 days, it was ≤21 days in 17 patients. The mean and maximum IRA of DECT was analyzed and correlated to the SUV_{max} of ^{18}FDG PET-CT.
Results: A moderate correlation was found between SUV_{max} and maximum IRA in all tumors (n=37;r=0.507;p=0.025) . A strong correlation wasfound in patients with study intervals ≤21 days (n=17;r=0.768;p=0.017). Analysis of histological subtypes of lung cancer showed a strong correlation between SUV_{max} and maximum IRA in the analysis of all patients with NSCLC (r=0.785;p=0.001) and in patients with NSCLC and study intervals ≤21 days (r=0.876;p=0.024). Thoracic LN showed a moderate correlation between SUV_{max} and maximum IRA in all LN (r=0.570;p=0.047) and those of patients with study intervals ≤21 days (r=0.654;p=0.010).
Conclusion: DECT could serve as a valuable functional imaging test for patients with NSCLC as the IRA of DECTcorrelates with SUV_{max} of ^{18}FDG PET-CT.

Keywords: Functional Imaging, Dual Energy CT, angiogenesis

Poster Session 2 - Imaging Tuesday, 5 July 2011 12:15-14:00

P2.308 AT PERIPHERAL AND CENTRAL LUNG TUMORS, THE IMPORTANCE OF SUV MAX VALUE OF PET-CT AND TUMOR NECROSIS IN SELECTION OF DIAGNOSTIC METHODS

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Background: At Peripheral And Central Lung Tumors, The Importance Of Suv Max Value Of Pet-Ct And Tumor Necrosis In Selection Of Diagnostic Methods
Methods: In this study,we wanted to compare , tissue necrosis and the intensity with the SUV max values at PET-CT in the diagnosis of central and peripheral lung tumors. 45 (88.3%) were male and 6 (11.7%) were female, mean age of 66.59 ± 10.05, 34 (66.7%) peripheral and 17 (33, 3%) central , total of 51 cases with lung tumors , the presence of necrosis and the intensity were compared with SUV max values at PET-CT for the selection of diagnostic methods.
Results: In peripheral tumors ten of them were diagnosed with transthoracic fine-needle aspiration biopsy, 7 cases with bronchial biopsy, 6 cases with bronchial brushing,two cases with bronchial lavage, two cases with mediastinoscopy, three cases with endobronchial biopsy and 4 cases with thoracotomy. In central tumors eight of them were diagnosed with endobronchial biopsy, three cases with bronchial biopsy, one case with bronchial brushing, one case with transbronchial fine needle aspiration biopsy, one case with mediastinoscopy and three cases with thoracotomy. Tumors were evaluated with PET-CT SUV max values and necrosis; in peripheral tumors, 11 of them with central necrosis, 6 of them peripheral necrosis and 3 cases had both central and peripheral necrosis. There was no necrosis in 14 cases and the mean SUV max values of 13.02 ± 6.43. In central tumors, one of them with central necrosis, two of them with peripheral necrosis, and 2 of them had both central and peripheral necrosis, therefore 12

cases had no necrosis and the mean SUV max values of 12.81 ± 5.58. The patients were evaluated in terms of FDG uptake, involvement in 21 cases (41.2%) diffuse, 9 cases (17.6%) non-homogeneous lateral and in 21 cases (41.2%) medial active. There was no statistically significant difference with FDG uptake of tumor type, tumor location and how the diagnosis had demonstrated . (P = 0.078) In peripheral tumors have diagnosed with transthoracic fine-needle aspiration biopsy, if in PET-CT the rates of necrosis were between 25-75%, we can say that the SUV max values were high.

Conclusion: At Lung tumors, tumor localization, is important in obtaining tissue diagnosis. Currently bronchoscopy is preferred as a priority. But the diagnostic rate of bronchoscopy in peripheral tumors, not at the desired level despite new technologies, such as EBUS and superdimension. In addition, the presence of necrosis in tumors by the pathologist makes it difficult to diagnose correctly. For this purpose, we compared taking into account tumor localisations, diagnostic methods, tumor necrosis and tumor the PET-CT SUV max values, and we would like to contribute to the pathologist obtain a more suitable material for the diagnosis. As a result, at peripheral tumors, necrosis was found with a high SUV max values are important. At central tumors, we found that a high SUV max values guiding the diagnosis.

Keywords: necrosis, SUV max, PET-CT

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.309 FOLLOW- UP USING FLUORESCENCE BRONCHOSCOPY FOR THE PATIENTS WITH PHOTODYNAMIC THERAPY TREATED EARLY LUNG CANCER

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Background: Auto fluorescence bronchoscopy (AFB) is a new endoscopic tool that improves visualization of neoplastic changes in the bronchial mucosa. . In this study, we examined the usefulness of autofluorescence bronchoscopy (SAFE-3000) during follow-up of photodynamic therapy (PDT) - treated early central lung cancer by precise histological analysis of the photodynamic therapy (PDT) treated lesions. .

Methods: Between December 1999 and August 2010, 13 patients with 16 centrally located early lung cancer (CLELC) lesions, have been treated by PDT and also been followed - up after the PDT by the auto fluorescence bronchoscopy (SAFE-3000). Fluorescence bronchoscopy was performed between 1 and 60 months after photodynamic therapy. PDT procedures were performed using porfimer sodium or talaporfin sodium and an Excimer Dye Laser or a diode laser system.The total energy of the laser irradiation was 100 J/cm^2, 150 mW/cm^2, and the duration of irradiation was usually 10 to 20 min. Before the PDT, we performed SAFE-3000 with a diode laser (408 nm) to define the base line fluorescence intensity emitted from the tumor. After the PDT, we performed SAFE-3000 to determine the change in the intensity of fluorescence emitted from the tumor as compared with that observed before the PDT. Cytological and histological examinations via fiber optic bronchoscope were performed at 1, 2 and 3 months and thereafter at 3-month intervals in the first year and 6-month intervals after the second years after PDT. The antitumor effect of the initial treatment was evaluated on the basis of the change in the intensity of the fluorescence emitted from the tumor after PDT compared with that observed before the PDT, morphologic appearance, and the findings on histopathologic examination of biopsy specimens. Biopsy specimens were taken from all suspicious and abnormal lesions detected by AF bronchoscopy and WL bronchoscopy.

Results: Of the 16 early carcinomas treated, 14 (87.5%) had complete response (CR), 2 (12.5%) had no response (NR) after initial PDT. Among the 14 carcinomas achieving a CR, 4 (29%) recurred locally from 6 to 12 months after initial PDT. A total of 62 surveillance auto fluorescence bronchoscopies (average; 4.5/ patient) and 47 biopsies (average; 4/ patient) were performed after PDT. The addition of the SAFE-3000 examination to conventional bronchoscopy increased the sensitivity of screening from 69 % to 100%, which yielded a relative sensitivity of 145% with a negative predictive value

of 100%. Out of 14 CR lesions, 9 lesions finally reverted to normal fluorescence. CR cases that did not show normal fluorescence were relapsed cases or a patient with complete response whose treated lesion showed fibrosis in the sub mucosa. Histopathological finding of the complete response sites which demonstrated temporal fluorescent defect consisted of inflammatory lesions, goblet cell hyperplasia, basal cell hyperplasia, squamous metaplasia or dysplasia.
Conclusion: Our results confirm that SAFE-3000 allows accurate assessment of the quality and efficacy of PDT.
Keywords: photodynamic therapy, Fluorescence bronchoscopy, Lung cancer

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.310 ENDOBRONCHIAL ULTRASONOGRAPHY WITH A GUIDE SHEATH (EBUS-GS) FOR THE DIAGNOSIS OF PERIPHERAL PULMONARY LESIONS WITH CAVITATION.

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Background: Transbronchial biopsy (TBB) from cavitary lesions may induce the dissemination of the pathogens or tumor cells, which is generally regarded as contraindication. It is important to diagnose cavitary lesions safely and less invasively. TBB using endobronchial ultrasonography with a guide sheath (EBUS-GS) may be one of promising methods to overcome this problem, because of less bleeding by wedging the GS in the target bronchus. The aim of this study was to assess the usefulness of EBUS-GS for the diagnosis of peripheral pulmonary lesions (PPLs) with cavitation.
Methods: We retrospectively reviewed 57 consecutive patients with 59 cavitary PPLs who underwent TBB using EBUS-GS between August 2003 and January 2011 at our institute.
Results: The mean diameter of cavitary lesions was 28 mm. Fifty-nine PPLs with cavitation consisted of 40 malignant lesions (34 primary lung cancer, and 6 other diseases) and 17 benign lesions (6 nontuberculous mycobacteriosis, and 2 tuberculosis ,and 9 other diseases), and 2 lesions without diagnosis. A definitive diagnosis was established by TBB using EBUS-GS in 39 lesions (66.1%) malignant lesions,26/40 (65.0%) and benign lesions,13/17 (76.5%). Forty-one cases in which the EBUS probe was positioned within the lesions had a higher diagnostic yield (82.9%) than 9 cases in which the probe was positioned adjacent to the lesions (55.6%) or 9 cases in which the probe was outside of the lesions (0%) There were no major complications ,including dissemination of the pathogens or tumor cells.
Conclusion: EBUS-GS is a reliable and safety method for the diagnosis of PPLs with cavitation.
Keywords: bronchoscopy, cavitary lesion

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Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.311 NARROW BAND IMAGINING (NBI) VCIDEOBRONCHOSCOPY IN DETECTION OF PREMALIGNANT BRONCHIAL LESIONS

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Background: Narrow band imaging (NBI) is one of the newest image enhancement technologies investigated for the use in diagnostic bronchoscopy. It is designed for detection of abnormal submucosal blood vessels. The major aim of this study was to investigate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of WLB and NBI in detection of premalignant bronchial lesions.
Methods: This was a prospective, randomized trial that included 88 patients scheduled for routine bronchoscopy. Major indications included: radiological suspicion for lung cancer, additional evaluation of known lung cancer, follow up after surgical treatment, positive sputum cytology, and prolonged cough. Patients were randomized in two

groups, first group was examined by white light videobronchoscopy (WLB) alone, and group two was examined by combination of WLB and NBI. Squamous metaplasia, mild, moderate, severe dysplasia and CIS were regarded as positive results (premalignant lesions). In each patient at least one, but no more than three biopsies were taken from places designated as visually pathological, and at least one biopsy was taken from normal mucosa. We were using EVIS LUCERA SPECTRUM video processor, and BF T160 (Olympus Co.) videobronchoscope.
Results: There were 34 males and 9 females in group one. Average age was 54 ±14 years. Sensitivity, specificity, PPV and NPV of WLB (group I) in detection of precancerous lesions were 55.6%, 55%, 41.7% and 68.2%, respectively. Corresponding values for metaplasia were 33.3%, 55%, 39% and 93.8%; for mild dysplasia 53.3%, 55%, 14%, 89.6%, respectively. Corresponding values for moderate dysplasia were 58.3%, 55%, 12.5%, 92.3%, respectively, and for severe dysplasia 60%, 55%, 26.9% and 83.3%, respectively. In group two there was 35 males and 10 female patients, average age 57±12. Sensitivity, specificity, PPV and NPV for WLB+NBI in detection of premalignant lesions were 75%, 85.9%, 86.7% and 73.7% respectively. Corresponding values for sensitivity, specificity, PPV and NPV of NBI in detection of each premalignant lesion were given in table 1.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Metaplasia	75	85.9	42.9	96.1
Mild dysplasia	52.2	85.9	50	86.9
Moderate dysplasia	78.4	85.9	70.7	90.1
Severe dysplasia	87.5	85.9	70	94.8

Conclusion: NBI showed higher sensitivity and specificity for detection of premalignant lesions than WLB alone. Further studies are necessary to investigate the role and potential of this technology in detection of premalignant bronchial lesions.
Keywords: narrow band imaging, Lung cancer, interventional pulmonology, bronchoscopy

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P2.312 CLINICAL PROGNOSTIC FACTORS FOR COMPLICATIONS FOLLOWING ND:YAG LASER RESECTION OF CENTRAL, ADVANCED STAGE LUNG CANCER

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Background: Nd:YAG laser resection is one of the most established interventional pulmonology techniques for immediate desobstruction of malignant central airway obstruction (CAO). Major aim of this study was to investigate complications rate and identify clinical risk factors for complications in patients with advanced lung cancer.
Methods: This was a retrospective analysis of 464 laser resections performed at our institution from January 2005 to December 2009. Complications after laser resection were defined as: severe hypoxemia, global respiratory failure, arrhythmia requiring treatment, haemoptysis, pneumothorax, pneumomediastinum, pulmonary edema, trachea-esophageal fistulae and death. Risk factors were defined as: acute myocardial infarction within 6 months before treatment, hypertension, chronic arrhythmia, chronic obstructive pulmonary disease (COPD), stabilized cardiomyopathy, previous external beam radiotherapy, previous chemotherapy and previous interventional pulmonology treatment.
Results: There was 76.1% male and 23.9% female patients in the study, 76.5% were current smokers, 17.2 former smokers and 6.3% of non smokers. Majority of patients had squamous cell lung cancer (70%), small cell lung cancer was identified in 18.3%, adenocarcinoma in 3.4% and metastases from lung primary in 8.2%. Overall complication rate was 8.4%. Statistically significant risk factors were: age (p=0.001), current smoking status (p=0.012), arterial hypertension (p<0.000), chronic arrhythmia (p=0.034), COPD (p<0.000), and stabilized cardiomyopathy (p<0.000). Independent clinical risk factors were age over 60 years (p=0.026), arterial hypertension (p<0.000), COPD (p<0.000) and smoking over 60 pack years (p=0.012).
Conclusion: Closer monitoring of patients with identified risk factors is advisable prior and

immediately after laser resection. In order to avoid or minimize complications special attention should be directed towards patients who are current smokers (over 60 pack years), over 60 years of age, with arterial hypertension or COPD.
Keywords: Lung cancer, Nd:YAG laser resection, interventional pulmonology, bronchoscopy

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.313 IMPACT OF COMBINED PET-CT AND EBUS-TBNA ON STAGING OF PATIENTS WITH SUSPECTED LUNG CANCER

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Background: Endobronchial unltrasound with transbronchial needle aspiration (EBUS-TBNA) has been proposed as a safe, less-invasive approach to mediastinoscopy to evaluate possible mediastinal lymph node involvement in patients with lung cancer. Herein, we evaluated the impact and predictive value of EBUS-TBNA in lung cancer patients with radiologically suspected mediastinal metastatic lymph nodes in the Positron-Emission-Tomograpgie combined with CT scan (PET-CT).
Methods: This study is a single-institutional retrospective review of cases with suspected or confirmed lung cancer undergoing mediastinal staging with PET-CT followed by mediastinoscopy/surgery after negative evaluation via EBUS-TBNA in the year 2010.
Results: A total of 118 patients underwent EBUS-TBNA after PET-CT during the study period. Seventy (59.4%) patients were radiologically N2/3 positive in the PET-CT, in 32 (46%) cases radiologically positive findings were confirmed via EBUS-TBNA. Thirty-eight (55%) EBUS-TBNA negative patients were further investigated either by subsequent mediastinoscopy (n=20) or primary surgery (n=17). Mediastinoscopy or surgery found metastatic nodes in 5 and 4 patients, respectively, for a patient-specific negative predictive value of EBUS-TBNA of 73% (95% CI, 56% to 89%) with a sensitivity of 77.5% and a specificity of 100%. Twenty-four (34%) patients predicted with mediastinal involvement in the PET-CT were actually without mediastinal metastatic nodes. Evaluated average lymph node size was 10mm.
Conclusion: Endobronchial unltrasound can effectively be used to evaluate mediastinal lymph node involvement in patients with lung cancer and PET-CT positive findings. However, in this early experience more than 30% of patients with predicted mediastinal lymph node involevement in the PET-CT were pathologically negative in the EBUS-TBNA for position N2/3 challenging the exclusive use of the PET-CT and demanding cytological/histological evaluation of the mediastial nodes to ensure appropriate therapy.
Keywords: PET-CT, EBUS-TBNA, NSCLC, Staging

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Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.314 SAFE BRNO EXPERIENCE

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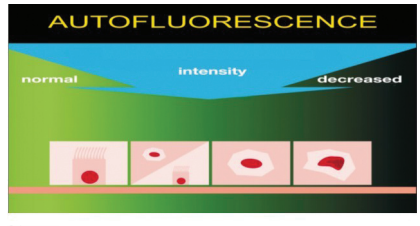
Background: Description of the morphological features of bronchial carcinogenesis (Scheme 1) in vivo by use of autofluorescence bronchoscopy.



Methods: Yearly repeated bronchoscopy in persons (n=361) with high risk of lung cancer by Autofluorescence endoscopy SAFE-1000 Pentax

during dozen years (1999-2010). Both white light bronchoscopy (WLB) and autofluorescence (AFB) mode are feasible at the same investigation. Hematoxylin-and-eosin histopathology and immunohistochemistry p21 and ki67 were used.
Results: Eleven morphological units of bronchial premalignancy are defined. They are divided into two classes: Superficial Spreading Lesion – 1/ invisible islet and 2/ spot, 3/ redness islet and 4/ spot, 5/ spider, 6/ swollen and thickened mucosal fold, 7/ granular, 8/ mixed lesion; and Protruding Lesion – 9/ nodular, 10/ wart-like 11/ polypoid. Superficial spreading lesions are of high variability. Roughening in WLB and arenaceous depiction at AFB mode of the surface of the lesion represent evolving risk of malignant transformation. Irregular margin of the lesion (star shaped; spider) is important sign of advanced lesion. Superficial spreading lesions with distinct limitation (border) represent by histopathology early premalignant processes. Protruding lesion with smooth surface in WLB and low decreased autofluorescence signal output is not risky; Protruding lesion with smooth surface and deep decreased autofluorescence characteristic is at risk of malignant development or it is malignant. Wart-like surface of the protruding lesion represents advanced lesion at risk. The cogency of overdiagnosis and underdiagnosis issue of every particular lesion in the course of time were studied. There are defined three classes of the lesions regardless of their superficial spreading or protruding nature in general: 1/ Quiet – oncologically unimportant, in the course of time disappearing lesion 2/ Ambiguous – representing biologically uncertain unit inviting follow-up endeavour, and 3/ Persistent – proliferative lesion at risk needed particular attention from the clinical point of view.
Conclusion: To detect early bronchial premalignancy low output ilumination intensity and mild autofluorescence signal amplification are needed. A part of advanced premalignant bronchial lesions at risk is recognizable by naked eye.
Keyword: Autofluorescence; Bronchoscopy; Carcinogenesis; Morphology

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.315 NAVIGATED BRONCHOSCOPY – A RESEARCH PLATFORM USING INTRAOPERATIVE CONE BEAM CT

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Background: Bronchoscopy has limitations in diagnosing pulmonary lesions, and the bronchoscopist must rely on preoperative x-ray or CT evaluations, and inadequate peroperative fluoroscopy guided maneuvers (small, sparse, peripheral opacities often visible only in one plane). Preoperative imaging based navigation systems also have limitations due to lung movement caused by endobronchial instruments and respiration. Thus, we are developing a navigation system to improve targeting of lung lesions and to reduce repeated examinations.
Methods: The navigation system is based on electromagnetic (EM) tracking, navigation and visualization software, and intraoperative cone beam CT (CBCT) images, in which the position of the bronchoscope, biopsy equipment and lung lesions are presented in real-time to the bronchoscopist. The bronchoscopic track is displayed in volume rendering view or orthogonal slices selected from the images by the position and orientation of the bronchoscope tip. The set-up was designed to evaluate feasibility and accuracy in a pig model that closely resembles the human lung anatomy. Three different experiments were performed: 1) Evaluating the ability of CBCT to detect foreign bodies of different x-ray opacity, and act as basis for navigated bronchoscopy. Four foreign objects of different materials were placed in different lung segments; a plastic tube, a glass ball, a wooden ball and a metal ring; 2) Pinpointing the foreign bodies with a tracked catheter advanced all the way to the foreign objects; and 3) Influence of CBCT equipment on the EM tracking field. In experiment 3, the C-arm was moved continuously, from a position approximately 1 m outside the electromagnetic field towards its center.
Results: Experiment 1 showed that CBCT was superior to fluoroscopy, providing more detailed anatomical information. The plastic tube and wood ball were not recognizable in fluoroscopy or the

initial CBCT images, but unlike fluoroscopy later CBTC scans could locate them on indirect signs as they caused atelectasis (lung segment collapse). In experiment 2, CBCT confirmed the position of the tracked catheter tip next to the foreign objects in correspondence with the navigation system and visual bronchoscopic inspection. In experiment 3, with the C-arm turned on and approximately 1 m away from the target, we observed an accuracy comparable to those stated by the vendor of the tracking system, i.e. less than 0.5 mm. We saw an increasing error as the C-arm approached the tracking field, and the positions started to drift in a sine-wave fashion. The jitter did not increase, and the readings where not randomly distributed, as one maybe would have expected if the EM field was corrupted. We measured a range of drift up to ~13 mm in one of the sensors. We also noticed that the positional readings did not drift around their "true" position, but were shifted in all three planes.
Conclusion: The live animal navigated bronchoscopy platform yielded a high diagnostic accuracy and feasibility, serving as a valuable tool for accurate diagnostic investigation and research purposes. But care must be taken when performing navigation with the C-arm in the field.
Keywords: navigation, bronchoscopy, tracking, cone beam CT

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.316 ENDOBRONCHIAL ULTRASONOGRAPHY FOR PERIPHERAL LUNG MALIGNANCIES; ANALYSIS FOR THE DETERMINANT OF SUCCESSFUL DIAGNOSIS

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Background: We use endobronchial ultrasonography (EBUS) for the cases anticipated difficulties in the diagnosis by usual X-ray fluoroscopy guided bronchoscopic examinations. We evaluated the ability of EBUS to diagnose the peripheral lung malignancies and analyzed the cases which could be diagnosed and the cases which couldn't be diagnosed. Then we considered the factors which provided difficulties in diagnosis by EBUS.
Methods: From January 2009 to November 2010, 45 patients had undergone EBUS in our hospital. VBN was used for 33 of the 45 patients. EBUS and virtual bronchoscopic navigation (VBN) were used at physicians' discretion. An ultrasound probe (UM-S20-17S; OLYMPUS), a bronchoscopy (BF-P260F; OLYMPUS), a VBN software (Bf-Navi; OLYMPUS) were used. Statistical software (SPSS version 16) was used for statistical analysis, and $p < 0.05$ was considered statistically significant.
Results: Twenty-four of the 45 patients were diagnosed malignancies (21; primary lung cancer, 2; metastatic lung cancer, 1; malignant lymphoma), two were diagnosed benign disease (1; non-tuberculous mycobacteriosis, 1; organizing pneumonia) and remained 19 weren't diagnosed with this procedure. Finally, 36 were diagnosed malignancies and nine were diagnosed benign disease by this or other procedures. We analyzed the 36 patients who diagnosed malignancies to assess the diagnostic yield for peripheral lung malignancies. Diagnostic yield of malignancy was 66.7% (24/36). Diagnostic yields according to the location of the ultrasound probe were 87% (20/23) of "within", 36.4% (4/10) of "adjacent to", and 0% (0/3) of undetectable lesions by EBUS. Diagnostic yields according to diameter of the lesion were 0%(0/1) of <10mm, 61.5%(8/13) of >=10mm to <20mm, 66.7%(10/15) of >=20mm to <30mm, 85.7%(6/7) of >=30mm. According to the location of the lesion, diagnostic yield was 14.3% (1/7) of lower lobe superior segment and 79.3% (23/29) of other locations. By multiple logistic regression analysis including the location of the ultrasound probe, diameter of the lesion and the anatomical location of the lesion, the location of the ultrasound probe was the independent determinant of successful diagnosis ($P = 0.002$). Twenty of the 23 patients whose lesions in which the probe was located "within" could be diagnosed but remained three patients could not be diagnosed. These three lesions located lower lobe basal segment. We considered it was attributed to respiratory displacement. Diagnostic yields of lesions undetectable by X-ray fluoroscopy was 50% (4/8). There were no complications with the patients who had undergone EBUS.
Conclusion: EBUS provided the diagnosis to the peripheral lung lesions which were difficult to be

diagnosed by usual X-ray fluoroscopy and expanded indication of bronchoscopic examinations. The location of the ultrasound probe was the independent determinant of successful diagnosis.
Keywords: EBUS, bronchoscopy, peripheral lung lesion, Lung cancer

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.317 NARROW BAND IMAGING IMPROVES PREOPERATIVE FLUORESCENCE ASSESSMENT OF UPPER AND LOWER AIRWAYS IN HEAD AND NECK CANCER PATIENTS

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Background: Autofluorescence (AF) has been used to improve the detection of preneoplastic lesions of the bronchus and the head and neck (H&N). It is known to have a high false positive rate. Narrow band imaging (NBI) has better specificity but reportedly a poorer sensitivity. We hypothesised that combined AF and NBI inspection would improve overall specificity without impacting sensitivity.
Aim: To detect additional lesions to the primary head and neck cancer and to determine how these impacted on overall management.
Methods: H&N cancer patients had white light (WL), AF and NBI inspection of the upper aerodigestive tract and tracheobronchial tree at panendoscopy. In the H&N region, AF and NBI inspection was performed unblinded. AF and NBI bronchoscopy of the tracheobronchial tree were done by two different bronchoscopists with findings reported independently. Detected lesions were graded as per established scoring systems and lesions considered abnormal by any imaging modality were biopsied. For statistical analysis, histological findings of moderate dysplasia or worse were considered significant. Results are reported on a per lesion basis.
Results: There were a total of 74 patients in this series. In the H&N region there were 27 known primary squamous cell carcinomas detected and these were excluded from final analysis.
In the H&N there were 22 significant lesions detected, and in the bronchus there were 17 significant lesions. The relatives sensitivities and specificities of white light, autofluorescence and narrow band imaging are summarized in the attached table. 11/74 (15%) patients had additional findings detected by AF and NBI which impacted on definitive management. The 17 endobronchial lesions of moderate dysplasia or worse are currently undergoing bronchoscopic surveillance.

Head and neck region	White light	Autofluorescence	Narrow band imaging
True Positive	7/22 (32%)	21/22 (95%)	21/22 (95%)
False Positive	1/13 (8%)	11/13 (85%)	3/13 (23%)
Sensitivity	32% (95% CI, 0.16-0.53)	95% (95% CI, 0.78-0.99)	95% (95% CI, 0.78-0.99)
Specificity	92% (95% CI 0.67-0.98)	15% (95% CI, 0.04-0.42)	77% (95% CI, 0.45-0.88)
Bronchus	White light	Autofluorescence	Narrow band imaging
True positive	2/17 (12%)	13/17 (76%)	15/17 (88%)
False Positive	2/41 (5%)	20/41 (49%)	7/41 (17%)
Sensitivity	12% (95% CI, 0.03-34%)	76% (95% CI, 41%-83%)	88% (95% CI, 66%-97%)
Specificity	95% (95% CI, 0.84-0.99)	51% (95% CI, 0.36-0.66)	83% (95% CI, 0.69-0.91)

Conclusion: AF and NBI inspection adds to WL evaluation in these patients. NBI improves specificity in both regions and can influence definitive management.
Keywords: Autofluorescence, narrow band imaging, Preneoplasia, Early central lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.318 MAJOR PULMONARY RESECTION AFTER INDUCTION CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CARCINOMA.

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Background: Locally advanced Non-Small-Cell Lung Cancer is a heterogeneous group of disease with stages IIIA and IIIB. The optimal

treatment for stages IIIA/B (N2/3) NSCLC remains controversial. Previous trials have shown efficacy of various treatments for different stages. Induction chemotherapy or chemoradiotherapy trials show that both approaches in the neoadjuvant setting are feasible. An outcome following induction therapy depends on residual mediastinal lymph nodes involvement by carcinoma. Surgery as initial therapy is beneficial for patients with T3, N1 or T3-4, N0-1 disease (T4 due to satellite lesion/s within the same lobe/lung). Lobectomy may be generally safely performed following induction therapy, while pneumonectomy or lobectomy/bilobectomy with chest wall resection/reconstraction may carry a high and possibly unacceptable rate of perioperative mortality.

Methods: 9 patients (mean age - 71.9 years; 8 male and 1 female), all smokers, with stages IIIA/B Lung Carcinoma were treated at our Hospital. All patients were preoperatively diagnosed (5 adenocarcinomas, 4 squamous cell carcinomas); 6 of them by TTNA, 2 by Bronchoscopy and 1 by Mediastinoscopy and staged by CT of the chest, PET-CT and/or Mediastinoscopy. Patients with T3/N0/1 disease (stages IIB/IIIA) were considered for curative resection. Patients with T3/T4,N2/3 disease (stages IIIA/IIIB) were considered for neoadjuvant chemotherapy according to tumor pathology. Postchemotherapy the patients restaged by CT of the chest and/or PET-CT or mediastinoscopy (in IIIB disease) and considered for curative resections.

Results: One patient with T3N0 adenocarcinoma underwent Mediastinoscopy, that was negative, and curative RUL with En-Block Chest Wall (2-5 ribs) & T3-T5 transverse processes resection. Other 8 patients preoperative stages were: T1N2 – 1 patient, T2N2 – 2 patients, T2N3 – 1 patient, T3N2 – 2 patients, T4N1 – 1 patient and T4N2 – 1 patient. They underwent neoadjuvant chemotherapy according to the Institutional protocol (4 patients with adenocarcinoma received course of Olimpta and Platinum and 4 patients with squamous cell carcinoma - Gemzar with Platinum). Curative resections that done after chemotherapy were: 1 Right Pneumonectomy, 1 RML/RLL Bilobectomy with Chest Wall (7-9 ribs) resection and reconstruction , 1 LUL Lobectomy with En-Block Chest Wall (4-6 ribs) resection, 2 LLL and LUL Lobectomies with segmentectomies of adjacent lobe (superior segment of LUL and posterior segment of LLL) and 3 Lobectomies (RUL,RLL,LLL). Postoperatively 7 from 8 patients were downstaged to: T1N0 – 3 patients, T2N0 – 2 patients, T3N0 – 1 patient and in 1 were not found residual tumor. Eighth patient not changed the stage and stayed T3N2. The postoperative complications were: broncho-pleural fistula with empyema – 1 patient, empyema – 1 patient, air leak – 2 patients, chylothorax - 1 patient, lobar atelectasis – 1 patient. Mean hospital stay was 21.1 days (range 6-107 days).

Conclusion: The treatment strategy for stage IIIA/IIIB Non-Small Cell Lung Carcinoma should involve a multimodality approach. Combined modality therapy by induction chemotherapy and surgery may be beneficial in selected cases, with low morbidity in patients that underwent only lobectomy and high morbidity in patients after pneumonectomy and lobectomies or bilobectomies with chest wall resection or reconstraction.

Keywords: Non-Small Cell Lung Carcinoma, Induction Chemotherapy, Lobectomy, Chest Wall Resection, Pneumonectomy, Reconstraction, Neoadjuvant

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P2.319 ENDOBRONCHIAL ULTRASOUND (EBUS) GUIDED BRONCHOSCOPY FOR THE DIAGNOSIS OF PERIPHERAL LUNG CANCER LESIONS

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Background: Lung cancer presents as peripheral lesions in 25-30% of the cases. Endoscopic diagnosis is essential for the prevention of futile thoracotomies. Chest physicians usually perform bronchoscopy under fluoroscopy guidance in an attempt to sample a peripheral solitary pulmonary nodule (SPN). Yields range from 25 to 58% for lesions <2 cm, and 60 to 83% for lesions > 2 cm. For a successful biopsy, therefore, knowledge of the relationship of the target lesion to the airway is essential. Conventional diagnostic procedures have limitations in availability and results. The major aim of this study was to determine sensitivity of EBUS guided transbronchial biopsy (TBB), catheter biopsy (CB) and brush-biopsy.

Methods: In this study we prospectively evaluated sensitivity of EBUS guided TBB, CB and brush-biopsy in diagnosis of peripheral lung lesions. We evaluated 48 patients, who met all of the inclusion criteria, not having any exclusion. The radial EBUS was carried out via 20 MHz probe (Km-BS20-26R). After identification and localization of peripheral lesion, TBB, CB or brush-biopsy were carried out in order to establish patohistological diagnosis.
Results: Radial EBUS guided sampling was performed in 48 patients with peripheral lesions (14-58 mm measured on CT findings). In 32 patients lesion was visualized by radial probe. The histopathological and cytological diagnosis was established in 23 patients (malignancy in 15 pts, benign tumor in 1 pts or inflammation in 6 pts). Transbronchial biopsy shows the highest sensitivity (0.77) when compared to the other two sampling procedures - catheter biopsy (0.27) and brush biopsy (0.36).
Conclusion: Peripheral lung cancer lesions can be successfully diagnosed using radial ultrasound probe without need for fluoroscopy or CT guidance. TBB exceeds in sensitivity the other sampling procedures.
Keywords: Endobronchial Ultrasound, bronchoscopy, interventional pulmonology, Solitary pulmonary nodules (SPN)

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P2.320 COMPARISON OF 21 GAUGE AND 22-GAUGE ASPIRATION NEEDLE DURING ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION: A RANDOMISED TRIAL

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Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a safe minimally invasive diagnostic modality. The quality and the quantity of EBUS-TBNA aspirates depends on puncture technique and size of the needle used. A dedicated 22-gauge (G) needle is typically used for EBUS-TBNA. A new EBUS-TBNA 21 G needle has recently been introduced to improve the quantity and quality of the biopsy sample. The efficacy of the larger gauge needle has been reported in a study from Nakajima (Respirology (2011) 16, 90-94). This trial compared the diagnostic yield from both needles in same lymph notes. The study presented was designed as prospective comparison of both 22G and 21G biopsy needles in two independent groups.
Methods: Between July and October 2010, 60 patients randomly divided in 2 groups underwent EBUS-TBNA in our clinic. 31 patients obtained diagnostic assignment with a 21 G needle and 29 patients using a 22 G needle. The dedicated 22 G and 21 G needles (Olympus, NA-201SX-4021 and N-201SX-4022) where used for the complete diagnostic assay of each patient. The histological and cytological findings where obtained by the same experienced pathologist without any knowledge about the type of needle used. Data was analysed by descriptive statistics with respect to quality of histologic/cytologic material in tumour tissue and/or lymph-node-tissue.
Results: The distribution of diagnoses was comparable in both groups (21 G needle/22 G needle) with respect to lung cancer (23/19), other malignant tumors (2/6), Sarcoidosis and Tbc (2/2). Inflammatory changes were distributed evenly (3/3). In both groups we found coequal statements of all sample portions (1,2 or 3 per stage). In the 21G-needle group a diagnosis could be obtained in all cases (31/31) either by histology or cytology. In the 22G-needle group the material obtained was not sufficient for a pathology diagnosis in 5 of 29 cases (p=0,022 in fishers exact test). Including only the cytological findings, in the performance of both needles in specimen quality no difference could be found. Blood contamination was present in both groups coequally without significant differences: 21G/22G: 35%/28% in cytological and 33%/30% in histological findings.
Conclusion: We evaluated the difference of the cytopathological sample quality of the samples between the use of 21G and 22G EBUS-TBNA needles in two randomised groups (31/29 patients). Our data suggest that the cytological and histological structure of the samples obtained by a 21G needle may produce better results. Due to the potential impact on the diagnostic yield of EBUS depending on the needle used our results should be confirmed in a larger series.
Keywords: histology/cytology, bronchoscopy, untrasound-guided transbronchial needle aspiration, Lung cancer

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P2.321 SINGLE CENTRE EXPERIENCE IN TUNNELLED PLEURAL AND ABDOMINAL CHEST DRAIN INSERTION

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Background: BTS guideline 2010 outlines use of tunnelled indwelling pleural catheter (TIPC) as second line management in recurrent malignant pleural effusion (MPE) and first line management in MPE with an underlying trapped lung in patients with an expected life expectancy of more than one month. To assess the indications, practice of TIPC insertions in our institute and compare with previous studies.
Methods: Retrospective study of 50 patients. Data collected from the Radiology Information System (RIS), case notes, questionnaires and telephonically.
Results: Divided into demographic data, economic analysis and quality of life analysis. A) Demographic data: 50 patients (29 female, 21 male) Average age 62.5years, range 35-89years 28 for pleural effusion, 22 for ascites, 27 of 28 procedures for pleural effusion were under ultrasound guidance, 1 under CT guidance 11 complications. The most common complication was asymptomatic pneumothorax in 7 patients. Other complications included displacement/ migration of drain, loculation, infection and pyopneumothorax. TIPC removed in 5 patients due to successful complete drainage of fluid Average lifespan following drain insertion 52.6 days. 5 patients were alive with drain in situ at the time of data collection. B) Economic analysis: Cost of TIPC insertion including that of the kit was calculated at £262 and compared with repeated routine chest drain insertions. 15 patients had a total of 22 drains, costing £774. 9 patients had failed pleurodesis. 7 patients had a total of 9 aspirations. TIPC found to be more cost effective in the short term. However, long term economics needs to be considered in view of requirement for home care support. C) Quality of life issues: Difficulties in obtaining the data outlined. Of the notes available, 15 patients improved following the tunnelled drain. 8 patients did not show improvement and were readmitted for other reasons. 1 patient died the day after TIPC insertion.
Conclusion: Post TIPC complication rate in our centre was comparable with the existing evidence. TIPC is cost effective in the short term. TIPC is a good alternative to repeated chest drainage and should be considered as first line management in cases of recurrent MPE.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.322 FACTORS ASSOCIATED TO INFORMATIVE EBUS TBNA PROCEDURES. RESULTS OF A PROSPECTIVE MULTICENTER STUDY ON 198 PATIENTS (EVIEPEB STUDY)

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Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is increasingly being performed for the evaluation of the mediastinal staging in NSCLC.
The objective of this study is to identify the factors associated to the informative procedures in a multicenter prospective French study (EVIEPEB; ClinicalTrial.gov identifier NCT00960271).
Methods: Patients with mediastinal lymph nodes underwent EBUS-TBNA in 19 French centers as part of a prospective study. All the procedures were performed by the same operator in each center. The procedure was considered informative if lymphocytes were observed on the cytological preparation. A minimum of 9 out of 10 consecutive procedures were required to be informative in each center to meet the quality criteria of the study. The size and location of the lymph node, the number of needle aspirations per node, and the anesthesia procedure were compared between informative and non-informative cases.
Results: 18 of the 19 centers met the quality criteria over a one-year period, and 198 patients were included. No serious adverse event was reported. 325 cytological samples were analyzed. The endoscopic procedures were informative in 88% of the patients [min: 40% - max: 100%] and in 80% of the sampled stations (262 out of 325). Informative EBUS-TBNA were associated to a larger diameter of the lymph node (mean: 15.7 vs. 13.6 mm; p=0.0012), and to a greater number of needle aspirations per node (median: 3 vs. 2; p<0.001). The station site and the anesthesia procedure were not different between informative and non-informative procedures.
Conclusion: Learning curve of EBUS-TBNA to access a 90% rentability can be reached shortly. High rate of informative procedures is associated to a mean lymph node size of 15 mm and to a minimal number of 3 punctures per site. Rentability of the method does not seem to be dependent on the anesthesia procedure or on the node location.

Supported by a grant from INCa (Institut National du Cancer).
Keywords: EBUS-TBNA, Endoscopy, Diagnostic procedure, Mediastinal staging

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P2.323 DIAGNOSIS ACCURACY OF EBUS-FNA IN THE RESTAGING OF MEDIASTINAL DISEASE OF THE PATIENTS WITH NOT SMALL CELL LUNG CANCER (NSCLC).

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Background: Nodal down-staging after induction treatment in patients with resecable stageIII-N2 NSCLC is the best prognostic factor for proceeding with surgery. The EBUS is expected to be a good test used to study the mediastinal nodal disease after the induction treatment. **AIM:** To compare the diagnostic yield of EBUS and PET-CT in the mediastinal restaging of patients with stage IIIA-N2 NSCLC.
Methods:
We reviewed all the patients stage IIIA NSCLC with involvement of one mediastinal lymph node station, who had made neoadjuvant therapy between July 2009 and September 2010. From six patients who met these criteria, we selected the ones in which staging and restaging of the mediastinum was performed using both, PET-CT and EBUS, with subsequent histological confirmation for those who were confirmed negative. Data were collected from the PET-CT and the EBUS, performed for initial staging and response assessment.
Results: Four male smokers with NSCLC were selected for this study. They had a mean age of 62.2 years old. The cytological diagnosis in three of them was adenocarcinoma and for the other one was squamous cell carcinoma. All of them were treated with chemotherapy (2 cycles of cisplatin/etoposide) and 50 Gy of radiotherapy. Five nodal stations were studied, being two of them from the same patient. The attached table shows the nodal stations studied, the SUV values after the neoadjuvant treatment, the degree of metabolic response according to the

EORTC and the treatment after the restaging. PET-CT from one of the patients showed complete metabolic response (CMR), which was later confirmed by surgery (lobectomy). PET-CT from two of the patients showed partial metabolic response (PMR), which was confirmed by EBUS (positive cytology) only in one of them, the other one had a negative cytology result not confirmed surgically. PET-CT from one of the patients showed stable metabolic disease (SMD) which was confirmed by EBUS. PET-CT showed progressive metabolic disease (PMD) in one of the patients, which was confirmed by EBUS. All the patients who had persistent disease, completed afterwards a total dose of radiotherapy of 70 Gy and received 2 cycles of chemotherapy.

Adenopathy	Pthological Anatomy	RESTAGING PET result		EBUS restaging	Further treatment	Surgical treatment
		Decrease FDG uptake (%)	Metabolic response			
8	ADK	-100%	CMR	Negative	Surgery	Negative
7	ADK	- 82%	PMR	Negative	QT+RT	NA
4L	ESC	-69%	PMR	Positive	QT+RT	NA
4R	ADK	0%	SMD	Positive	QT+RT	NA
4R	ADK	>100%	PMD	Positive	QT+RT	NA

Conclusion: Although changes in mediastinal PET-CT uptake show high concordance with EBUS, pathological confirmation is still superior and therefore necessary. Echoendoscopy (EBUS and/or EUS) is the choice test for mediastinal restaging.
Keywords: Lung cancer, Mediastinal restaging, EBUS-FNA

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P2.324 THE INFLUENCE ON LUNG SEGMENT AND TUMOR MOVEMENT BY BRONCHOSCOPIC INSTRUMENTS – IMPACT ON NAVIGATED BRONCHOSCOPY

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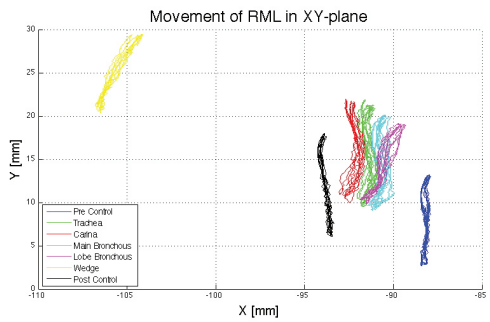
Background: Developing a platform for navigated bronchoscopy, we have suspected that the bronchoscope influences the movement of the lung, especially the adjacent segments, changing the position and movement pattern. We therefore wanted to measure to what extent instruments like the bronchoscope influences the target movement during respiration.
Methods: Using a novel method, balloon catheters with electromagnetic sensors were placed in the right lung of a mechanically ventilated live pig, in the periphery of the lower, middle (RML) and accessory upper lobe. The movement of the lung was recorded while the bronchoscope was advanced stepwise towards the sensor in the middle lobe, ending in a "wedge" position, where it fills out the diameter and jams. The sensors sense their position in an electromagnetic field set up by an external transmitter, with a precision of ~0.5 mm.
Results: The bronchoscope did not affect lung segment movement significantly while positioned in trachea, main bronchus or lobe bronchus. When placed in a wedge position, the bronchoscope caused the following, more pronounced in the nearest segment : 1) the adjacent lung segments were displaced; 2) first displaced, the respiratory movement decreased, and 3) the direction of respiratory movement changed (see figure).



Conclusion: Using our novel live animal model, we succeeded demonstrating that the bronchoscope caused major changes in lung segment movement when it was moved as close to the target as possible. All changes appeared in a pattern and with a magnitude implicating clinical significance for navigated bronchoscopy. Care must be taken when navigating based on preoperative images.
Keywords: lung movement, tracking, bronchoscopy, navi

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P2.325 ACCURACY OF ELECTROMAGNETIC TRACKING IN NAVIGATED BRONCHOSCOPY WITH A PROTOTYPE FIELD GENERATOR IN AN INTERVENTIONAL OR SETTING

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Background: We have studied the accuracy and robustness of a new prototype window field generator (WFG), in an interventional radiology suite with a robot cone beam CT (rCBCT). The goal was to compare the performance the WFG to a standard field generator (SFG), both part of the Aurora electromagnetic tracking (EM) system (NDI, Waterloo, Ontario, Canada), and to study the influence of the rCBCT on both tracking systems. The main purpose is development of a one-stop solution for navigated bronchoscopy and improved success rate in targeting peripheral lung lesions, and the WFG allows for simultaneous X-ray imaging and position tracking.
Methods: The field generators was mounted under the OR table, imposing no restrictions to the movement of the rCBCT. An accuracy phantom was used, a Plexiglas cube with 225 predefined positions (bottom of drilled holes). The phantom was placed on the OR table in the center of the tracking system's measurement volume. In this way, our experimental setup represented a navigation volume relevant for a bronchoscopy. A 6DOF sensor catheter was used to sample the phantom's 225 positions (100 samples). This was repeated with the C-arm inside and outside the tracking system's measurement volume, for both field generators. For the robustness measurements we performed similar measurements with 4 tracked tools inside the phantom with the C-arm in different positions and rotations.
Results: The SFG appears to provide a smaller RMS position error, while the WFG has less maximum and variance of the error. The C-arm caused a strong disturbance on the EM tracking systems. The influence is greater on the SFG, increasing the RMS error with about 7 mm, compared to 4 mm for the WFG. The results when using the SFG have a larger spread of the error as well. Moving the C-arm into the EM field, along or perpendicular to the operating table, caused a decrease in the distance between two sensors of up to 13 mm. The measured sensor distance was close to constant as a function of the C-arm position when the C-arm was at a large distance (> 0.5 m) from the EM field.
Conclusion: The WFG outperformed the SFG, with and without the influence of the C-arm, with respect to RMS error and spread of the angle of the tracked catheter. The EM field was strongly affected by the rCBCT. When the C-arm is in a fixed position, the influence is constant at a given position in the field, but not constant throughout the field. The influence from the C-arm is negligible once it is moved out of the field. Care should be taken if one wants to perform navigation and imaging with a C-arm system simultaneously.
Keywords: accuracy, navigation, bronchoscopy, cone beam CT

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Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.326 A NEW METHOD FOR IN-VIVO LUNG MOVEMENT TRACKING – FOR DIAGNOSIS AND THERAPY IN LUNG MEDICINE

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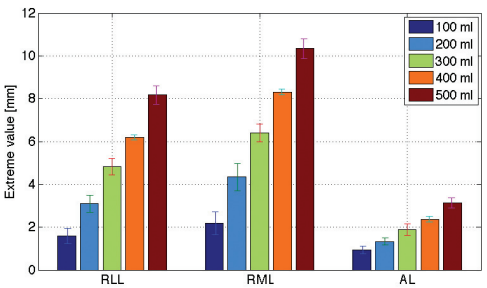
Background: Respiratory lung movement is a major challenge in bronchoscopic lung cancer diagnostics and radiation therapy. The current methods for evaluating lung segment and tumor movement (CT / MRI / fluoroscopy / internal and external markers) have important limitations. CT involves a high radiation dose, MRI is incompatible with metallic equipment, and both have poor temporal resolution. External evaluation is not precise enough. To study the impact of respiratory movement for image guided tumor diagnostics, we needed a method that overcomes these limitations.
Methods: Three electromagnetic sensors mounted inside balloon catheters were placed using a bronchoscopy-fluoroscopy procedure, in the right lung of a mechanically ventilated live pig; in the periphery of the lower (RLL), middle (RML) and accessory upper lobe (AL). The movement of the sensors was recorded in different animal positions on the OR table and at different tidal volumes. The sensors sensed their position at 40 Hz in an electromagnetic field set up by an external transmitter, with a precision of ~0.5 mm. The validity and reliability of the method were evaluated in terms of precision and functionality.
Results: As expected, increasing the ventilation volume increased the respiratory movement (see

figure), and the right lung moved significantly less in a right lateral than a left lateral position. The RML and AL sensors showed only a small reduction of movement in the lateral position. The supine position allowed the right lung to move significantly more than any lateral position. The sensors were easily placed and removed. No systematic position drift in tracking or fluoroscopy was registered, indicating that sensors remained in the chosen location throughout the experiment (~5 hours). The method was highly valid, reliable and accurate.



Conclusion: The novel method for tracking lung segment movements during respiration was stable, accurate, the equipment was reusable and fulfilled the purpose. We found a high spatial and temporal resolution and the method will be easy to implement in a bronchoscopic suite as a research tool for navigated bronchoscopy, radiation therapy and the study of lung physiology.

Keywords: tracking, navigation, lung movement, bronchoscopy

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P2.327 THE STUDY OF STENT AND PDT COMBINATION THERAPY FOR MALIGNANT AIRWAY STENOSIS

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Background: Centrally located early lung cancers can be treated with photodynamic therapy(PDT) for the curative intent. On the other hand, airway symptom due to advanced or end-stage lung cancer can be relieved immediately by means of bronchoscopic procedure. Moreover airway stent maintains symptom free and quality of life. But there are some problems after stenting such as restenosis by granulations and tumor growth, moving of the stent and difficulty in mucus expectoration. In this study, we evaluated the efficacy and feasibility of combination therapy, which is inserting clear type stent following photodynamic therapy using NPe6.

Methods: We inserted the clear type stent(Dumon Gold Studded Stent: NOVATECH) in the central airway of pigs and then we performed the NPe6-PDT. One week later, we examined the pathological changes and evaluated the efficacy of NPe6-PDT through the clear type stent.

Results: The laser output decreased 22.2% by passing by the clear type stent. Normal part of trachea was irradiated with a 664nm laser at the dose of 100J/cm^2 (power output: 180mW, irradiation time: 9 min 16 sec) and the part of trachea covered by stent was irradiated with a 664nm laser at the dose of 100J/cm^2 (power output: 180mW, irradiation time: 11min 55 sec). We were able to obtain the same effect of NPe6-PDT at the part of trachea covered by stent compared with the normal part of trachea.

Conclusion: We can conclude that PDT after inserting the clear type stent is effective and feasible. This treatment may contribute the maintenance of the patients with the advanced lung cancer in the central airway.

Keywords: stent, airway stenosis, photodynamic therapy

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Poster Session 2 - Surgery Tuesday, 5 July 2011 12:15-14:00

P2.328 PATIENT SELF-REFERRAL FOR CHEST X-RAY TO INCREASE EARLY DETECTION OF LUNG CANCER IN LEEDS, UNITED KINGDOM.

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Background: Lung cancer is responsible for 22% of all UK cancer deaths. 5 year survival rates in the UK lag behind other European and North American nations, and recent evidence has suggested that this may relate to later diagnosis. Leeds Teaching Hospitals NHS Trust (LTHT) serves a local population of 770,000 and diagnoses the largest number of new cases of lung cancer in any hospital nationwide (553 in 2009). The majority of patients present with late stage disease (72% stage III/IV). There is wide variation in rates of referral for chest X-ray (CXR) by general practitioners (GPs - primary care clinicians) across Leeds. Median CXRs per 1,000 population per year (2008-2009) were 30 (IQR 25-40, Range 7-101). Local audit revealed significant delay in referral for CXR and variable adherence to recommendations for CXR referral criteria issued by the National Institute for Clinical Excellence (NICE).
Methods: NHS Leeds and LTHT undertook a joint campaign to improve awareness of early symptoms of lung cancer to promote early referral for CXR, funded by the National Awareness and Early Diagnosis Initiative. Public awareness was assessed at the project outset using the validated Cancer Awareness Measure. A social marketing approach was used to promote the NICE recommendation for CXR referral (3 weeks of persistent and unexplained respiratory symptoms - predominantly cough, haemoptysis, breathlessness and chest/shoulder pain). 12 talks were given to healthcare professionals (GPs, community health educators, community matrons, respiratory nurses and pharmacists). A variety of marketing communication tools were used including bus adverts, posters, postcards and beer mats. Self-referral CXR was established where patients 50yrs or over could self-present for CXR after 3 weeks of cough or other chest symptom without medical referral. All community healthcare professionals were encouraged to direct symptomatic patients to the self-referral service. Outcome measures were numbers of CXRs ordered, numbers and stages of lung cancers diagnosed, proportions of patients undergoing radical therapy and 1 year survival rates.
Results: Pre-campaign market research of 630 members of the public revealed poor knowledge of early lung cancer symptoms. Perceived difficulty in making an GP appointment, and reluctance to waste doctor's time were two of the most common reasons for failure to consult regarding symptoms. The marketing communication campaign, healthcare professional campaign and self-referral CXR service all initiated in January 2011. During the first seven weeks 95 patients had presented for self-referral CXR, of which 3 patients had confirmed lung cancer. There was a 30% increase in the number of GP-ordered CXRs compared to the same period in 2010 (557 ± 65 per week vs 428 ± 55 respectively, mean ± SD, $p<0.001$), and a 70% increase in fast-track lung cancer clinic referrals compared to 2010 as a whole (16.0 ± 6.0 per week vs 9.4 ± 3.1 respectively, mean ± SD, $p<0.05$). Further data on CXR numbers and lung cancer diagnoses and stage will be available by the late-breaking deadline.
Conclusion: Review of CXR rates and lung cancer diagnoses, stage, treatment and outcome during the campaign will allow evaluation of the success of such an approach.
Keywords: Early Detection, Chest X-ray, Social marketing

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P2.329 DOES ROUTINE USE OF EBUS-TBNA AND EUS-FNA IMPROVE THE ACCURACY OF STAGING OF NON SMALL CELL LUNG CANCER PATIENTS – A NATIONAL TUMOR REGISTRY BASED STUDY

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Background: Evaluation of the extend of disease or stage (TNM) is a prerequisite for correct treatment of lung cancer. Several studies have showed that biopsies and fine needle aspirations obtained by EBUS-TBNA and EUS-FNA yield similar results as mediascopy, which previously have been considered the gold standard for evaluation of mediastinal nodal

involvement in NSCLC. Thus EBUS-TBNA and EUS-FNA should now be considered as procedures which are equally effective as mediastinoscopy in staging while at the same time being more gentle to the patient.
Methods: We therefore used data from a population based lung cancer registry to evaluate the association between frequency of use of EBUS-TBNA/ EUS-FNA and precision of mediastinal diagnostic work-up. EUS in diagnostics and staging of lung cancer have been used in several centres for more than a decade and since 2005 several centres have inter grated EBUS TBNA in their procedures
Results: The material consisted of 7000 operated patients since 2003. The use of endoscopic ultrasound (EBUS-TBNA/EUS-FNA were mostly used in one region and mediastinoscopy in another. The concordance between cN and pN were higest and equal in the regionswhere mainly mediastinoscopy were used and the reion where Endoscopic Ultrasound were used
Conclusion: For the first time it is possible to get an impression of the impact of the use of EBUS-TBNA and EUS-FNA in a national populationof lung cancer patients**.** The were no difference in the cN/pN ratio in the areas where they used mediastinoscopy and where they used endoscopic Ultrasound
Keywords: Lung cancer, Endoscpic Ultrasound, National results

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P2.330 ACHIEVING TISSUE DIAGNOSIS, STAGING AND MOLECULAR ANALYSIS OF LUNG CANCER WITH ENDOBRONCHIAL ULTRASOUND- FINE NEEDLE ASPIRATION (EBUS-FNA)

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Background: Lymph node involvement has both prognostic and therapeutic implications in lung cancer. To limit inherent risks of mediastinoscopy, we integrated endobronchial ultrasound with fine needle aspiration (EBUS-FNA) in the evaluation of thoracic lymphadenopathy.
Methods: We report our single institution's results over a two year period from September 2008 to September 2010. We identified 173 patients with thoracic lymph nodes suspicious for malignancy, namely greater than one cm in short axis or PET-positive.
Results: We performed 180 EBUS-FNA of thoracic lymph nodes on these 173 patients with no major complications. EBUS-FNA of thoracic lymph nodes provided adequate tissue for pathologic evaluation in 159 (92%) of 173 patients. We found malignancy in 104 patients (60%), benign lymph node tissue in 41 patients (24%) and granulomatous lymph node tissue in 14 patients (8%). We found lung cancer in 86 patients (50%) including 41 with adenocarcinoma (24%), 21 (12%) with small cell lung cancer, 18 (10%) with squamous cell carcinoma, 5 (3%) with poorly differentiated non-small cell lung cancer and one with large cell cancer (<1%). Ten patients (6%) had extrathoracic malignancies metastatic to mediastinal lymph nodes. Eight patients (5%) had recurrent lung cancer. Eight patients (5%) had non-diagnostic samples, 6 patients (4%) had atypical lymph nodes and 4 patients (2%) had benign pathology that conflicted with a high clinical suspicion of malignancy. Of these 18 patients with unclear pathology, seven (40%) had repeat EBUS-FNA. Only one of these revealed malignancy with the second EBUS-FNA. The remaining 17 patients underwent mediastinoscopy, thoracoscopy or CT-guided fine needle aspiration which provided a tissue diagnosis of malignancy in 14 patients. Of the 65 patients found to have non-small cell lung cancer, 8 (12%) had stage II disease (by N1 involvement), 25 (38%) had stage IIIA disease, one (2%) had stage IIIB disease, 26 had stage IV disease (40%) and 5 (8%) did not complete staging. Only one of these patients received an additional invasive procedure to confirm distant metastasis. Of the 21 patients with small cell cancer, 14 (66%) had limited disease and 7 (33%) had extensive disease. Samples from EBUS-FNA were analyzed for molecular analysis in 22 of our 41 adenocarcinoma patients (52%). Only 2 of these (9%) were inadequate sample size for analysis. Of the 20 patients who did have molecular analysis, 2 (10%) had KRAS mutations and 1 (5%) had an EGFR mutation.
Conclusion: EBUS-FNA is a powerful, safe and accurate diagnostic procedure in the evaluation

of patients with suspected lung cancer and lymphadenopathy. EBUS-FNA is capable of detecting a wide array of tissue pathologies including recurrent lung cancer and extrathoracic malignancies metastatic to thoracic lymph nodes. EBUS-FNA can refine clinical staging by CT or PET by providing samples from hilar and mediastinal lymph nodes. EBUS-FNA samples are also sufficient in quantity to analyze molecular markers. In summary, EBUS-FNA can provide a tissue diagnosis, accurate staging and mutational analysis for gene-targeted treatment of lung cancer.

Keywords: molecular analysis, Tissue Diagnosis, Lung Cancer Staging, Endobronchial Ultrasound

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P2.331 EXPERIENCE OF TBLB USING THIN BRONCHOSCOPY WITH VBN

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Background: It is said that diagnostic yield for small peripheral pulmonary lesion is increased with virtual bronchoscopic navigation(VBN). We reviewed utility of VBN on Transbronchial lung biopsy (TBLB) with thin bronchoscopy.
Methods: We had 41 cases TBLB examinations by 2.8mm bronchoscopy with VBN from Oct. 2008 to Dec. 2010. VBN images were created by Bf-Navi of Olympus company, using 1mm thin slice CT.
Results: VBN images showed 5.2±0.7th bronchial branches automatically. VBN images, added bronchial branches to pulmonary lesion manually, expressed 5.8±0.7th bronchial branches finally. We reached the object while recognizing 5.8±0.7th bronchial branches on TBLB examination. Object persons were 26 men and 15women, average age was 68.8±7.2 years old. The average size of pulmonary lesions were 18.1±6.0mm. (4cases in less than 10mm, 23 cases in from 11 to 20mm, 10cases in from 21 to 30mm, 4cases in more than 31mm). The characteristics of lesions was 2cases in pure GGO, 9cases in partial solid lesion , 30cases in solid lesion. Total diagnostic yield was 80.5% (33/41 cases). That was, especially, 70.4% (19/27 cases),limited in less than 20mm lesions. Diagnostic rate was 100% (14/14 cases) in more than 21mm lesions. We studied relationship between the location of responsible bronchial branch and the properties of pulmonary lesions in less than 20mm lesions(table).

		location of responsible bronchial branch in the lesion	
		Central	Edge
charactaristics of lesions	PureGGO	none	0/2(0%)
	Partial solid	3/3(100%)	1/3(33%)
	Solid	9/10(90%)	6/9(67%)

Conclusion: We could identify about 6th responsible bronchial branch and reach that branch selectively with 2.8mm bronchoscopy. It was important that the responsible bronchial branch cut into central or solid part of lesion, needless to say tumor size, for increasing diagnostic rate.

Keyword: VBN

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Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.001 MATURE CIRCULATING ENDOTHELIAL CELLS IN THE PERIPHERAL BLOOD AS A MARKER OF CLINICAL EFFICACY IN NON-SMALL CELL LUNG CANCER THERAPY

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Background: Medical oncologists are increasingly using anti-angiogenic drugs, but identifying the best-suited drug and the optimal dosage and schedule for treatment of patients with lung cancer remain challenging issues. Circulating endothelial cells (CECs) and circulating endothelial progenitors (CEPs) are modulated in a variety of diseases including lung cancer, and are promising surrogate biomarkers in oncology. Here, we investigate the changing pattern of mature circulating endothelial cells (CECs) in non-small cell lung cancer (NSCLC)

patients before and after therapy and analyze its clinical implication in NSCLC therapy.
Methods: Fifty-seven NSCLC patients were divided into three groups according to their treatment modality; surgical operation, chemotherapy alone, and chemotherapy plus Endostar. The mature CECs were measured by flow cytometry in the peripheral blood of NSCLC patients and 18 healthy subjects.
Results: The number of mature CECs (mean ± SD) in NSCLC patients (n=57, 0.33357±0.20060%) were significantly higher than the number in healthy volunteers (n=18, 0.16923±0.13488%) (P=0.003). After treatment, the number of mature CECs decreased significantly in the surgical operation group (P=0.002) and in the chemotherapy plus Endostar group (P=0.004), but not in the chemotherapy alone group [If the difference is not significant, than you do not need to show a P-value]. After therapy, a statistically significant decrease of CECs was observed in patients with early NSCLC (P=0.04), but not in patients with advanced-stage NSCLC. A positive correlation between mature CECs and WBC was found before treatment of NSCLC (r=0.911, P<0.001).[P=0.000 is not possible.]
Conclusion: Surgical operation and chemotherapy plus Endostar is superior to chemotherapy alone in the treatment of NSCLC. Monitoring the number of mature CECs may be a promising predictive marker of the clinical efficacy in NSCLC therapy.
Keyword: non-small cell lung cancer; circulating endothelial cell; Endostar
A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.002 TAXANE-BASED CHEMOTHERAPY IS ASSOCIATED WITH GONADAL DAMAGE IN NSCLC MALE PATIENTS

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Background: Fertility is a major concern in cancer patients of reproductive age who are undergoing chemotherapy. Few studies regarding the gonadotoxic effects of taxanes have been performed, mostly on experimental animals. Inhibin B, a hormone primarily secreted by Sertoli cells, can be used as a direct marker of spermatogenesis in adult males. Loss of germ cells in men is known to cause a decrease in levels of inhibin B and increased levels of follicle-stimulating hormone (FSH). We conducted this study in order to assess the impact of taxane-based chemotherapy on fertility of non-small cell lung cancer (NSCLC) male patients by studying its effect on the male reproductive axis.
Methods: Forty male NSCLC patients aged 20-60 years old were included in the study. All of them had been scheduled to receive chemotherapy with a taxane (docetaxel or paclitaxel) in combination with gemcitabine or carboplatin. Serum levels of inhibin B, FSH and luteinizing hormone (LH) were measured before and after completion of chemotherapy. In half of the patients, bilateral testicular volume (BTV) was measured through testicular ultrasonography at these stages.
Results: The mean age of the patients was 53.05 years. Twenty-four patients received docetaxel-based doublets, whereas 16 patients were administered paclitaxel doublets. The median number of chemotherapy cycles received was three. The median levels of serum inhibin B before and after chemotherapy were 97.7 (range 1.04–1,753 pg/mL) and 40.1 pg/mL (range 0–668 pg/mL), respectively, and this reduction was statistically significant ($p<0.01$). On the contrary, median serum FSH levels showed a statistically significant increase from 6.65 (range 0.5–26.2 IU/L) to 10.3 IU/L (range: 2.6–32.3 IU/L), $p\leq0.001$. The above differences were found statistically significant when each of the docetaxel and paclitaxel were examined separately as well. The median inhibin B/FSH ratio showed a statistically significant decrease (15.6 to 4.72), $p\leq0.001$. The increase in median LH levels from 4.80 IU/L (range 0.9–13.6 IU/L) to 5.04 IU/L (range 2–13.7 IU/L) was not statistically significant ($p>0.05$). The BTV decreased from a median of 27.6 mL (range 13.8–37.3 mL) to 23.5 mL (range 9.2–32.8 mL). This difference was statistically significant ($p\leq0.001$), as was the decrease in each of the taxane groups separately. There was a significant inverse correlation between inhibin B and FSH concentrations as well as between FSH and BTV. Inhibin B and LH were not correlated to BTV.

Conclusion: Taxane-based chemotherapy causes a decrease in inhibin B levels, elevation of FSH levels and reduction of bilateral testicular volume, all of which indicate a significant gonadal damage immediately after completion of chemotherapy.
Keywords: Chemotherapy, gonadal damage, Non-small cell lung cancer, taxanes

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P3.003 THE COMBINATION CHEMOTHERAPY OF GEMCITABINE, CARBOPLATIN AND BEVACIZUMAB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The addition of bevacizumab in combination of paclitaxel and carboplatin showed significant benefits in progression-free survival and overall survival in patients with advanced non-small cell carcinoma. We are conducting a phase II clinical study of combination chemotherapy with gemcitabine, carboplatin and bevacizumab in same patients population.
Methods: The regimen consists of gemcitabine of 1,000mg/m2 on D1 and D8, carboplatin of AUC 5 and bevacizumab of 15mg/kg on D1. Treatment repeats every 3 weeks. The tumor response was checked every 2 cycles according to RECIST 1.1 criteria.
Results: Twenty-four patients enrolled in this study till now. 23 patients were male. The median age of patients was 68 (55~79) Years. Thirteen patients were stage IV or recurrent disesase, 7 were IIIB and 4 were IIIA. Ten patients were squamous cell carcinoma, 11 were adenocarcinoma and 3 were unclassified non-small cell carninoma. Fifteen patients had ECOG performance status of 1 and 9 had 2. Total 93 cycles of therapy were administered and median cycles of therapy were 4 (1~8). Eleven of 21 evaluable patients showed partial responses, 6 had stable disease. The overall response rate was 52%, disease control rate was 76%. In total 93 cycles grade 3 and 4 neutropenia were 14% and 1%, respectively. Grade 4 thrombocytopenia were 1% and grade 3 anemia were 7%. Non-hematologic toxicities were mild and manageable, but two patients complained grade 3 general weakness and one grade 4 pneumonia.
Conclusion: The addition of bevacizumab in combination of gemcitabine and carboplatin is active in terms of response rate. We need more enrollment and longer follow-up.
Keywords: Non-small cell lung cancer, gemcitabine, Carboplatin, bevacizumab

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P3.004 IMPROVEMENT IN SURVIVAL BUT NOT SKELETAL MORBIDITY IN STAGE IV NON-SMALL CELL LUNG CANCER PATIENTS WITH BONE METASTASES: TIME TO CONSIDER BONE TARGETED THERAPY?

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Background: Bone metastases are common in non-small cell lung cancer (NSCLC) and cause significant morbidity in the form of pain, skeletal-related events, and decreased quality of life. Because stage IV NSCLC is associated with poor survival, therapy directed at skeletal disease (e.g. bisphosphonates) is generally not currently the standard of care. However, with significant advances in the systemic management of metastatic lung cancer over the last decade, we propose that patients with bone metastases will have improved survival, and as such may now be candidates for bone targeted therapies.
Methods: This was a retrospective cohort study of 987 patients diagnosed with stage IV NSCLC at 2 institutions. Demographic data, as well as the frequency of bone metastases, specific treatments received, overall survival, and frequency of skeletal-related events were collected from patients who presented to these centres in 1998, 2003, and 2008. Results were then compared across the three time periods.
Results: Bone was the most common site of metastasis, occurring in approximately half of all

patients, a proportion that was stable over time (49% in 1998, 54% in 2003, 54% in 2008). While the use of systemic therapy increased significantly over time, very few patients received IV bisphosphonate therapy. Overall survival from the time of diagnosis of bone metastases improved significantly across cohorts (P <0.001), with an actuarial probability of survival of 10.0% at 2 years among patients diagnosed in 2008, compared with a probability of only 0.6% among those diagnosed in 1998, and 3.6% in 2003. However, the proportion of patients experiencing skeletal-related events did not differ significantly between time cohorts, with no improvement over time in the frequency of radiation to bone (71% in 1998, 74% in 2003, 70% in 2008; P = 0.714), surgery to bone (8% in 1998, 10% in 2003, 10% in 2008; P = 0.616), or spinal cord compression (8% in 1998, 4% in 2003, 10% in 2008; P = 0.091).
Conclusion: While the overall survival of patients with bone metastases from NSCLC has improved over the past decade, the use of bisphosphonates is not standard practice, and the frequency of skeletal-related events remains unchanged. These results support further investigation into the use of bone targeted therapies in the setting of metastatic lung cancer, to reduce skeletal morbidity and improve quality of life in these patients, who are now living longer.
Keywords: NSCLC, stage IV, bone metastases, bisphosponates

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P3.005 ONGOING PHASE II STUDY OF PEMETREXED PLUS CARBOPLATIN OR CISPLATIN WITH CONCURRENT RADIATION THERAPY FOLLOWED BY PEMETREXED CONSOLIDATION IN PATIENTS WITH FAVORABLE-PROGNOSIS INOPERABLE STAGE IIIA/B NON-SMALL-CELL LUNG CANCER: UPDATE

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Background: There is no consensus chemotherapy regimen with concurrent radiation therapy (CRT) for inoperable Stage IIIA/B non-small cell lung cancer (NSCLC). Pemetrexed (P) synergizes with ionizing radiation, as well as carboplatin (Cb) and cisplatin (C) in preclinical models. These doublets have shown efficacy and favorable toxicity profiles in Phase II/III trials.
Methods: In this open-label randomized non comparison Phase II trial, 98 patients with inoperable Stage IIIA/B NSCLC were randomized (1:1) to P plus Cb (PCb) or P plus C (PC) intravenously (IV) every 21 days for 3 cycles. All patients received CRT 64–68 Gy (2 Gy/day, 5 days/week, Days 1–45). Consolidation P 500 mg/m^2 IV every 21 days for 3 cycles began 3 weeks after completion of CRT. The primary endpoint of this ongoing trial is 2-year overall survival (OS); secondary endpoints include toxicity, overall response rate (ORR), time to progression (TTP), and median survival.
Results: Since June 2007, 98 patients have been enrolled (PCb: 46; PC: 52). Mean dose compliance was PCb: 94.9% P, 94.9% Cb; PC: 89.7% P, 87.2% C. Mean dose compliance for CRT was PCb: 95.7%; PC: 86.7%. Dose interruptions occurred with 39 patients. The ORR rates were PCb: 56.5% (complete response [CR], 6.5%; partial response [PR], 50.0%); PC: 46.2% (CR, 1.9%; PR, 44.2%). One-year OS was PCb: 68.1% (95% confidence interval [CI], 51.2-80.2); PC: 71.9% (95% CI, 56.4-82.7); 2-year OS was PCb: 32.4% (95% CI, 13.8-52.7); PC: 56.1% (95% CI, 36.9-71.5). Median OS was PCb: 18.7 (95% CI, 12.9-not assessable [N/A]) months; PC: 25.9 (95% CI, 23.2-N/A) months. Selected toxicities are shown in Table 1. Table 1. Select Treatment-Related Toxicities, %*

	Grade 3		Grade 4	
	PCb	PC	PCb	PC
Anemia	10.9	3.8	0	1.9
Neutropenia	15.2	9.6	6.5	3.8
Febrile neutropenia	4.3	0	0	0
Thrombocytopenia	2.2	3.8	4.3	1.9
Dehydration	6.5	9.6	0	0
Dysphagia	2.2	0	0	0
Esophagitis	4.3	3.8	0	1.9
Fatigue	6.5	1.9	0	0

PC, pemetrexed plus cisplatin; PCb, pemetrexed plus carboplatin * No grade 5 toxicities have been reported

Conclusion: Overall, P plus either Cb or C in combination with CRT appear well tolerated in treatment of locally advanced NSCLC. Efficacy data will be updated at the meeting.

Keywords: NSCLC, Pemetrexed, concurrent radiotherapy, chemoradiotherapy

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P3.006 SECOND LINE CHEMOTHERAPY WITH PEMETREXED (P) FOR PATIENTS IN STAGE IIIB/IV NON SMALL CELL LUNG CANCER (NSCLC).

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Background: Pemetrexed is recommended as second line treatment for stage IIIB / IV NSCLC after failure of first line chemotherapy. The aim of our study is to analyze activity and toxicity of pemetrexed in second line treatment of advanced and metastatic lung cancer.

Methods: Since october 2007 to december 2009, 27 patients with advanced and metastatic NSCLC were treated with second line chemotherapy and received pemetrexed 500 mg/m^2 10 minutes infusion day 1. All patients received full vitamin supplementation. Response and toxicity were assessed using WHO criteria.

Results: 27 (1 F and 26 M) patients were enrolled, and all are evaluable for response and toxicity. Median age was 60.4 years (range m 47years – M 76years). Histology was adenocarcinoma in 12 patients, squamous cell cancer in 13 patients and carcinoma with large cell in 2 patients. Fifteen (15) patients had IV stage and twelve (12) patients had IIIB stage disease. The main reported grade III / IV events are: neutropenia 4 %, anemia 16 %. Common non hematologic grade III / IV toxicities include nausea 48 %, and asthenia in 24 % of patients. Response rate was (CR + PR) 12 %. Stable disease was achieved in 28 % of patients. Median survival was 11 months.

Conclusion: Pemetrexed is well tolerated in second line treatment. This treatment shows an encouraging median survival on second line chemotherapy for patients with advanced or metastatic NSCLC on recurrent disease.

Keywords: NSCLC, second line chemotherapie, Pemetrexed

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P3.007 FIRST LINE CHEMOTHERAPY WITH PEMETREXED PLUS CISPLATIN IN ADVANCED NONSQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): A COMPARISON OF TWO PHASE III TRIALS

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Background: In a recent phase III trial (JMDB), patients with stage IIIB/IV NSCLC treated with pemetrexed/cisplatin had similar outcomes compared with those treated with gemcitabine/cisplatin (Scagliotti et al 2008). However, a preplanned subgroup analysis showed a significant improvement in survival for patients with nonsquamous histology treated with pemetrexed/cisplatin (Scagliotti et al 2009). The phase III PARAMOUNT trial investigated the efficacy/safety of pemetrexed continuation maintenance therapy after pemetrexed/cisplatin induction therapy in patients with advanced nonsquamous NSCLC. We evaluated whether results of the pemetrexed/cisplatin induction regimen of PARAMOUNT were confirmatory of results of the pemetrexed/cisplatin-treated nonsquamous patient subpopulation of JMDB.

Methods: The JMDB trial randomized 1725 chemonaive patients with advanced NSCLC of all histologies and an ECOG performance status of 0/1. Of 1252 nonsquamous patients, 618 were randomized to pemetrexed/cisplatin. Patients received cisplatin 75 mg/m^2 (day 1) with either gemcitabine 1250 mg/m^2 (days 1, 8) or pemetrexed 500 mg/m^2 (day 1), every 21 days, for a maximum of 6 cycles. PARAMOUNT was a double-blind, placebo-controlled trial that enrolled 939 chemonaive patients with advanced nonsquamous NSCLC and a performance status 0/1 to receive 4 cycles of induction pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) on day 1 of a 21-day cycle. Patients who did not progress on induction therapy randomly received maintenance therapy with pemetrexed or placebo. This comparison examines the response and safety data of the nonsquamous patients treated with pemetrexed/cisplatin in JMDB and the patients treated with induction pemetrexed/cisplatin in PARAMOUNT.
Results: In the JMDB trial, among 618 nonsquamous patients randomized to pemetrexed/cisplatin, 604 were treated, with 71% completing ≥4 treatment cycles, and 47% completing all 6 cycles (median=5 cycles). In PARAMOUNT, among the 939 enrolled patients, 68% completed 4 cycles of induction pemetrexed/cisplatin (median=4 cycles). The tumor response rates (30.1% and 28.6%) and disease control (response plus stable disease) rates (74.5% and 63.8%) were similar for PARAMOUNT and JMDB. Among the patients who had a response (CR/PR) in the JMDB trial, 90.5% achieved the response within the first 4 cycles. The pattern of grade 3-4 treatment-related toxicities (neutropenia, anemia, nausea/vomiting, fatigue) was similar in PARAMOUNT and JMDB nonsquamous treated patients, but the incidence of laboratory (13.7% and 21.4%) and nonlaboratory toxicities (14.8% and 21.9%) was higher in JMDB. The percentage of possible treatment-related deaths (1.2% and 1.0%) and serious adverse events (14.2% and 16.4%) were comparable between PARAMOUNT and JMDB.
Conclusion: The PARAMOUNT results for patients treated with induction pemetrexed/cisplatin confirm the findings for nonsquamous patients treated with pemetrexed/cisplatin in JMDB. The two trials demonstrate consistent response and disease control rates for the pemetrexed/cisplatin combination as first-line treatment for patients with advanced nonsquamous NSCLC. In addition, the types of toxicities reported in the two trials are similar, but the incidence is higher in JMDB, possibly due to the increased number of cycles given. The toxicity profiles in both trials are consistent with the known safety profile of pemetrexed/cisplatin.
Keywords: Cisplatin, nonsquamous, first-line, Pemetrexed

Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.008 HOW DO ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS OVER 70 FARE ON FIRST LINE PLATINUM DOUBLET CHEMOTHERAPY?

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Background: Platinum doublet chemotherapy is standard of care in good performance status, advanced stage (IIIb/IV) NSCLC with a 1 year survival advantage of 9% and an absolute increase in median survival of 6 weeks (Cochrane Database of Systematic Reviews 2010). Data on chemotherapy in an elderly population (≥70) is limited in trials. Ironically the median age of ≥ Stage III NSCLC patients is 70 in our catchment area of 2.3 million. A small (n=76) Japanese trial in >75 years old did not find any difference in efficacy between single agent and platinum doublet chemotherapy [1].
Methods: A retrospective case note audit was carried of patients aged ≥ 70 with stage III/IV disease. 200 patients received first line chemotherapy between 1/1/2004 and 31/12/2008. Data recorded was: age, gender, performance status, co-morbidities, stage, histology, chemotherapy regimen (cycle number, dose intensity/delays/reductions), toxicity (CTCVAE4.0), response rates and date of death.
Results: Results are presented from the analysis of the 1st 100 patients. The median age of the audit population was 74 (70-84), 63% were male; 62% had an ECOG PS 0-1 and 36% had a PS 2. 61% had stage IV, 23% stage IIIb and 16% stage IIIa disease. 98% of the patients had platinum doublet chemotherapy, commonest being gemcitabine/carboplatin (81%). Approximately 75% of the patients had at least 3 cycles of chemotherapy with

64% completing all 4 cycles. Drop out rate was 26% due to falling PS or toxicity of which the majority, 18%, stopped after one cycle of chemotherapy. There was a 43% overall response rate with a further 25% disease stabilisation. 11% of patients progressed on treatment and in a further 18% response was not assessed as treatment was stopped early after 1-2 cycles. Majority of ≥ Grade 3 toxicity was haematological. 38% of the patients had ≥ 20% dose reduction of either one or both chemotherapy agents in cycle 1, this increased to 44% by the end of second cycle of chemotherapy. 33% patients were admitted with pyrexia on chemotherapy. Further details are limited as most patients were admitted to referring hospitals. Median length of hospital stay was 4 days (range 1-15). Chemotherapy related mortality, death within 30 days of receiving last cycle of chemotherapy was 9%, 4 of these patients had progressed on chemotherapy. Median progression free survival from date of diagnosis of 14 months and 1 year overall survival was 45%.
Conclusion: Our results from an unselected population show a better median progression free survival (14.0 vs. 6.3 months) from platinum doublet chemotherapy than seen in a recent trial comparing platinum doublet chemotherapy to single agent chemotherapy (Quiox et al, ASCO 2010). As expected patients with a PS 0-1 had a significantly better survival 13 vs. 9 months for PS 2 patients (p=0.01). Elderly patients if carefully selected do appear to benefit from platinum doublet chemotherapy despite the reduced dose intensity. The full analysis will be submitted before the late breaking abstract deadline. References
1. Tamya, A., T. Naito, T. Takahashi, et al. Gan To Kagaku Ryoho, 2010. 37(10): p. 1897-1901.
Keywords: Advanced NSCLC, Elderly, Chemotherapy, outcome

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.009 CLINICIANS' VIEWS ON EGFR TESTING: GETTING THE PROCESS RIGHT FOR NEW ZEALAND

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Background: Clinicians' views on EGFR testing: Getting the process right for New Zealand Background This paper reports the preliminary findings of a survey to ascertain clinicians' views on introducing Epidermal Growth Factor Receptor (EGFR) testing in New Zealand. In advanced non small cell lung cancer (NSCLC) tyrosine kinase inhibitors (TKIs) and EGFR testing offer new hope to many patients. In New Zealand, Maori, the indigenous population, have the poorest outcomes from advanced NSCLC, and therefore treatment options that benefit this population are of considerable importance. Funding for second line erlotinib therapy was introduced in late 2010, with no funding for first line therapy in New Zealand. Currently no EGFR testing is undertaken in New Zealand; patients can pay privately for sample testing in Australia. The EGFR mutation rates of New Zealand ethnic populations with NSCLC, including Maori, have not been tested. International research demonstrates TKI response rates vary from 15% when EGFR status is unknown to 80% when EGFR mutation is positive. Therefore, introducing EGFR testing here may enable more effective targeted therapy with improved patient outcomes, with the potential for a reduction in health inequalities.
Methods: Following ethical approval, an anonymous electronic survey was sent to a range of clinicians involved in diagnosing and managing NSCLC in New Zealand, including radiation and medical oncologists, respiratory physicians, pathologists, and advanced trainees in these specialties. Questions included who should be tested, wait times for results, costs, specific test type, and preferences for a centralized or localized service. The preliminary results are discussed in this paper.
Results: 41 clinicians, representing all disciplines and from 9 of the 20 District Health Boards, responded. Findings included that 67% strongly agreed that treating NSCLC with targeted therapy was an important health issue. However, opinions differed on who should be tested; from only patients in research studies to everyone for whom active therapy was considered. 71% of clinicians had not arranged EGFR tests for any patients, and only one clinician had tested more than 10% of their Maori NSCLC patients for the EGFR mutation. Most clinicians were in favour of a centralized

service, with uncertainty regarding test method. 45% felt there were no drawbacks to introducing EGFR testing here, however others had concerns including costs (34%), the lack of expertise (24%), and potential clinical implications (10%). Over 60% were prepared to arrange additional biopsies for EGFR testing and 80% wanted a turnaround of less than two weeks. Fewer than 50% of clinicians were very familiar with other NSCLC molecular tests, including ALK fusion gene.
Conclusion: Whilst most clinicians who responded had little experience with EGFR testing, they supported the introduction of EGFR testing into New Zealand. However, clinicians also identified issues, such as expertise, that need to be dealt with while work to introduce the testing is undertaken
Keywords: EGFR, NSCLC

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P3.010 CHEMOTHERAPY IN PATIENTS WITH STAGE IV NON-SMALL CELL LUNG CANCER.THE WREXHAM MAELOR HOSPITAL EXPERIENCE.

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Background: Wrexham Maelor Hospital in North Wales serves approximately 250,000 people. The lung cancer multi disciplinary team sees approximately 100 newly diagnosed non-small-cell lung cancer (NSCLC) patients a year. Of these 40 % are stage IV on presentation. We present the outcome data of our stage IV lung cancer patients.
Methods: The study period was January 2007 to December 2008. Total 48 stage IV (TNM 6th Edition) were treated with platinum doublet chemotherapy with the commonest regimen being Gemcitabine 1250mg/m^2 and Carboplatin AUC 5 given every 3 weeks for 4 cycles. The patients treated with chemotherapy represented 60% of the total referred stage IV Non Small Cell Lung Cancer during this period. CT staging was repeated after cycle 2 and after conclusion of chemotherapy if required or clinically indicated. Chemotherapy was stopped if progressive disease was noted or due to patient intolerance. Eligible patients for this retrospective analysis was required to have histological proven non-small cell lung cancer, stage IV and not previously treated. Patients were required to have a WHO Performance Status of 0 to 1, adequate bone marrow reserve and renal function and no previous malignancy.
Results: There were 34 males and 15 females. The median age at presentation was 67.5 years (53 -82). Toxicity was predominantly haematological. Grade 3-4 neutropenia was noted in 25 patients during chemotherapy (52%). No grade 3-4 thombocitopenia occurred and 1 patient died within 30 days of receiving chemotherapy. Twenty patients needed one or more blood transfusions (48%). There were 31.5 % partial response, 30 % stable disease and 38.5 % progressive disease in response to chemotherapy. No complete response was recorded. The median overall survival was 8.8 months (3-44). The 1,2 and 3 year OS were 23%, and 14.5% and 6.5 % respectively. The estimated time to progression was 3.5 months and only one patient is still alive after 40 months follow-up.
Conclusion: Using the same inclusion criteria as described in the Sandler and other phase III studies, the results in our institution are in keeping with the published data. It is encouraging that the results of the randomised controlled trial using a doublet with platinum agent and Gemcitabine are applicable to a standard population. However we have noticed increased incidence of neutopenia and blood transfusion rate compared with published data from phase III trials.
Keywords: stage IV, Chemotherapy, survival, gemcitabine and carboplatin

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P3.011 PEMETREXED PLUS PLATINE IN FIRST LINE FOR TREATMENT OF ADVANCED AND METASTATIC NON-SQUAMOUS CELL LUNG CANCER.

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Background: Pemetrexed was initially approved as second-line monotherapy in advanced NSCLC, and then in first line of non-squamous cell lung cancer in association with platine. In this study, we evaluate the efficacy and toxicity of pemetrexed plus platine in patients with advanced non-squamous cell lung cancer in chemo naive patients.
Methods and Patients: From October 2009 to December 2010, twenty two (22) patients with non squamous cell lung cancer stage IIIB or IV were treated in first line with pemetrexed 500 mg/m^2 day 1 plus cisplatine 70 mg/m^2 on day 1 or carboplatine AUC6 (for patients more than 60 years. All patients received full vitamin supplementation and the response and toxicity were assessed using Recist criteria. Twenty two patients were enrolled, and all are evaluable for response and toxicity. Eighteen (18) male and 4 female, and the median age was 61,8 (range 46 -69) years. Six (6) patients had IIIB stage and 16 patients had IV stage disease. Large cell cancer was found in 5 patients, adenocarcinoma in 17 patients.
Results: No complete response were observed, partial response was observed in 8 (36%) patients, stable disease was achieved in 4 (18%) patients, and disease progression was observed in 10 (45%) patients. Toxicities grade 3 and 4 was 17 %, mainly hematological (leucopenia and anemia).
Conclusion: Pemetrexed plus platine is well tolerated and active. Larger and longer follow-up studies may be needed to determine the real impact in survival of the association pemetrexed plus platine in non squamous cell lung cancer.
Keywords: Pemetrexed, Adenocarcinoma, advanced stage

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.012 ERLOTINIB (TARCEVA®) IN THE TREATMENT OF A NON-SELECTED POPULATION OF 1735 PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) FROM THE CZECH REPUBLIC

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Background: The human epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) erlotinib (Tarceva®) is approved for use in advanced, pretreated NSCLC. This analysis presented examines data obtained from the Czech population of NSCLC pts who received erlotinib.
Methods: Data of all 1735 NSCLC pts treated with erlotinib between 12/2005 and 12/2010 in the Czech Republic are summarised. We evaluated efficacy and toxicity. Retrospective analyses were carried out to determine if any associations were seen between specific characteristics and either median Progression Free Survival (mPFS) or median Overall Survival (mOS), PS, gender, smoking status, histology and toxicity were also assed. Erlotinib

was administered orally 150 mg/day until disease progression. The difference in response relative to baseline characteristics was determined using Pearson Chi-square test. Differences in OS and PFS relative to baseline characteristics were evaluated for significance using log-rank test.
Results: Of the 1735 patients with advanced NSCLC, 617 (35.6 %) were female and 1118 (64.4%) male, 374 (21.6%), non-smokers, 686 (39.5%) former smokers and 675 (38.9%) current smokers. Median age was 65 years. Erlotinib was used as 1st line therapy in 14.4%, as 2nd line in 47.3% and as 3rd line in 38,3% patients. At the time of indication for erlotinib, disease states were ECOG PS 0 in 132 (7.6%), PS 1 in 976 (56.3%), PS 2 in 382 (33.5%) and PS 3 in 45 (2.6%) pts. The most patients were stage IIIB (32.0%) and stage IV (58.0%). Adenocarcinoma was confirmed in 45.9%, squamous-cell carcinoma in 39.2%, large–cell carcinoma in 4.0% and non specified carcinoma in 9.4% pts. CR was confirmed in 0.6%, PR in 123 7.1% pts, SD in 44.1% of pts; 23.0% of pts progressed and 25.2% pts were not evaluated. Major toxicities were skin toxicity in 56.7% and diarrhoea in 24.3 pts, but the therapy was finished due to toxicity grade 3-4 only in 5.0%. Median survival (95% CI) was 7.5 months (6.9; 8.1). Probability of 3-months survival was 74.8%, of 6-month survival was 56.7% and of one-year survival was 16.7%. PFS (95% CI) was 2.9 months. The probability of 3-months PFS was 51.2%, of 6-month survival 30.4% and of one-year PFS 16.7%. The differences between the lines of treatment were not statistically significant ($p = 0.744$). The differences between groups of pts according to PS (0+1 vs. 2+3) were statistically significant ($p < 0.001$). The best median survival (17.6 month) was in the group of pts with PS 0. Statistically significantly longer ($p< 0.001$) was mOS and mPFS survival in patients with skin toxicity, in female pts, in non-smokers and in pts with adenocarcinoma.
Conclusion: Erlotinib (Tarceva ®) in this non-selected group of pts with advanced NCCLC was well tolerated, with evidence of antitumor activity in 1st, 2nd and 3rd line of therapy. The statistically significant best ($p < 0.001$) outcomes were seen the results in patients who had PS 0+1, skin toxicity, or were female, non-smokers, or had adenocarcinoma. The results from the Czech Republic are better then the data from BR.21 study and comparable with the results of TRUST.
Keywords: performans status, Advanced NSCLC, erlotinib, Efficacy

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P3.013 A PHASE II STUDY OF INTERMITTENT IMATINIB MESYLATE AND WEEKLY PACLITAXEL IN PATIENTS AGED 70 OR OLDER WITH ADVANCED NON-SMALL CELL LUNG CANCER

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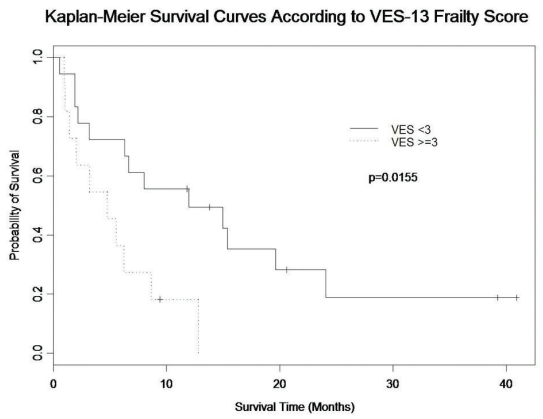
Background: In epithelial tumors including non-small cell lung cancer (NSCLC), interstitial hypertension is a barrier to chemotherapy delivery, and is mediated by platelet derived growth factor receptor (PDGFR) expressed by matrix fibroblasts. Antagonizing PDGFR with imatinib may improve intra-tumoral delivery of paclitaxel, thereby increasing response rate (RR).
Methods: This single-stage, open-label, multicenter phase II study evaluated the efficacy of weekly paclitaxel (90 mg/m^2 on day 3, 10, 17 of 28-day cycle) and imatinib pulses (600 mg daily on day 1-4, 8-11, 15-18) in elderly patients with advanced NSCLC. Eligible patients were aged ≥ 70 with untreated stage IIIB-IV NSCLC and ECOG performance status 0-2. Primary endpoint was RR (RECIST 1.0). Secondary endpoints included median progression free and overall survival (PFS, OS), toxicity, and tissue correlatives of PDGFR pathway activation. The Charlson Comorbidity Index (CCI) and Vulnerable Elder Survey-13 (VES-13) were measured at baseline for correlation with RR, PFS and OS.
Results: Between 9/1/2006 and 4/15/2010, 34 patients enrolled. Median age was 75, 91% were non-Hispanic white, and 68% were male. Eleven of 29 (38%) patients were frail by VES-13 score. Histology was 47% adenocarcinoma, 29% squamous cell, 18% poorly differentiated, and 6% other. Patients who withdrew or died before response assessment were considered non-responders. Overall RR was 11/34 (32% with 95% CI 17%-51%), all partial responses, which met the primary endpoint. Median PFS and OS were 3.6 and 7.3 months,

respectively. Fourteen patients experienced 18 serious adverse events (SAE), including 4 deaths on treatment (1 infection, 1 pneumonitis, 2 cardiac). Neuropathy ≥ grade 2 occurred in 8 (24%), and myelosuppression ≥ grade 3 in 7 (21%). The CCI did not predict RR, PFS or OS. VES-13 score was a significant predictor of PFS and OS. Frail patients had significantly worse median PFS (3.2 vs. 4.5 months; p=0.02) and OS (4.8 vs. 12 months; p=0.02) than non-frail. Biomarkers of PDGFR pathway activation will be presented at the meeting.



Conclusion: The combination of imatinib and paclitaxel had excellent activity as measured by RR, however PFS and OS were typical for elderly patients with advanced NSCLC. Toxicity was acceptable. Further evaluation of this combination may be justified in patients selected for PDGFR pathway activation. The VES-13 was a powerful predictor of survival outcomes in this population.

Keywords: Non-small cell lung cancer, Elderly, VES-13, PDGFR

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P3.014 CLINICAL IMPACT OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION IN N2(+) NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH PLATINUM-BASED NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY

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Background: Epidermal growth factor receptor (EGFR) mutation is suggested to be associated with radiosensitivity of non-small cell lung cancer (NSCLC) in vitro. We attempted to analyze the clinical impact of EGFR mutation on the response to platinum-based neoadjuvant chemoradiotherapy (CCRT) in N2(+) NSCLC patients.

Methods: 161 patients with mediastinoscopy-proven N2(+) NSCLC received platinum-based neoadjuvant CCRT at Samsung Medical Center between 1998 and 2006. EGFR mutation was assessed by Peptide Nucleic Acid(PNA)-mediated PCR clamping method in 98 patients with available remained tumor tissue. 88 patients were finally included in analysis, excluding patients with indeterminate EGFR mutation results or patients who were lost to follow up during CCRT

Results: Among 88 patients, adenocarcinoma was 55.7% (n=49) and squamous carcinoma was 37.5% (n=33). EGFR mutation (exon 19 deletions or L858R) was detected in 13 patients (14.8%), and KRAS mutation in 2 patients (2.3%). After neoadjuvant CCRT, 5 patients showed progressive disease, pathologic downstaging of lymph nodes(LN) to N0 or N1 was achieved in 44 patients (50%), and pathologic CR in 13 patients (14.8%). Achievement of pathologic CR or pathologic downstaging of LNs were not associated with EGFR mutation status. With a median follow-up of 73.8 months, no significant differences were observed in overall survival (OS) or progession free survival (PFS) according to EGFR mutation status (OS 28.2 months vs 33.6 months in EGFR mutation positive vs. negative patients, p=0.125; PFS 15.2 months vs. 18.0 months in EGFR mutation positive vs. negative patients,p=0.631), respectively.

Conclusion: In N2-positive NSCLC patient, EGFR mutation status was not associated with cinical outcome in response to neoadjuvant CCRT, in terms of response rate, PFS or OS. Further study should be needed to confirm the association between EGFR mutation status and radiosensitivity in NSCLC patients.

Keywords: Epidermal growth factor receptor, Non small cell lung cancer, Radiotherapy

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P3.015 OPEN-LABEL, RANDOMISED MULTICENTRE, PHASE II TRIAL OF ORAL VINORELBINE (NVBO) OR INTRAVENOUS VINORELBINE (NVBIV) WITH CISPLATIN (CDDP) IN PATIENTS (PTS) WITH ADVANCED NON SMALL CELL LUNG CANCER (NSCLC): A CHINESE EXPERIENCE

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Background: Aim of the study : to evaluate efficacy (CR, PR) of the two formulations with CDDP in advanced NSCLC. Progression-free survival (PFS), overall survival (OS) and safety were secondary objectives.
Methods: NVBo, 60 mg/m² (arm A) and NVBiv, 25 mg/m² (arm B) were delivered on D1, D8, repeated every 3 weeks. Doses were increased at cycle-2 (NVBo 80 mg/m² - NVBiv 30 mg/m²) according to haematological tolerance. CDDP doses were 80 mg/m² D1 every 3 weeks in both arms. Pts received a maximum of 4 cycles in the absence of progression.
Results: Between 1/2008 and 6/2009, 132 pts were randomised at 6 investigational centres (cut-off date for final analysis : January, 15th 2010 - arm A 67 pts, arm B 65 pts). One patient in arm A was not treated. Among the 131 treated patients, 92 (71.9%) pts (54 - 84.4% arm A, 38 - 59.4% arm B), escalated NVBo and NVBiv doses and 36 did not (10 arm A, 26 arm B). Among the 131 pts analysed by an independent panel review, PR was 25.8% (95% CI [15.8-38.0]) in arm A and 23.1% (95% CI [13.5-35.2]) in arm B, with a disease control (PR+SD) of 72.7% (95% CI [60.4-83.0]) in arm A and 72.3% (95% CI [59.8-82.8]) in arm B. Other secondary endpoints were not yet reached at the cut-off date : for duration of response only 8/32 pts (25%) progressed, and for Overall Survival only 12/131 pts (9.2%) died : 8/66 arm A and 4/65 arm B (median follow-up 3.2 months). Median dose intensity for NVBo was 44.7 mg/m²/week, 15.6 mg/m²/week for NVBiv, with a relative dose intensity (RDI) of 89.3% for NVBo and 81.5% for NVBiv. The CDDP median dose intensity was 24.6 mg/m²/week in arm A and 24.5 mg/m²/week in arm B, with a RDI of 92.1% and 91.6% respectively. Grade 3/4 neutropenia : 29 pts and 43 cycles in arm A, 56 pts and 106 cycles in Arm B. Febrile neutropenia : 4 (6.1%) pts in arm A and 6 patients (9.2%) in arm B. Grade 3 anaemia : 6 (9.1%) pts and 10 cycles in arm A and 13 pts (20%) and 18 cycles in arm B, with grade 4 anaemia in 3 pts (4.6%) only in arm B. The most frequent non haematological disorders were nausea (8 pts Grade 3 - 12.1% arm A; 6 pts Grade 3 - 9.2% arm B) and vomiting (10 pts Grade 3 -15.2%, 1 pt Grade 4 - 1.5% arm A; 9 pts Grade 3- 13.8%, 1 pt Grade 4 - 1.5% arm B). Diarrhea was reported in 16 (24.2%) and 12 (18.5%) pts in arm A and arm B, respectively.
Conclusion: Both arms testing NVBo and NVBiv with CDDP reported similar efficacy results. The recommended NVBo dose titration from 60 to 80 mg/m² allowed to improve the haematological tolerance by keeping the same efficacy. NVBo is a step forward in the treatment of NSCLC since it optimises treatment convenience thanks to its oral formulation while maintaining a high level of efficacy.

Keywords: Advanced Lung Cancer, Chemotherapy, Navelbine oral, Vinorelbine

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P3.016 IMPACT OF THE 7TH EDITION OF TNM CLASSIFICATION (UICC7) IN NON-SURGICAL CASES OF ADVANCED NON-SMALL CELL LUNG CANCER

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Background: The 7th edition of the TNM classification (UICC7) in lung cancer has recently

been published. However, the impact of this new staging system has not yet been well examined in advanced non-small cell lung cancer (NSCLC), especially in non-surgical cases. In this study, we validated the prognostic value of this new staging system in advanced NSCLC patients who did not undergo surgery.
Methods: A total of 511 patients who were newly diagnosed to have NSCLC and were treated without surgery at our hospital between January 2005 and January 2010 were identified and reclassified according to the UICC7 criteria. All patients had either histologically or cytologically confirmed NSCLC and were clinically staged as either IIIA, IIIB or IV according to the 6th TNM classification (UICC6) criteria. The primary outcome measure was to compare the stage-specific overall survival (OS) of advanced NSCLC using both the UICC6 and UICC7.
Results: The patient characteristics were as follows: male/female: 338/ 173; median age: 66 years (30-81); histology, adeno/ squamous/ large/ other: 330/ 91/ 35/55; PS, 0/1/2/3/4/unknown: 264/ 194/ 30/ 13/ 5/ 5. Based on UICC6, 511 patients were staged as 69 IIIA/ 136 IIIB/ 306 IV. After reclassifying the case according to UICC7, 90 patients (17.6%) were differently staged (IIIA/IIIB/IV: 77/ 74/ 360). In addition, 9 IIIA, 17 IIIB, 59 IIIB and 5 IV cases were restaged to IIIB, IIIA, IV and IIIB, respectively. The reasons for these differences were due to malignant effusion being classified as M1 instead of T4 (59 cases), ipsilateral same-lobe nodules as T3 instead of T4 (6 cases), ipsilateral different-lobe nodules as T4 instead of M1 (5 cases) , peribronchial lymph node as the no.4 R node instead of the no.3 node (9 cases) and extension as T4; stage IIIB instead of T4N1; stage IIIA (11 cases). The median OS of stage IIIA, IIIB and IV of UICC6 were 23.8 months, 26.1 months and 13.3 months, respectively and the median OS of stage IIIA, IIIB and IV of UICC7 were 29.0 months, 22.8 months and 14.3 months, respectively. The OS curves of stage IIIA and IIIB of UICC6 were substantially overlapped, whereas the OS curves of stage IIIA, IIIB and IV cases according to UICC7 could be clearly distinguished.
Conclusion: The UICC7 staging system is therefore considered to be able to better predict advanced NSCLC than UICC6, even in non-surgical cases.
Keywords: UICC7, TNM classification, Advanced NSCLC

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P3.017 CURATIVE TREATMENT VS. BEST SUPPORTIVE CARE IN ADVANCED NON-SMALL CELL LUNG CANCER OVER AGE 70

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Background: With the introduction of new chemotherapeutics showing better efficacy and low side effects, curative treatment (CT) in lung cancer has been extended to over aged patients in recent years. However, the patients and their family provide negative minds for the definitive treatment of curative aim in aged person. It was reevaluated whether the curative anticancer treatment including chemotherapy and/or radiation therapy of curative aim had a survival benefit comparing to best supportive care(BSC) especially in aged advanced lung cancer subjects.
Methods: The data was retrieved retrospectively from medical records of 618 patients who had been diagnosed as non-small cell lung cancer (NSCLC) in tertiary university hospital from 2000 through 2007. The analysis was confined to 146 subjects of stage IIIb or IV NSCLC over 70 years old, excluding cases of insufficient data, chemotherapy less than two times, or follow up loss after diagnosis. For the staging, 7th edition of TNM staging was applied.
Results: The mean age at diagnosis was 77 years old (range: 70-95). In good performance group (ECOG, 0-1) was 109 patients(75%) and bad performance group(ECOG, 2-3) was 37(25%). The mean survival time following the diagnosis was 10.0± 12.8 months(m). As compared to BSC(n=92), the curative treatment group(n=54) showed the better survival rate (CT median 7± 0.9 m, 95% confidence interval [CI]: 5.2-8.8 vs. BSC median 4± 0.8 m, 95% CI: 2.3-5.7, p= 0.008). Within good performance group, the better survival rate was also shown in curative treatment group than BSC (CT median 7 ± 0.9 m, 95% CI: 5.2-8.8 vs. BSC median 4 ± 1.1 m, 95% CI: 1.8-6.2, p= 0.036). Contrarily, within bad performance group, there was no significant survival gain in curative treatment over BSC(CT median 10 ± 5.0m, 95% CI: 0.3-19.7 vs. BSC median 3 ± 1.5m,

95% CI: 0.2-5.8, p= 0.076).
Conclusion: The survival benefit was observed in curative treatment, especially in good performance status, compared to best supportive care. In relatively poor performance status over ECOG 1, although the outcome of survival time had a little superior tendency in curative treatment comparing to supportive care without statistical significance, meticulous attention should be given in treatment decision. In over 70 years old, advanced NSCLC, we recommend that treatment of curative aim has to try in good performance status and in relatively bad performance, the decision should be individualized carefully.
Keywords: Lung cancer, survival, curative treatment, best supportive care

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P3.018 MESSENGER RNA VACCINATION IN NSCLC- FINDINGS FROM A PHASE I/IIA CLINICAL TRIAL

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Background: Based on self-adjuvanted mRNA molecules we developed a novel vaccination technology using a therapeutic cancer vaccine for non small cell lung cancer (NSCLC). CV9201 contains five mRNAs encoding NSCLC associated tumor antigens (NY-ESO1, Mage-C1, Mage-C2, Survivin, 5T4). Here, we report preliminary results of a phase I/IIa trial. Stage IIIb/IV NSCLC patients that showed no tumor progression after first line chemo- or chemo-radiotherapy were treated with CV9201. Primary endpoint was assessment of safety and tolerability of CV9201 and secondary endpoints were evaluation of induction of immune response and assessment of anti-tumor activity.
Methods: Patients were vaccinated intra-dermally up to five times in max. 15 weeks. A total of 9 patients were vaccinated in the phase I part of the study, 3 patients each at three different dose levels (400μg, 800μg and 1600μg total mRNA administered). The highest dose level was then continued within the phase IIa part. Blood samples were taken before the first vaccination and two weeks after the 3rd and 5th vaccination respectively, and peripheral blood mononuclear cells (PBMCs) were isolated. PBMCs were later on analyzed for induction of effector and memory T-cell subsets, B-cells and CD4+CD25++ T regulatory cells. Antibody production was analyzed by IgM and IgG ELISA against the vaccination antigens used and antigen-specific T-cell responses were analyzed by IFN-g ELISPOT, ICS and tetramer analysis.
Results: Phase I safety analysis showed neither vaccine-related serious adverse events nor dose-limiting toxicity. Most notably treatment related grade 1 injection site reactions and grade 2 fever were reported. After 3 vaccinations, frequency of B-cells increased. In 41% of the 17 patients analyzed so far a significant ($P < 0.01$) shift from IgD+CD38+/- naïve B-cells towards IgD+CD38++ germinal center founder B-cells by > 2 fold was observed. T-cell population tends to shift from effector to memory subtype 2 weeks after the final vaccination. Antigen-specific antibodies, CD4+ and CD8+ T-cell responses were detected after vaccination with CV9201.
Conclusion: The interim analysis indicates that vaccination with CV9201 induces an adaptive immune activation and detectable antigen-specific humoral and cellular immune responses. Further, this novel class of vaccines appears to be safe and well tolerated by patients with advanced NSCLC.
Keywords: GC-founder B-cells, antigen-specific

T-cell responses, mRNA vaccination, immune therapy

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P3.019 EFFECT OF ALK KINASE INHIBITOR (CRIZOTINIB)AGAINST ALK FUSION GENE POSITIVE LUNG CANCER PATIENTS AND THE PATTERN OF RECURRENCES

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Background: Anaplastic lymphoma kinase (ALK) fusion gene-positive lung cancer accounts for 4-5% of non-small cell lung carcinoma. A clinical trial of the specific inhibitor of ALK fusion-type tyrosine kinase(Crizotinib) is currently under way.
Methods: ALK fusion gene products were analyzed immunohistochemically with the materials obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from mediastinal lymphnodes of lung cancer patients. After we obtained informed consent and eligibility criteria, 3 patients were enrolled for the Pfizer Study of Crizotinib (PF02341066), Clinical Trial A8081001, conducted at Seoul National University.
Results: Case 1 A 48-year-old male patient had ALK fusion gene positive lung adenocarcinoma (T3N2M1 stage IV). was enrolled in a trial of crizotinib (PF02341066) at Seoul National University. Almost all the bone and lymph node metastases disappeared except for those at the left vertebral arch of L5. The control of the primary and metastatic tumors continued for 11 months until multiple brain metastases were found. Case 2 A 49-year-old female, with T1N3M1 stage IV ALK positive adenocarcinoma was enrolled to the study from July 2009. A PET scan performed 5 weeks after the initiation of the therapy showed marked reduction of bone and lymph node metastases. The response was stable until the end of July 2010 when multiple brain metastases were found. Case 3 A fifty-four-year-old female started the study from November 2009. A PET scan demonstrated complete disappearance of the primary tumor as well as all the metastases except for a bone metastasis to the right 8th rib. Control of the tumor was observed until Des 2010 when she complained dyspnea with local recurrence and both side pleural effusion. Initial response was encouraging but all three cases had recurrence within 12 months. Two cases in distant metastasis to brain and one in local recurrence. ALK fusion gene expression in the recurrences of brain or pleural effusion by immunohistochemical methods was negative in case 1 and positive in case 2 and 3.
Conclusion: ALK kinase inhibitor, Crizotinib, is effective in ALK fusion gene positive lung cancer patients but further analysis is necessary for the prevention of recurrences . .
Keywords: Crizotinib, Lung cancer, recurrence, EML4-ALK

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P3.020 TWO NSCLC PATIENTS ACHIEVED PR BY ARQ 197 MONOTHERAPY - FINAL RESULT OF THE FIRST ASIAN PHASE I TRIAL OF SELECTIVE C-MET INHIBITOR ARQ 197

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Background: Tivantinib (ARQ 197) is a selective, non-ATP competitive inhibitor of c-MET, a receptor

tyrosine kinase implicated in tumor cell migration, invasion and proliferation. In this first Asian phase I study that was conducted in Japan, we examined the drug's safety profile, pharmacokinetics, biomarkers and preliminary antitumor activity and determined Recommended-phase-2 dose (RP2D) in patients (pts) with metastatic solid tumors. ARQ 197 is mainly metabolized by CYP2C19 of which is known; it is reported that the ratio of the poor metabolizer (PM) of CYP2C19 in Asian countries is around 20 % and much higher than Western countries. We established RP2D of ARQ 197 for extensive metabolizer (EM) and PM pts separately while RP2D in western countries was determined to be 360 mg bid.
Methods: ARQ 197 was administered orally at 8 dose levels from 70 to 360 mg bid in a standard 3+3 dose escalation design. We tested CYP2C19 genotype in advance and enrolled EM and PM pts separately from 120 mg bid.
Results: Forty-seven pts consisted of 33 EM pts (median age: 61.0 yrs; ECOG PS 0/1: 15/18; median prior therapies: 4) and 14 PM pts (median age: 59.5 yrs; ECOG PS 0/1: 6/8; median prior therapies: 4) were treated. The most common drug-related adverse events (AEs) were fatigue, leukopenia, anemia, neutropenia and anorexia. The severe AEs were hematologic toxicities such as neutropenia. Gr.4 neutropenia occurred in 1 of 6 EM pts at 360 mg bid and 3 of 7 PM pts at 240 mg bid, which identified each dosage as RP2D for EM and PM respectively. At 240 mg bid, the ARQ 197 C_{max} and $AUC_{0\text{-}12}$ of PM pts were respectively, which might lead higher incidence of severe neutropenia at lower dose in PM pts. Two NSCLC pts, both of whom were PM at 240 mg bid and treated 4 or more prior systemic chemotherapies including EGFR-TKI, achieved partial response and 16 pts (34.0%) had stable disease (SD) for >= 16 weeks, especially 6 of 25 pts (24.0 %) in NSCLC had SD for >= 28 weeks. Findings from biomarker study will be also presented.
Conclusion: ARQ 197 was well tolerated. The most common adverse events were hematologic toxicities. CYP2C19 polymorphism clearly affected the exposure to ARQ 197 which led different RP2Ds, 360 mg bid for EM pts and 240 mg bid for PM pts. ARQ 197 monotherapy showed a clear sign of activity against NSCLC. Further study for NSCLC is warranted.
Keywords: ARQ 197, Tivantinib, c-Met tyrosine kinase inhibitor, CYP2C19 polymorphism

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P3.021 3D-CT GUIDED PERCUTANEOUS RADIOFREQUENCY ABLATION AGAINST ADVANCED NON-SMALL CELL LUNG CANCER:SHORT TERM EFFECT ASSESSMENT

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Background: Although the most effective treatment for lung cancer is surgery at present, 70% of lung tumors are not suitable for potentially curative resection. There are two main reasons that account for the unsuitability of surgery as the prime treatment modality: advanced stage due to lack of effective early diagnostic method and poor operation tolerance due to advanced age or co-morbid medical conditions. In recent years, Radio Frequency Ablation (RFA), a newly-developed local physiotherapy, has been applied as an alternative therapeutic strategy for lung cancer, receiving remarkable clinical effect.
Methods: After 2007,2, we used RITA radiofrequency therapeutic equipment to treat advanced non-small cell lung cancer under the guidance of spiral CT (Siemens) and three dimensional reconstruction of the image. The target temperature is 90 centidegree. We inserted the electrode needle into tumor, opened anchor electrodes and ablated according to tumor size and shape. Insertion of electrodes was similar as in percutaneous pneumocentesis biopsy. By virtue of CT scan, which revealed tumor size, position and its anatomical relation with neighboring organs, such as diaphragm, heart, great vessels and pleural wall, we chose the nearest position to tumor, measured and figured out the inserting angle and depth, making sure that the vital part would not be injured by mistake and all the tumor should be covered by ablation. With local anesthesia, electrode needle was inserted into tumor and the insertion was checked by CT. Afterwards, we opened anchor electrodes to maximum diameter as planned and scanned CT to locate the main needle and every anchor needle. Finally we ablated when all the steps above met requirements. After lesion ablation, we closed the anchor electrodes and ablated Needle-tract. Chest CT was then re-checked to observe pneumothorax

and bleeding, which may be managed immediately if necessary.
Results: We performed 29 RFAs on 25 patients. In the follow-up, 10 of them showed tumor shrinkage by CT scan . There were 23 showed lack of tumor-uptake value by SPECT scan and 2 showed lower tumor-uptake value. There were 5 cases of fever, 7 pneumothorax, and 5 bleeding. Among the 7 cases of pneumothorax, 2 were relieved by drainage and the other 5 were not treated because their conditions were self-limited. No serious complications or perioperational death occurred.
Conclusion: CT-guided percutaneous RFA is safe and practical for lung cancer. It has satisfactory short-term effect to reduce tumor burden.
Keywords: Advanced Non-Small Cell Lung Cancer, radiofrequency ablation

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P3.022 PONDERING SYMPTOMS MAGNITUDE IN QUALITY OF LIFE FOR BRAZILIAN LUNG CANCER PATIENTS: A CLUSTER ANALYSIS

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Background: Patients with lung cancer have more symptoms distress than patients with other type of cancer, especially near the end of life. The aim of this study was to examine the prevalence of symptoms in lung cancer patients; to identify subgroups (cluster solutions) according to symptoms magnitude; and to compare the quality of life among the identified symptoms subgroups.
Methods: This is a cross sectional study using a hierarchical agglomerative cluster analysis. Subject characteristics and the scores of the Quality of Life Questionnaires (EORTC QLQ-C30, FACT-L and SF-36) were obtained from all included lung cancer patients. The cluster analysis took into account a set of symptom magnitude measure from the EORTC QLQ-C30 symptom scales (higher prevalence): fatigue, pain, dyspnea and insomnia, which are not standardized assessment for functioning and global quality of life.
Results: A distinct and interpretable three-cluster solution was identified by an order of magnitude of the four most prevalent symptoms. The three subgroups were called as: Mild Symptom Group (n=30; 60%); Moderate Symptom Group (n=14, 28%); Severe Symptom Group (n=6, 12%). To evaluate quality of life, the average score values for each scale of EORTC QLQ-C30, FACT-L e SF-36 were stratified by the cluster solution. The Severe Symptoms Group had the worst quality of life based not on total scores alone, but rather on integrated dimensions, in all three instruments studied.
Conclusion: Increasing in the magnitude of symptoms had a negative impact on quality of life of lung cancer patients. We highlight the importance of evaluation by cluster of symptoms as an important issue to assess quality of life in patients with chronic diseases such as lung cancer.
Keywords: symptom cluster, Lung cancer, Quality of Life

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P3.023 FIRST-LINE MODIFIED SCHEDULE OF GEMCITABINE WITH A LOWER DOSE THAN STANDARD IN VERY ELDERLY OR PS 2 PATIENTS WITH ADVANCED NSCLC

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Background: Monochemotherapy with gemcitabine (Gem) is often the treatment of choice in elderly or poor performance status (PS) patients with advanced non-small cell lung cancer (NSCLC). Our study was aimed to assess the efficacy and tolerability of a modified schedule of Gem using a lower dose than standard.
Methods: From May 2009 through December 2010, fifty patients (43 males and 7 females with a median age of 76 years (64 to 85) with advanced NSCLC (stage IIIB 34,0% and IV 66,0%) were enrolled. Histology were: squamous 39,6%, adenocarcinoma 31,2%, large cell 6,2 %, undifferentiated 4,2 %, undetermined 18,8%. Only eight patients (16,0%) had a WHO PS 0 whereas nineteen (38,0%) were PS 1 and eleven (46,0%) PS 2. All patients received first-line chemotherapy with 6 cycles of Gem 1000 mg/sq on days 1 and 8 every 4 weeks.

Results: At the time of analysis 35 patients were evaluable for response. Partial response (PR) was achieved in 7 patients (20,0%), stable disease > 12 weeks (SD) in 16 (45,7%) whereas 12 had progressive disease (34,3%). Importantly, the clinical benefit rate (PR + SD) was 65,7%. Quality of life was mesured with EORTC QoL 3.0 Questionary. Both pain and PS improved in 6 patients (17,1%) whereas 19 (54,2%) had an improvement in pain with no worsening of PS. We observed only grade 2 NCCTs version 3 haematological toxicities including anemia, leucopenia, neutropenia and trombocytopenia. Not febrile neutropenia occurred in 4 patients (11,4%). Overall, we did not observe any not-haematological treatment-related event.
Conclusion: Our data show that a modified schedule of Gem with a lower dose intensity than standard may be beneficial in terms of both disease control and tolerability when employed in elderly or PS 2 patients with advanced NSCLC. These data are similar to published data in elderly. At ASCO meeting we present all data about 50 pts enrolled.
Keywords: Lung cancer, PS 2
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P3.024 INDIVIDUALIZED CHEMOTHERAPY IN THE ADVANCED NSCLC PATIENTS BASED ON THE MRNA LEVEL OF BRCA1 AND RRM1

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Background: Experimental evidence suggests that BRCA1 overexpression enhances sensitivity to docetaxel and resistance to cisplatin and RRM1 overexpression enhances resistance to gemcitabine. In order to further investigate the effect of BRCA1 and RRM1 mRNA levels on outcome in advanced NSCLC, we performed this phase II clinical trial, testing the hypothesis that customized therapy would confer improved outcome over non-customized therapy.

Methods: RNA was isolated from fresh tumor tissue. The chemotherapy regimen that patients received was based on their BRCA1 and RRM1 mRNA levels: both low, cisplatin plus gemcitabine(GP); both high novelbine plus cisplatin(NP); BRCA1 low and RRM1 high, cisplatin plus docetaxel(DP); BRCA1 high and RRM1 low, novelbine plus gemcitabine(GN).
Results: From Dec 2005 to Nov 2008, 94 metastatic or local advanced NSCLC patients in our institute were enrolled into this study. The median age was 58 years old and 76% were male. Among them, 21 patients received GP, 30 patients received TP, 43 patients received NP and no patient received NP chemotherapy. GP group got a numerically higher response rate, longer median time to progression and median overall survival time than the other 2 group. The response rate in the GP,TP and NP group were 42.9%, 36.7% and 27.9% respectively(P=0.568), Median time to progression was 5.6,5.0,4.8 months (P=0.975)and median overall survival was 12.5,11,9.7 months(P=0.808) respectively(Seen in Table 1). Table 1, Efficacy of patients according to the treatment group

Regimen	N	Response			TTP	OS
		PR	SD	PD		
GP	21	9	9	3	5.6	12.5
TP	30	11	10	9	5.0	11
NP	43	12	19	12	4.8	9.7
Total	94	32	38	24	5	11

PR: partial response, SD: stable disease, PD: progression disease

Conclusion: Chemotherapy customized according to BRCA1 and RRM1 expression levels is associated with numerically higher response rate and longer TTP and OS time in the GP group, which may be caused the controversial function of the BRCA1 and RRM1 mRNA at the initiation period of this trial, and suggested that BRCA1 and RRM1 mRNA levels could be used as biomarker in individual therapy in NSCLC.
Keywords: Non small cell lung cancer, Individualized chemotherapy, BRCA1, RRM1

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P3.025 AN OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE IB/II STUDY OF ERIBULIN MESYLATE ADMINISTERED IN COMBINATION WITH PEMETREXED VERSUS PEMETREXED ALONE AS SECOND-LINE THERAPY IN PATIENTS WITH STAGE IIIB OR IV NON-SQUAMOUS NSCLC: PRELIMINARY PHASE IB RESULTS

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Background: Eribulin mesylate (E7389, Halaven™) is a fully synthetic analog of the marine sponge natural product halichondrin B that inhibits microtubule dynamics, triggering apoptosis of cancer cells following prolonged mitotic blockade in vitro. In a previous Phase II study in NSCLC patients treated with a median of two prior therapies, eribulin had an overall PR rate of 9.7% and median OS was 9.6 months. Treatment options in second-line NSCLC have demonstrated modest clinical benefit. Pemetrexed, as monotherapy, has demonstrated a median PFS of 2.9 months in this disease setting.
Methods: The current trial is an open-label, multicenter, randomized study consisting of Phase Ib (three ascending doses of eribulin in each of two parallel dosing schedule arms to determine the MTD) and Phase II (randomized design to determine safety and preliminary efficacy) in patients with measurable, non-squamous NSCLC, previously treated with one cytotoxic chemotherapy regimen for stage IIIB with malignant pleural effusion or stage IV disease.

Results: In Phase Ib, 15 patients (median age, 53.5 years; 10 male) were enrolled; a median of two cycles (range, 1–8) were delivered. In Arm 1, 10 patients were escalated from 0.9 to 1.4 mg/m^2 eribulin with pemetrexed (500 mg/m^2) on Day 1 of each 21-day cycle. In Arm 2, 5 patients were dosed with 0.7 mg/m^2 eribulin on Days 1 and 8, with pemetrexed (500 mg/m^2) on Day 1 of each 21-day cycle. DLTs are summarized below.

Arm	Eribulin dose (mg/m^2)	n	# DLTs	DLTs
1 (Day 1 eribulin/Day 1 pemetrexed)	0.9	4	0	
	1.4	6	3	Grade 3 transaminitis Grade 4 febrile neutropenia Grade 4 thrombocytopenia
2 (Day 1 and 8 eribulin/ Day 1 pemetrexed)	0.7	5	2	Grade 3 transaminitis Grade 4 pneumonia

The MTD for Arm 1 was 0.9 mg/m^2, but was not determined for Arm 2 as the acceptable DLT frequency was exceeded at the initial dose level. The most common adverse events at the MTD in Arm 1 were neutropenia (4 patients), leukopenia (3 patients), anemia (3 patients), fatigue, rash, cellulitis, hypokalemia, asthenia, nausea, diarrhea, and anorexia (2 patients each). The best response at the MTD in Arm 1 was PR (2 patients). Median PFS at the MTD in Arm 1 was 5.25 months.
Conclusion: The recommended Phase II dose of 0.9 mg/m^2 with pemetrexed 500 mg/m^2 was generally well tolerated with an expected toxicity profile. Encouraging clinical activity was noted on this schedule. Owing to lack of determination of an MTD in Arm 2, the Phase II portion of the study will be amended to a 1:1 randomization of Arm 1 (Day 1 eribulin plus Day 1 pemetrexed) versus Arm 2 (Day 1 pemetrexed alone).
Keywords: Eribulin, E7389, NSCLC, lung

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P3.026 SURVIVAL AFTER RADIOFREQUENCY ABLATION (RFA) FOR 100 CASES OF LUNG NEOPLASMS

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Background: Surgical resection is the preferred treatment in selected patients with pulmonary neoplasms. In older than 70 years or have compromised cardiopulmonary status or coexistent medical problems patients, radiofrequency ablation (RFA) may offer an alternative option. Our objectives were to evaluate the long-term outcomes after RFA in 100 patients with pulmonary neoplasms.
Methods: One handred cases of unresectable lung tumors with 106 lesions were underwent RFA therapy.To evaluate the long-term therapeutic effect and complications of lung tumors using spiral CT scanning and SPECT in 1-3 months after RFA.
Results: One hundred patients underwent RFA for lung neoplasms (62 men,38 women;median age, 66.6 years; range, 36 to 91 years).Eighty-six patients with primary lung neoplasms and 14 patients with pulmonary metastases underwent RFA. Treatment was complete in all cases,no procedure-related deaths occurred in all of the 106 ablation procedures and serious morbidity associated with the procedures. The median overall survival for the entire group of patients was 13.0 months, the 1 and 2 years overall survival for total of were 51% and 32.5% respectively. No differences in overall survival noted between patients with primary lung neoplasms or lung metastases (p=0.922). The median overall survival for the early stage of patients was 28.0 months, 2-year overall survival for early stage primary lung cancer patients were 57.7%.
Conclusion: RFA is a safe and effective procedure in unresectable lung tumors. CT-guided radiofrequency ablation is a minimally invasive treatment option. RFA could act as an alternative treatment to inoperable early stage lung cancer and cytoreductive treatment for advanced lung cancer.
Keywords: radiofrequency ablation, survival, Lung neoplasms

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P3.027 PHASE II TRIAL OF ERLOTINIB IN PREVIOUSLY TREATED PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Erlotinib has been shown to have an antitumor activity as a single agent against previously treated NSCLC. The objective of this study was to assess the efficacy and safety of erlotinib in patients with relapsed NSCLC.
Methods: Patients with histologically or cytologically confirmed NSCLC, more than 20 years in age, performance status 0-2, with a history of receiving one or two chemotherapy regimen(s) were eligible for the study. Treatment was consisted of erlotinib (150 mg/day) on everyday. The primary endpoint was the response rate (RR), and planned sample size for this phase II study was 38 patients (Simon's two-stage minimax design).
Results: Thirty-three patients were enrolled and 33 patients (22 males/11 females, median age, 69 years) receive protocol treatment in this phase II trial. The histological diagnosis was adenocarcinoma in 24 patients (72.7%), squamous cell carcinoma in 5 patients (15.2%), and unclassified in 4 patients (12.1%). Twelve patients (36.4%) were PS0, 16 patients (48.5%) were PS1, and 5 patients (15.1%) were PS2. The progression free survival time was 131 days. The overall response rate was obtained in 27.3% of the patients. Ten patients (30.3%) had EGFR mutation-positive tumors and 12 patients (36.4%) had EGFR mutation-negative tumors. EGFR mutations in 11 patients (33.3%) were not analyzed. Disease control rate was 51.5%. The response rates of EGFR mutation-positive/negative/unknown patients were 50.0%/16.7%/18.1%, respectively. The progression free survival time of EGFR mutation-positive/negative/unknown patients were 418 days/52 days/115 days, respectively.

Conclusion: Erlotinib is an active regimen for EGFR mutation-positive patients with NSCLC:
Keywords: erlotinib, Non-small cell lung cancer, phase II trial

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.028 PRELIMINARY EVIDENCE OF ACTIVITY OF ACE-041, A NOVEL INHIBITOR OF ALK1-MEDIATED ANGIOGENESIS, IN PATIENTS WITH REFRACTORY NSCLC TREATED IN A PHASE 1 DOSE-ESCALATION STUDY

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Background: Activin receptor-like kinase-1 (ALK1), a type I receptor in the TGF-beta superfamily, is selectively expressed on activated endothelial cells and is required for vascular maturation and the development of capillary beds. ALK1 is widely expressed on human tumor endothelium, including approximately 25% and 35% of non-squamous and squamous NSCLC tumor biopsy samples tested. ACE-041 is an ALK1 ligand trap, which binds with high affinity to BMP9 and BMP10, and prevents activation of ALK1 receptors. In xenograft studies using mice implanted with Calu-6 lung tumors, treatment with ACE-041 significantly decreased tumor vascularization and burden compared to vehicle-treated mice. A Phase 1 clinical study of ACE-041 in advanced, heavily pre-treated cancer patients was recently fully enrolled and results for patients with NSCLC are presented here.
Methods: This was a multi-center Phase 1 study to evaluate the safety, tolerability, PK, PD and preliminary antitumor activity of ACE-041 in patients with advanced cancer who had previously progressed on chemotherapy and/or anti-VEGF therapy. A total of 37 patients were enrolled; the first 25 patients were enrolled in 7 dose-escalating cohorts (0.1 to 4.8 mg/kg SC; treatment cycle 3 weeks) and an expansion cohort of 12 patients was enrolled at either 0.8 or 1.6 mg/kg.
Results: ACE-041 was generally well-tolerated. Common AEs included fatigue, peripheral edema, nausea, anemia, headache, anorexia, and dyspnea. Possibly or probably related SAEs in 4 patients included fluid overload (2), CHF, and LV dysfunction. Edema and fluid overload were dose-dependent and responded to diuretic therapy. Due to DLT of fluid overload seen at higher dose levels, dose expansion was performed at intermediate dose levels. Of the 37 patients enrolled, six were NSCLC patients, (3 with squamous and and 3 with non-squamous histology). Three of the six NSCLC patients had periods of stable disease, including a non-squamous NSCLC patient who had 8 cycles (24 weeks) of ACE-041 at 0.4 mg/kg, a squamous NSCLC patient who has had 6 cycles (18 weeks) of ACE-041 at 1.6 mg/kg, and a squamous NSCLC patient who has had 12 cycles (36 weeks) of ACE-041 at 3.2/1.6 mg/kg (still on study at time of abstract submission). The preliminary estimate of median progression-free survival for the NSCLC patients in this study was 17.5 weeks (95% CI: 8.6 - 22.0 weeks). Of the 5 NSCLC patients with FDG-PET scans available, the mean maximal change in SUV was -34% (range: -14%, -62%). The one NSCLC patient (squamous histology, stable disease, 6 cycles of ACE-041) with DCE-MRI scans available had a 30% and 37% decrease in Ktrans from baseline to days 15 and 43, respectively, indicating a reduction in tumor blood flow.
Conclusion: ACE-041 is a first-in-class angiogenesis inhibitor that targets the ALK1 receptor pathway. Preliminary results for this Phase 1 data show that ACE-041 was generally well-tolerated and demonstrated antitumor activity in patients with NSCLC refractory to other therapies. A Phase 2 study of ACE-041 in NSCLC patients is being planned.
Keywords: ACE-041, ALK1, activin receptor-like kinase-1, angiogenesis inhibitor

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P3.029 PEMETREXED + GEMCITABINE VS CARBOPLATIN+GEMCITABINE: A RANDOMIZED NON-INFERIORITY PHASE II STUDY IN ONE CENTER

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Background: The standard treatment for inoperable non-small cell lung cancer is a combination of cytostatics, one of which should be a platinum compound. We questioned whether the platinum could be replaced with a modern cytostatic.
Methods: From January,2006 to October,2009, patients in PS WHO 0-2 and Stage III Bwet or IV according to the then used TNM classification were randomized to either Gemcitabine 1250 mg/m^2 day 1 and 8 + Carboplatin 5 AUC day 1 (GC arm), or Pemetrexed 500 mg/m^2 + Gemcitabine 1500 mg/m^2 every third week (PG), after informed consent. In this way the length of treatment was the same and the total dose of Gemcitabine almost the same.
Results: Forty-six patients were randomized to the PG group, and 50 to the GC. At least one course was given to 43 PG and 48 GC. There groups were well matched in smoking habits, type of cancer, age etc. Mean age was 69 years. In the GC group, dose adjustment was necessary in 58%, and in the PG 27% of the patients. The side effects were similar with grade 3 (mainly hematological) in 31% of AC and 33 in the PG groups, respectively. The mean TTP in both groups was 5 months. Mean survival was 10 months in GC and 15 months in the PG group.
Conclusion: Replacing Carboplatin with Pemetrexed in the first-line treatment of NSCLC will not increase side effects. There was a tendency to better survival in the Pemetrexed group, but the study was not powered to show this. Further studies with the combination Pemetrexed + Gemcitabine seem warranted.
Keywords: NSCLC, Cytostatics, gemcitabine, Pemetrexed

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P3.030 CLINICAL BENEFITS OF SEQUENTIAL ADMINISTRATION OF DOCETAXEL AND INTERMITTENT ERLOTINIB AS A SECOND-LINE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC), A PHASE II RANDOMIZED STUDY

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Background: Erlotinib (E) has shown efficacy in 2nd line treatment in patients with advanced NSCLC; however, the combination of E and chemotherapy (CT) in first line therapy has not demonstrate to be superior to CT alone, probably due to an antagonism between CT and E concurrently administered. Several preclinical and phase I studies have suggested that sequential administration of E and docetaxel could avoid the suggested negative interaction and hence optimize the benefit in patients (P) with advanced NSCLC. This randomized phase II was designed to address the clinical benefit obtained with the use of sequential administration of docetaxel and intermittent E.
Methods: 70 p with advanced NSCLC progressing to previous platinum based chemotherapy for advanced disease were randomized (1:1):
• Group A (n = 34): Docetaxel 75 mg/m^2 day 1 and intermittent E (day 2-16), up to 4 cycles, followed by E in monotherapy
• Group B (n = 36): E in monotherapy.
Treatment was administered until unacceptable toxicity or disease progression. Primary endpoint: rate of p free of progression at 6 months; secondary endpoints: progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. The study has completed enrolment. Data from 32 p included are shown: 15 in Group A/17 in Group B.
Results: Baseline characteristics: non-

adenocarcinoma (71%), current/former smokers (93.7%), male (90.6%) and stage IV (83.9%). 6 months PFS: 14.3% in the sequential arm. Median PFS: 2.3 months (m) in Group A (95% CI 1.9 – 3.1) and 3.1 m in Group B (95% CI 2.0 – 4.5). Median OS: 4.9 m (95% CI 2.7 - -) in group A, slightly different than in Group B (6.0 m; 95% CI 2.5 – 6.0). DCR: 25% in the experimental group (95% CI 0.5 – 49.5) and 50% (95% CI 23.8 – 76.2) in group B. Adverse events (AEs), including skin rash and diarrhea, were all generally tolerable. Although the incidence of treatment-related AEs was higher in Group A than in B, AEs leading to dose reduction were more frequent in the E arm (11.8% vs. 6.7%).
Conclusion: Data from 6 months PFS of the sequential arm may suggest a potential benefit of the combination, although this preliminary analysis shows no impact in the PFS and OS of this sequential treatment. Final analysis of the study will be reported.
Keywords: erlotinib, Docetaxel, Sequential erlotinib

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.031 A PRECLINICAL AND CLINICAL PHASE I/II STUDY OF ABT-751 IN COMBINATION WITH CARBOPLATIN IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED LUNG CANCER

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Background: Lung cancer is the leading cause of cancer-related death in the United States. New effective treatments for advanced stage non-small cell lung cancer (NSCLC) are needed. Combination chemotherapy using drugs that could act cooperatively at different targets are appealing to consider for the treatment of advanced NSCLC. In this study, we conducted in vitro studies as well as a phase I/II clinical trial to explore the effects of combining a novel microtubule-interfering drug (ABT-751) and the US FDA-approved drug carboplatin, as both drugs were previously shown to have anti-neoplastic effects against lung cancer based on preclinical or clinical evidence.
Methods: For in vitro studies, the human lung cancer cell lines HOP62, A549 and U1571 were each studied to determine the single agent anti-neoplastic effects of ABT-751 as well as the combined effects of ABT-751 with carboplatin. The primary endpoint of the in vitro studies were induced growth inhibitory response in these lung cancer cells, the secondary endpoints were induction of apoptosis and the repressed expression of the cell cycle regulator cyclin D1. We conducted a phase I/II clinical trial of the combination of ABT-751 and carboplatin in patients with advanced previously treated NSCLC. The primary endpoint for the phase I portion of the trial was determination of the maximum tolerated dose (MTD) of the combination, the secondary endpoints were dose-limiting toxicity (DLT) and side effects profile. For the phase II portion of the trial, the primary efficacy endpoint was objective response rate after two cycles of treatment, the secondary endpoints were median survival, time to progression, and evaluation of pharmacodynamic markers in pre-treatment versus post-treatment buccal swabs.
Results: In vitro studies of the combination of ABT-751 and carboplatin showed cooperative growth inhibitory effects associated with increased apoptosis in HOP62 and A549 cells and decreased cyclin D1 expression in HOP62 cells. These findings were translated into the clinic with the enrollment of 20 patients with advanced NSCLC previously treated with a carboplatin-containing regimen. Nineteen patients received study treatment. The MTD for ABT-751 was 125mg twice daily for 7 days with carboplatin AUC of 6 given every 21 days. DLTs included fatigue, neutropenia and ileus. The most common side effects were constipation, anemia, thrombocytopenia, nausea and fatigue. These doses of ABT-751 and carboplatin were used in the phase II portion of this trial. Two patients (11%) had a partial response after two cycles. The median survival was 11.7 months (95% CI 5.9-27.0) and the time to progression was 2.8 months (95% CI 2.0-2.7). Four of the six paired pre-treatment versus post-treatment buccal swab samples showed a decrease in cyclin D1 expression in the post-treatment as compared to the pre-treatment swabs.
Conclusion: The combination of ABT-751 and

carboplatin induces apoptosis in lung cancer cell lines but has moderate activity in advanced NSCLC previously treated with carboplatin. Further studies in chemotherapy-naïve patients are warranted.
Keywords: ABT-751, Carboplatin, Phase I/II clinical trial, Advanced stage NSCLC

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P3.032 EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION TESTING AND FIRST LINE TREATMENT WITH GEFITINIB IS A DOMINANT STRATEGY IN THE TREATMENT OF ASIAN AND EUROPEAN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Gefitinib improves response rates, progression-free survival and quality of life (QOL) when compared to chemotherapy in patients with advanced NSCLC who have activating EGFR mutations. Yet, little is known about the cost-effectiveness (CE) of EGFR mutation testing followed by therapy guided by mutational status.
Methods: A decision-analytic model was developed to determine the CE of EGFR testing and guided therapy with 1st line gefitinib and 2nd line chemotherapy for patients with activating mutations (and 1st line chemotherapy and no gefitinib for patients without) vs. standard care: first line chemotherapy and gefitinib at progression in unselected patients. Clinical data are derived from three published randomized clinical trials and societal costs from three cancer centers in Singapore and one in Italy. Health effects were expressed as quality-adjusted life years (QALY) gained. Costs include medications, physician visits, laboratory tests, scans, hospitalizations and treatment of adverse events. All costs and incremental cost-effectiveness ratios (ICER) were expressed in 2010 Singapore Dollars (S$) or 2010 Euros. A secondary analysis compared 1st line gefitinib with 1st line chemotherapy in patients with activating EGFR mutations. Sensitivity analyses were conducted to assess the robustness of the results.
Results: EGFR testing and first line treatment with gefitinib is a dominant strategy (i.e., it has lower costs and greater effectiveness) compared to no testing, 1st line chemotherapy and 2nd line gefitinib in unselected patients in Singapore and Italy. Because the main savings in the testing arm result from not providing gefitinib to those patients who are less likely to benefit, these findings hold regardless of the prevalence of patients with activating mutations. In the secondary analysis, 1st line gefitinib was also dominant when compared to 1st line chemotherapy in patients with activating EGFR mutations, primarily due to better QOL.
Conclusion: Based on these data, EGFR testing and first line treatment with gefitinib for patients with activating mutations should become the standard treatment in advanced NSLC. In this era of exponentially increasing costs the use of biomarkers may improve patient selection and the CE of new therapies
Keywords: gefitinib, Epidermal growth factor receptor, Cost-effectiveness

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P3.033 EFFICACY OF CARBOPLATIN, PEMETREXED AND BEVACIZUMAB FOLLOWED BY MAINTENANCE GEFITINIB IN ADVANCED NON-SQUAMOUS NON SMALL CELL LUNG CANCER - A STUDY FROM NORTH INDIA

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Background: Platinum based doublet is the first line treatment for advanced NSCLC. Apparently pemetrexed and bevacizumab are approved for their use in first line non-squamous NSCLC. We have tried the combination of carboplatin with pemetrexed and bevacizumab in advanced non-squamous NSCLC

Methods: Fifteen patients were treated at Sir Ganga Ram Hospital during the last two years for non squamous NSCLC with three drug combination using carboplatin, pemetrexed and bevacizumab. There were twelve males and three females. Median age was 55 years. There were nine smokers and six non smokers. The sites of metastasis were as follows : pleural effusion – 7 pts., bones – 3 pts., liver – 2 patients, adrenal 3 pts., CNS – 3 patients, lymph nodes -7 pts., contralateral lung – 5 pts. ECOG status was 0 in 10 cases, 1 in 2 cases and 2 in 3 cases. 4 out of 15 cases underwent pleurodesis. Histopathology was large cell type in 2, adenocarcinoma in 10 and poorly differentiated carcinoma in 3 cases. Doses of the drugs were as follows : carboplatin AUC 6, pemetrexed 500mg/sq. mt, and bevacizumab 500mg/sq.mt given every three weeks. Premedication with folic acid, vitamin B12 and dexamethasone was given.

Results: Median number of cycles used were six. Four patients received less than five cycles. The chemo-protocol was well tolerated, only three patients had delay in their doses and two patients required G-CSF. There was mild epistaxis in four cases. Eight patients achieved partial response (53%), four stable disease and three progressive disease. Three patients progressed in the CNS. All the patents were given gefitinb 250 mg as maintenance therapy after completion of chemotherapy. Five (two smokers and three non smokers)out of these patients have sustained their responses beyond 18 months and three are still alive. Median overall survival is not reached at 11 months follow up

Conclusion: Carboplatin, pemetrexed and bevacizumab combination is effective and safe for management of advanced non-squamous NSCLC.

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P3.034 SECOND LINE ERLOTINIB IN NON-SMALL CELL LUNG CANCER: A LOCAL EXPERIENCE

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Background: In November 2008 NICE issued guidance recommending Erlotinib as an alternative to Docetaxol as second-line treatment for patients with non-small cell lung cancer (NSCLC) [1]. This guidance was based on evidence from the TAX 317 trial [2] and BR21 [3] trials respectively. In addition it took into account the clinical and cost effectiveness (within NHS resources) of Erlotinib, having considered evidence regarding the nature of the condition and the benefits of Erlotinib, as presented by NSCLC patients, their representatives and clinical specialists [1, 2, 3]. Second-line Erlotinib is now widely used in the North Wales Cancer Treatment Centre and we thus decided to review our local use of the drug.

Methods: Data was collected retrospectively on 26 patients commenced on second-line Erlotinib for progressive NSCLC having previously received 1st line platinum doublet chemotherapy (Carboplatin/Gemcitibine). Demographic data included the patient's age and sex, as well as the histological sub-type. The dates of commencing and discontinuing treatment, in addition to date of patient's death were all recorded, enabling us to calculate length of treatment and time from discontinuation until death. We also assessed the length of treatment per histological sub-type. The presence and grade of side-effects from Erlotinib were recorded as well as any dose adjustments. Clinical and radiological progression was assessed, where formally documented.

Results: Twenty-six patients (14 female, 12 male) commenced treatment between August 2009 and December 2010.The average age was 67 (range 44-82). Histological sub-type stratification showed 4 squamous cell, 2 broncho-alveolar, 9 adenocarcinoma and 11 patients with histology of NSCLC not otherwise specified. The average number of weeks on Erlotinib treatment was 19.7 (range 3-80). The average time from discontinuing treatment until death was 10.2 weeks. According to histological sub-type the mean number of weeks on erlotinib was calculated as 32.5 for squamous cell, 53 for broncho-alveolar, 7.2 for adenocarcinoma and 19.1 for NSCLC nos. Fifteen patients had documented radiological progression, associated with a clinical decline in 5. Eleven of these patients did not demonstrate clinical decline despite progression on radiology. Six patients had documented clinical decline not confirmed radiologically. Rash was the most commonly experienced side-effect with 14 patients developing it notably (n=7 grade 1, n=4 grade 2 and n=3 grade

3). Fatigue was experienced by 12 patients (n=5 grade 1 and n=7 grade 2). Diarrhoea occurred in 6 patients (n=4 at grade 1 and n=1 each of grade 2 and 3). No grade 4 side effects were noted. The majority of patients (n=22) stayed on the full dose (150 mg daily) with only 4 having a dose reduction (100mg daily).
Conclusion: This data gives us an overview of a local cancer unit's experiences of the use of second-line Erlotinib. As numbers are small no conclusions can be drawn but on the whole the treatment was tolerated well with manageable side-effects most commonly rash and fatigue. Mean length of treatment compares favourably with current data (1, 2, 3). Second-line Erlotinib thus provides us with a well tolerated and effective alternative to Docetaxol.
Keywords: erlotinib, second line, NSCLC

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P3.035 CLINICAL FEATURES OF PATIENTS WITH THROMBOSIS ASSOCIATED WITH LUNG CANCER

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Background: It has been known that cancer patients are often complicated with thrombosis. This has sometimes had a significant impact on treatment and prognosis. However, backgrounds are diverse, so at present standardized treatment is not possible. Therefore, we studied the clinical features of thrombosis associated with lung cancer.
Methods: A total of 307 lung cancer patients had visited our hospital in the previous three years (April 2007-March 2010). We extracted 45 patients in whom the presence of thrombosis was confirmed by diagnostic imaging such as ultrasound or CT, regardless of symptoms. A retrospective study was carried out based on medical records.
Results: Thirtyfour male cases (75.5%) and 11 female cases (24.5%), mean age 69.5 years, 17 cases of arterial thrombosis and 27 cases of venous thrombosis. One patient had both. The most common underlying disease was hypertension with 18 cases. By type of disease, there were 27 cases of deep vein thrombosis (60%) and 7 cases of pulmonary thromboembolism (16%, of whom 6 were complicated with venous thrombosis of legs). Other cases, such as arterial mural thrombus (aorta and superior mesenteric artery etc.), stroke, renal infarction, and splenic infarction were observed. By histology of lung cancer, 23 cases were adenocarcinoma, 10 cases were squamous cell carcinoma, 7 cases were small cell carcinoma, and there were 5 other cases (including unknown): by stage, many were StageIIIA or more advanced. On the other hand, Performance statuses (PS) at the time of detection of thrombus were as follows: "0" 7 cases (16%). "1" 14 cases(30%), "2" 12 cases(27%), "3" 8 cases (18%), and "4" 4 cases (9%), thus comparatively good PS patients accounted for the majority. By clinical symptoms, 30 cases (67%) had no symptoms. Chemotherapy was performed before thrombus found in 27 cases(60%).
Conclusion: Among patients with advanced lung cancer, regardless of clinical symptoms, general condition, and histological type, many had thrombosis. In addition, onset of thrombosis seriously affected many patients' QOL and prognosis. In advanced lung cancer, it is necessary to bear in mind the presence of thrombosis, immediately after diagnosis, especially before starting chemotherapy. In addition, attention to thrombosis as a paraneoplastic syndrome and increased use of bevacizumab require further study.
Keywords: thrombosis, pulmonary thromboembolism, Lung cancer

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P3.036 ERLOTINIB VS DOCETAXEL AS SECOND-LINE TREATMENT OF ADVANCED NSCLC: A REAL-WORLD COST-EFFECTIVENESS STUDY

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Background: The British Columbia Cancer Agency (BCCA) began funding erlotinib as a second-line treatment for advanced NSCLC in 2005. While the efficacy of the drug has been shown in clinical trials, real-world cost-effectiveness has not been shown. This study investigated the real-world cost-effectiveness of second-line erlotinib in patients treated across British Columbia, Canada.
Methods: This was a retrospective study of all patients who had been treated with second-line chemotherapy for advanced NSCLC at the BCCA since September, 2005. As pemetrexed is now frequently being used as a front line therapy with cisplatin, a comparison of second-line erlotinib to doctexal is relevant. The primary endpoint was cost-effectiveness, measured in terms of cost per years of life gained. The calculation of life years gained was based on the area under the Kaplan-Meier curve of overall survival, defined as days between start of second line chemotherapy and death or censoring. Analysis was performed from the perspective of the British Columbia Ministry of Health Services, and included the costs of drugs, radiation, hospitalization, appointments, tests, and home/community care.
Results: A total of 133 erlotinib patients and 68 docetaxel patients were identified. There were no significant differences in either survival or cost between the two groups in the real-world setting. Results are presented in the table. As costs and outcomes in the docetaxel arm were not significantly different from costs and outcomes in the erlotinib arm (incremental costs and effectiveness were both near zero), no ICER could be calculated.
Conclusion: Our analysis found that in terms of both costs and effectiveness (overall survival and progression-free survival), erlotinib and docetaxel are equivalent. This finding suggests that patients and physicians should make the decision of treatment modality based on patient preferences and other concerns, rather than on the basis of survival and cost.
Keywords: health economics, erlotinib, retrospective trial, Cost-effectiveness

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P3.037 LOW FEASIBILITY OF SECOND-LINE CHEMOTHERAPY IN PATIENTS WITH DIABETES MELLITUS IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer (NSCLC) is mostly diagnosed in the advanced stage, and chemotherapy is the treatment of choice. In patients with diabetes mellitus (DM) in NSCLC, chemotherapy could be insufficient for the following reasons: 1) uncontrollable glucose level due to corticosteroid use as an antiemetic drug, 2) renal deficiency, and 3) complication of DM such as peripheral neuropathy. We aim to investigate the feasibility of second-line chemotherapy with DM in advanced NSCLC.
Methods: Clinical information was retrospectively gathered for stage IIIB or IV NSCLC patients who started first-line systematic chemotherapy at our institution between January 1, 2004 and December 31, 2009. Patients who relapsed after surgery were excluded. Patients were assigned to the DM or non-DM (NDM) arm. Primary endpoint was to assess the feasibility of second-line chemotherapy. Secondary endpoint was overall survival (OS). Kaplan Meier and log-rank analyses were used for OS.
Results: Overall, 211 consecutively treated patients were collected at our institution. 33 patients were treated with DM and 178 with NDM. Patient characteristics of DM were: median age, 70 years (range: 49 -88); male/female, 28/5; Ad/Sq/others, 20/9/4; IIIB/IV, 16/17; ECOG Performance Status (PS), 0/1/2/3<=5/27/1/0; and platinum doublet/ others, 25/8. Those of NDM patients were: median age 67 years (range: 36-88); male/female, 114/64; Ad/Sq/others, 113/35/30; IIIB/IV, 50/128; PS, 0/1/2/3<=30/118/25/5; and platinum doublet/others, 129/49. The feasibility of second-line chemotherapy was slightly worse in DM than in NDM (51.5% vs. 57.9%, respectively). Patients who received third-line or more were also worse in DM than in NDM (18.2% vs. 29.2%, respectively). The median OS of

DM was shorter than that of NDM (366 days vs. 423 days, p=0.572).
Conclusion: The feasibility of second-line chemotherapy with DM in advanced NSCLC tended to be worse, but there was no significant difference between DM and NDM. Median OS of DM was similar to that of NDM. This study was retrospective and the clinical background was not well balanced. To confirm this study, a prospective cohort study is needed.
Keywords: NSCLC, Chemotherapy, diabetes mellitus

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P3.038 CLINICAL OUTCOMES AFTER ROUTINE DIAGNOSIS OF EGFR MUTATION: A MULTICENTRIC RETROSPECTIVE STUDY ABOUT 121 PATIENTS.

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Background: Epidermal growth factor receptor (EGFR) mutations in non small-cell lung cancer (NSCLC) were described seven years ago. When tumors harbour sensitizing mutations, patients are more likely to respond to tyrosine kinase inhibitors (TKI). Conversely some mutations are associated with drug resistance and some, less frequent, are not yet evaluated. Gefitinib can be delivered in first line therapy for mutated patients with stage IV NSCLC. In France, EGFR mutations detection is routinely performed in molecular genetic platforms. This retrospective study aims to determine clinical outcomes of mutated patients.
Methods: Medical files from patients with EGFR mutation diagnosed on the Rhône platform between 09/09 and 09/10 were retrospectively reviewed. Data including histologic type, TNM status, smoking history, sample origin, treatment administered and response to treatment were collected in all health centres that sent samples (University hospital 34%; secondary hospitals 36%; private clinics 30%).
Results: 133 mutations were found: 1 patient had 3 mutations and 10 patients had 2 mutations. Mutated patients are mainly women (63%) and 97.5% have an adenocarcinoma. 60.3% are never smokers, 28.1% are former smokers and 11.6% are current smokers (mean pack-year is 27.49 (1-100) for former and current smokers). Mean age is 66.43 (+/- 23.25 years). 5 patients present at least one EGFR resistance mutation mainly on exon 20 (2 undergo TKI: one in first line and one in second line). Among all, 85 patients (70.2%) received a TKI, mainly those with stage IIIb or IV disease (96.4%). Before TKI, 58.8% underwent chemotherapy, 14% thoracic radiotherapy and 23% thoracic surgery. TKI was first line treatment in 41% (71% gefitinib) and second or third line in 59% (56% erlotinib). Among patients who underwent TKI, the mean progression free survival (PFS) was 13 months (10.5-15.5). There were no significant differences in PFS between the "first line" and the "second line" groups (14 [2,012-25,988] months vs 13 [9.240-16.760] respectively; p=0.843). Responses observed were: complete in 4%, partial in 56% and stable in 19%. 21% had immediate progressive disease. There is no significant difference in mutated exon type and survival according to sex, age, smoking history or prior treatment by chemotherapy. Overall response observed is higher in case of exon 19 mutations (66% vs 33%; p=0.022) and lower in case of mutations in exon 20 that contains most of the resistance mutations (1.6% vs 98.4%; p<0.0001). Concordantly a significant difference in PFS is observed according to the location of sensitizing mutations. Exon 19 sensitizing mutations show better survival (15.0 [6.72-23.27] months) than exon 21 (13.0 [7.34-18.65] months) and 18 (4.0 [0-8.0] months) respectively (p=0.002). Advert effects are more frequent when patients are treated with erlotinib than with gefitinib as shown by dose reduction observed only in the erlotinib group (27.8% of patients).
Conclusion: This retrospective study highlights that survival is not affected by prior chemotherapy in case of activating EGFR mutation. Moreover sensitizing mutations on exon 19 show significant better survival than exon 21 and exon 18 respectively. Finally, gefitinib has a better tolerance profile than erlotinib. Further data will be available on meeting.
Keywords: EGFR mutations, Non small cell lung cancer, tyrosine kinase inhibitors, clinical outcome

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.039 A MULTICENTER PHASE II RANDOMIZED STUDY OF GEMCITABINE(G) WEEKLY FOLLOWED BY ERLOTINIB(E) AFTER PROGRESSION VERSUS E FOLLOWED BY G AFTER PROGRESSION IN ADVANCED NON SMALL CELL LUNG CANCER(NSCLC)IN VULNERABLE ELDERLY PATIENTS SELECTED WITH A COMPREHENSIVE GERIATRIC ASSESSMENT (CGA) (GFPC*0505)

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Background: Elderly patients (pts) is an heterogeneous population in which anticancer therapeutic decision is often difficult. The objective of this study was to evaluate the feasibility and activity of weekly G followed by E after progression versus E following by G after progression in vulnerable elderly advanced NSCLC patients selected on the basis of a CGA and Charlson score (CS)

Methods: This multicenter phase 2 study randomized chemonaive pts with stage IV and IIIB with pleural effusion received G1250mg/m^2 days 1,8, for a maximum of 18 weeks or until progression, followed by E until second progression (arm A) versus E in first line followed by G until second progression(arm B).Only vulnerable pts(without dependence for ADL and geriatric syndrom like falls, dementia , incontinence)(Table 1)were selected by CGA using a software (EGSK) included in a palm assistant with 10 items: socio-economic conditions, cognitive assessment, depression scale, nutritional risk, quality of life(QOL), ADL,IADL(Lawton), incontinence, falls, pain. Major endpoint was time to second progression (TTP2), secondary endpoints were response, time to first progression (TTP1), survival, safety, QOL. Table1

AGE (CHARLSON)	IADL (dependence)	ADL (dependence	Geriatric syndrom	Charlson Comorbidity	PS	Treatment
65-69y(2)	1	0	0	0-2	2	eligible
65-69y (2)	<2	0	0	3-4	0-1	eligible
65-69y (2)	<2	0	0	3-4	2	eligible
70-79y (3)	1	0	0	0-1	0-1	eligible
70-79y (3)	<2	0	0	0-1	2	eligible
70-79y (3)	<2	0	0	2-4	0-2	eligible
80-89 y (4)	1	0	0	0	0-1	eligible
80-89y (4)	<2	0	0	2-4	0-2	eligible

Results: 100 pts (94 available) were enrolled from aug 2006 to dec 2009 Patients: Male/Female 76/18, median age 78.2(44%>79 years); PS 0/1/2:30/47/14, median co-morbidity (CS) 1.74 (1-3), median IADL score 3.35 (1-4), median global geriatric index: 17.8/20 .Respectively for arm A and B, partial response was 13% and 14%,stable disease 26 % and 23%,progressive disease 61% and 63%(first line),TTP2 4.3 and 3.5 months, TTP1 2.5 and 2.2 months, median survival 4.4 and 4 months(no significant difference between 2 arms),1 year survival 27% arm A and 20% arm B. The main WHO Grade3/4 toxicity was fatigue 11% and anemia 9.% in arm A and in arm B fatigue 18% and diarrhea 6%.There was no decrease in QOL.

Conclusion: Preliminary analysis suggests that either the G followed by E or E followed by G appears to have acceptable toxicity but moderate activity ,comparable in term of efficacy to prior data in this vulnerable elderly NSCLC pts population with significant co-morbidities. Our trial confirms the necessity to identify the better tools in CGA to distinguish frail pts.

Keywords: Non small cell lung cancer, elderly patients, geriatric assessment, Chemotherapy

Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.040 GASTROINTESTINAL TOXICITY OF THE PAN-HER TYROSINE KINASE INHIBITOR (TKI) PF299804: ASSESSMENT BY PATIENT-REPORTED OUTCOMES IN 2ND/3RD-LINE AND REFRACTORY NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: PF299804, a potent, irreversible inhibitor of human epidermal growth factor receptor (EGFR)/HER-1, -2, and -4 tyrosine kinases, is active in erlotinib-sensitive and -resistant preclinical models. PF299804 had clinical activity in phase 2 trials of chemotherapy and EGFR TKI-refractory KRAS wild-type NSCLC[1] and compared with erlotinib in 2nd/3rd-line NSCLC.[2] Phase 3 trials are ongoing in both NSCLC settings. Gastrointestinal toxicities of diarrhea, stomatitis and mucositis are known class effects of EGFR targeted therapy, but Common Terminology Criteria (CTC) for AE grading does not fully characterize the patient's experience. Qualitative assessment from the patient's perspective of the burden of toxicity and changes over time further characterizes the impact of AEs. As current therapies are not curative, it is important to understand the impact of side effects when making treatment decisions.
Methods: In refractory (n=66, KRAS wild type) and 2nd/3rd-line (n=94) advanced NSCLC, ECOG PS 0–2, patients received oral PF299804 with assessments every 3 (refractory) or 4 (2nd/3rd-line) weeks. Patient-reported outcomes (PRO) were assessed by the EORTC Quality of Life Questionnaire [QLQ-C30], and its lung cancer module [QLQ-LC13).
Results: The most common (>10% incidence) gastrointestinal treatment-related (TR) AE in refractory/2nd/3rd-line were: diarrhea (85%/73%), stomatitis (24%/29%), and mucositis (11%/25%), all predominantly of Grade 1 severity; discontinuations were: refractory = 0, 2nd/3rd-line = 1 (diarrhea). EORTC QLQ-C30/LC13 data indicated that these AEs peaked early in therapy, between Weeks 2–6, in both refractory and 2nd/3rd-line and stabilized over the course of treatment. EORTC QLQ-C30 symptom scores: mean patient score at each assessment timepoint for refractory and 2nd/3rd-line NSCLC (scored on a 0–100 scale with higher scores indicating higher levels of symptoms).*

Refractory						
	Day 1 Cycle 1 (n=65)	**Week 3 (n=56)**	**Week 6 (n=51)**	**Week 9 (n=33)**	**Week 12 (n=33)**	
Diarrhea†	7.18	50.88	50.64	48.04	44.44	
Sore mouth	4.1	34.52	26.8	19.19	20.2	
Difficulty swallowing	2.05	8.33	11.76	9.09	9.09	
2nd/3rd-line						
	Day 1 Cycle 1 (n=90)	**Week 2 (n=80)**	**Week 4 (n=82)**	**Week 8 (n=64)**	**Week 12 (n=45)**	**Week 16 (n=38)**
Diarrhea‡	9.26	40.0	48.56	41.8	36.36	38.6
Sore mouth	6.67	39.17	36.59	28.12	22.96	21.93
Difficulty swallowing	5.93	22.5	20.33	16.67	8.89	7.89

n= number of patients answering each item at each assessment timepoint *A change ≥5 points is considered to be clinically meaningful when assessing these data †For diarrhea in refractory population, n=57, n=52, n=34 for weeks 3, 6 and 9, respectively ‡For diarrhea in 2nd/3rd-line population n= 81, n=63, n=44 for weeks 4, 8 and 12, respectively.

Conclusion: In clinical trials of PF299804 in refractory and 2nd/3rd-line NSCLC, the most common gastrointestinal TRAE were diarrhea, stomatitis and mucositis. Though these were relatively common, they were rarely a reason for discontinuation, and PRO for these TRAE peaked early in therapy and stabilized over time. PRO measures can provide insight into patient experience that is not captured by CTCAE grading. Furthermore, understanding the time course and patient impact of common gastrointestinal TRAE may better prepare patients and enable providers to anticipate when intervention can best be targeted in the course of care. 1. Campbell A et al. ASCO 2010; abstr 7596. 2. Ramalingam SS et al. ESMO 2010; abstr 365PD.
Keywords: EGFR TKI, Patient Reported Outcomes, Gastrointestinal Toxicity, PF-00299804

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.041 DERMATOLOGIC ADVERSE EVENTS OF THE PAN-HER TYROSINE KINASE INHIBITOR (TKI) PF299804: ASSESSMENT BY PATIENT-REPORTED OUTCOMES IN 2ND/3RD-LINE AND REFRACTORY NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: PF299804, a potent, irreversible inhibitor of human epidermal growth factor receptor (EGFR)/HER-1, -2, and -4 TKs, is active in erlotinib-sensitive and -resistant preclinical models. PF299804 had clinical activity in phase 2 trials of chemotherapy and EGFR TKI-refractory KRAS wild-type NSCLC[1] and versus erlotinib in 2nd/3rd-line NSCLC;[2] phase 3 trials are ongoing in both settings. A profound impact on Dermatologic Related Quality of Life (DRQoL) has been described with the EGFR inhibitor erlotinib[3] but Common Terminology Criteria (CTC) for AE grading may not fully characterize the patient's experience of side effects from therapy. Assessment of the AE burden qualitatively from the patient's perspective further characterizes the impact of AEs related to EGFR TKIs. As current therapies are not curative, it is important to understand the impact of side effects when making treatment decisions.
Methods: In refractory (n=66) and 2nd/3rd-line (n=94) advanced NSCLC, ECOG PS 0–2, patients received oral PF299804 with assessments every 3 (refractory) or 4 (2nd/3rd-line) weeks. The 10 question Dermatology Life Quality Index (DLQI) questionnaire was used to assess the impact of anti-cancer treatment on patients' DRQoL on Day 1 of each cycle. Total scores range from 0–30; subscale scores range from 0–6, with higher scores indicating a higher level of impairment.
Results: The most common dermatologic AE was acne; overall frequency in refractory = 66.7% (34.8% Grade (G) 1) and 2nd/3rd-line = 78.5% (38.7% G1), appearing initially on head and chest with later involvement of limbs and back. Other AEs (overall incidence, refractory; 2nd/3rd-line) were dry skin (37.9%; 23.7%), exfoliative rash (24.2%; 17.2%), pruritus (22.7%; 15.1%) and paronychia (9.1%; 25.8%). Late-emerging AEs (incidence in cycle 1 vs. later cycles), included dry skin (refractory: 19.7% vs. 30.5%; 2nd/3rd-line: 9.7% vs. 20.8%) and paronychia (refractory: 0 vs. 10.2%; 2nd/3rd-line: 10.8% vs. 20.8%). Mean patient DLQI Symptoms and Feelings subscale scores* and DLQI Total score** for refractory and 2nd/3rd-line NSCLC patients treated with PF299804

Refractory			
	Day 1 Cycle 1 (n=65)	**Week 6 (n=52)**	**Week 12 (n=34)**
DLQI Symptoms and Feelings subscale*	0.28/6	1.69/6	2/6
DLQI Total score**	0.48/30	3.81/30	4.94/30
2nd/3rd-line			
	Day 1 Cycle 1 (n=91)	**Week 4 (n=82)**	**Week 12 (n=44)**
DLQI Symptoms and Feelings subscale*	0.56/6	1.9/6	2.14/6
DLQI Total score**	0.88/30	3.91/30	5.82/30

*DLQI Symptoms and Feelings subscale: 0–6 where higher score = higher level of impairment; **DLQI Total score: 0–1 = 'no effect'; 2–5 = 'small effect'; 6–10 = 'moderate effect'; 11–20 = 'very large effect'; 21–30 = 'extremely large effect' on patient's life

Conclusion: In studies showing clinical activity of PF299804, dermatologic AEs were consistent with other EGFR inhibitors. As measured by DLQI, PF299804 dermatologic AEs had a small impact on patients' DRQoL. Understanding the time course and patient impact of dermatologic treatment-related AEs may enable providers to anticipate when intervention can best be targeted in the course of patient management. 1. Campbell A et al. ASCO 2010;abstr 7596. 2. Ramalingam SS et al. ESMO 2010;abstr 365PD. 3. Joshi SS et al. Cancer 116:3916-3923.
Keywords: PF-00299804, Dermatologic Toxicity, Patient Reported Outcomes, EGFR TKI

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Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.042 PROSPECTIVE MULTICENTER CLINICAL STUDY OF PEMETREXED AND CARBOPLATIN COMBINATION FOLLOWED BY MAINTENANCE PEMETREXED IN CHEMO-NAïVE PATIENTS WITH NON-SQUAMOUS NON-SMALL CELL LUNG CANCER - INITIAL ANALYSIS OF INDUCTION PERIOD.

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Background: Platinum-based chemotherapy is the standard first-line treatment for advanced non-small cell lung cancer (NSCLC); furthermore, recent phase III studies have shown a beneficial role of pemetrexed as a maintenance therapy. This is an ongoing clinical study of pemetrexed combined with carboplatin during an induction period followed by pemetrexed maintenance.
Methods: Eligible patients (pts) were previously untreated, unresectable stage IIIB, IV or postoperative recurrent nonsquamous NSCLC, ECOG Performance Status (PS) was 0–1 at study entry. Pts received carboplatin AUC 6 and pemetrexed 500 mg/m^2 on Day 1 of each of 4 three-week cycles as induction therapy. Pts with objective response and stable disease at the end of the induction period could continue on pemetrexed as maintenance therapy until disease progression or unacceptable toxicity. We report preliminary results of the induction period.
Results: Pemetrexed and carboplatin were administered as induction therapy to 109 pts. Median age was 63 years (range 38–78); 63.3% were male, 36.7% female. Other patient backgrounds: PS 0/1 (33.9%/66.1%), stage IIIB/IV/recurrent disease (30.3%/66.1%/3.7%), current/former smoker (8.3%/61.5%). The most frequently reported ≥Grade 3 toxicity was neutropenia (54%). Other ≥Grade 3 toxicities were also hematologic, including thrombocytopenia (41%) and anemia (28%). In addition, 20.2% of pts needed dose reductions and 67.9% dose delays. The relative dose intensities for pemetrexed and carboplatin were 88.8% and 89.5%, respectively. Red blood cells transfusion, platelet transfusion and G-CSF administration were required in 10%, 7% and 9 % of the patients. Rash (26%) and fever (17%) were relatively common non-hematological toxicity. There were no study related deaths. Serious adverse reactions including thrombocytopenia, anemia, and gastric ulcer were reported in 8 patients (7%). Of 109 pts evaluable for response (RECIST criteria), 42 pts (38.5%) achieved a partial response (either confirmed or unconfirmed) and 47 pts (43.1%) had stable disease in induction period. Seventy-five pts (68.8%) were completed induction period, and 60 pts (55.0%) entered into the maintenance period.
Conclusion: This prospective, nonrandomized, multicenter study suggested that pemetrexed plus carboplatin combination chemotherapy would be well tolerated and effective as a first-line therapy for advanced nonsquamous NSCLC.
Keywords: Pemetrexed, Carboplatin, NSCLC

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P3.043 DIFFERENT OUTCOMES IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) TREATED WITHIN OR OUTSIDE CONTROLLED CLINICAL TRIALS

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Background: Prognosis for advanced NSCLC is still unsatisfying despite a large number of clinical trials are enrolling patients (pts) to evaluate new therapeutic approaches and anticancer drugs. Independently from the final results of each clinical trial, the common perception is that the inclusion in clinical trials leads to improved outcomes in patients with cancer, even if there aren't clear data to make a statement about this issue. In any case, pts with cancer should be encouraged to be part of clinical trials on the basis of trials' unquestioned role in improving treatment for future pts. We conducted

a retrospective analysis in a single institution evaluating survival data and toxicity profile in advanced NSCLC pts treated with standard therapy or within controlled clinical trials.
Methods: We analysed 300 consecutive pts treated at the Thoracic Oncology Unit of San Luigi Gonzaga Hospital from 2004, January the 1st to 2010, December the 31st having these characteristics: histo/cytological diagnosis of NCSLC, stage IV who received at least 3 chemotherapy cycles, with a minimum follow-up of six months. In this pts population 178 (59%) were enrolled in controlled clinical trials (T) while 122 (41%) were treated with standard therapy (S) .
Results: the most important differences between the two groups were about median age at the time of starting first line treatment (61.2 in group T vs 64 years in group S), pts older than 70 years old (19% vs 27%, respectively) and ECOG/PS distribution (PS=2: 0 vs 9 pts, PS=1: 33 vs 53 pts, PS=0: 145 vs 60 pts in T and S group, respectively). Distinguishing different lines of therapy in T population: in pts enrolled in first line clinical trials only, median OS was 9.2 months, 18.1 months in pts enrolled in first and second line clinical trials, 15.3 months in pts enrolled only in second line clinical trials and 26.4 months in pts enrolled in first, second and third line studies. Any relevant differences was seen between group T and S in terms of toxicity.

	Group S	Group T
Pts eligible for second line treatment	43 (35%)	105 (59%)
Pts eligible for third line treatment	18 (15%)	45 (25%)
OS (months)	9.5	13.5
PFS (months)	6.3	7.1

Conclusion: This retrospective analysis done in a single institution documented a better outcome for pts enrolled in clinical trials compared to those treated with standard therapy (even without a statistical significance) with an higher percentage of pts reaching a second and third line therapies. This kind of analysis is burdened by a series of possible biases, which can be solved only with larger multicenter prospective dedicated studies.
Keywords: Advanced NSCLC, Clinical Trials

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P3.044 CHANGING PATTERNS OF CARE AND IMPROVED SURVIVAL IN ADVANCED STAGE NON-SMALL CELL LUNG CANCER (NSCLC): A SINGLE AUSTRALIAN CANCER UNIT EXPERIENCE.

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Background: Clinical trials and meta-analyses have demonstrated survival benefits of cytotoxic chemotherapy in advanced stage (stage 3 and 4) non-small cell lung cancer (NSCLC). To determine whether these controlled trial results translate into survival benefits in an unselected population, the database of the Cancer Registry at The Queen Elizabeth Hospital was analysed for all patients with stage 3 and 4 NSCLC to determine if changes in patterns of care in two completely separate 5 year time cohorts (1988 – 1992, cohort A and 2003 – 2007, cohort B) resulted in any overall improvement in survival.
Methods: Demographic, management and outcome data was determined from clinical records. Stage wise survival analysis was undertaken using the Kaplan-Meier product-limit method and the log-rank test. Factors influencing survival outcome were assessed using Cox proportional hazards regression.
Results: Data for 516 patients identified in the 2 cohorts are shown in Table 1.

	Cohort A (1988-1992) Total 210	Cohort B (2003-2007) Total 306
Males/Females	68%/32%	65%/35%
Predom histol squamous/adeno	33%/38%	30%/30%
Stage3/Stage 4	34%/66%	42%/58%
Never smokers	6%	11%
Median age	68 yrs	69yrs
Age 65 yrs or older	65%	63%
EGOG PS 0-2/3-4	75%/25%	75%/25%
Received chemotherapy*	4%	41%
Received radiotherapy	51%	50%

Table 1. * 60% chemotherapy regimens were gemcitabine/platinum combinations Median survival for all patients was significantly increased in cohort B compared with cohort A (HR 0.74, 95% CI 0.60-

0.89, p = 0.0018). Univariate analysis of outcomes in cohort B suggested that the majority of improvement in survival in cohort B appeared to be dependent on the use of chemotherapy (p = 0.0003), better performance status (PS)(p < 0.0001), stage 3 disease (p = 0.0004) and female gender (p = 0.004). Age over 65 and use of radiotherapy alone did not appear to affect outcome for either cohort.
Conclusion: In an unselected population, the median overall survival for patients with advanced stage NSCLC has improved significantly over a 15 year period. The most significant factor contributing to the improvement in survival appears to be the use of chemotherapy, which was 10 times more likely to occur in the more recent cohort and probably reflects the more general acceptance of chemotherapy as part of standard therapy that occurred over the same time period. The increased magnitude of difference in survival for stage 3 patients in the latter cohort of patients is likely to reflect the improved co-ordinated use of synchronous chemo-radiotherapy programs. A greater improvement in survival observed for females between the 2 cohorts may be related to gender differences in tumour biology resulting in variations in response to chemotherapy. A significant proportion of good PS patients still did not receive chemotherapy and reasons why such patients don't ever receive potentially beneficial therapy need to be explored.
Keywords: Chemotherapy, outcomes, Advanced stage NSCLC

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.045 FIRST LINE GEFITINIB IN EGFR MUTATION POSITIVE NSCLC IN AN ISRAELI COHORT: UNMET EXPECTATIONS.

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Background: Recent clinical trials have shown extremely high response rates, ranging from 55% to over 70%, to first line treatment with gefitinib in advanced NSCLC patients harboring mutations in the epidermal growth factor receptor (EGF-R). Based on these works, gefitinib was included in the Israeli Health Scheme for this select population since the beginning of 2010. The primary goal of this retrospective analysis was to study the efficacy of gefitinib in the first line treatment of EGFR-mutated advanced NSCLC patients in two Israeli tertiary hospitals.
Methods: The clinical data of patients tested positive for EGFR mutations from the Sheba Medical Center and the Meir Hospital since the beginning of 2010 were included in the current retrospective analysis. Analyses were based on demographic, clinical and molecular data.
Results: Since the beginning of 2010, EGFR mutations were identified in 20% of all patients evaluated, with a total of 38 patients testing positive for mutations. EGFR mutations were primarily exon 19 deletions (55%) and exon 21 L858R point mutations (26%), with the remaining mutations identified in exon 21 Leu861Gln (11%) and exon 18 Ala719Gly (5%). One patient's mutation status was not recorded in the chart. The median age of this cohort was 69 (range 45-85) with 24 of these females (63%). 23 were never smokers (61%) with 31 adenocarcinomas (81%), 2 patients with squamous cell carcinoma (5%) and the remaining diagnosed as of non-squamous origin. Of these 38 patients, 24 were treated with first line gefitinib for advanced disease. The majority of these patients (89%) had an ECOG performance status of 0-2. By the date of abstract submission, 19 of these patients have been evaluated for treatment response. Adverse events were generally mild and similar to published reports – 9 experienced grade 1-2 rash (47%), 6 experienced grade 1-2 diarrhea (32%) and one patient had grade 3 hypomagnesemia. 2 patients achieved a partial response (10.5%) as defined by the RECIST criteria, 12 had a documented best response of stable disease by RECIST criteria (63%), and 5 had progressive disease (26.5%). Of the 19 patients, 4 have died within 4 months of starting gefitinib. Thus, in this current retrospective study of the Israeli population, our response rate is significantly lower than expected. The null-hypothesis of a minimal 50% response rate (as seen for other western populations) is rejected with a P value of 0.02 using a two-tailed chi-square test.
Conclusion: Albeit the very small number of patients in this current retrospective study, the

low rate of radiological response suggests that in our tested population, the actual response rate is significantly lower than reported in the literature. Epidemiologic, pharmacogenetic and/or molecular mechanisms of resistance need to be explored to explain these differences.

Keywords: Advanced NSCLC, EGFR mutation, gefitinib

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P3.046 ASSOCIATION OF XRCC3 AND XPD751 SNP WITH RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN ADVANCED NSCLC PATIENTS

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Background: The purpose of this study was to investigate whether X-ray repair cross-complementing group 3 alleles Thr241Met, xeroderma pigmentosum group D variant alleles Lys751Gln affected clinical outcomes of 1st line platinum-based chemotherapy in advanced non-small cell lung cancer patients.
Methods: 355 patients were enrolled into this study and their genotyping of X-ray repair cross-complementing group 3 Thr241Met,xeroderma pigmentosum group D Lys751Gln were detected by the TaqMan assay plus the real time PCR method in theri peripheral blood lymphocytes. SPSS version 17.0 was used to do the χ^2 and Kaplan-Meier survival analysis.
Results: The median age was 59.5 years old and 68.5% of the patients were male. No relationship was found between the wild-type, heterozygous and homozygous polymorphic variants SNPs of XRCC3 241, XPD751 and genders, ages, histology, smoking status. Progression free survival(PFS) and overall survival(OS) were similar between the patients with wild-type, heterozygous and homozygous polymorphic variants of XRCC3 and XPD751. However, in the subgroup analysis, OS of the patients with XRCC3 C/C was significantly longer than the patients with C/T or T/T in the vinorelbine subgroup(14.0m vs 9.3m,P=0.042)and the taxanes subgroup (18.5m vs 7m,P=0.01).
Conclusion: XRCC3 gene Polymorphisms may play different roles in predicting the efficacy of platinum-based doublet chemotherapy according to different chemotherapy regimen, which warrant further prospective large-scale study.

Keywords: X-ray repair cross-complementing group 3, Polymorphisms, Xeroderma pigmentosum group D, Non-small cell lung cancer, Chemotherapy, Polymorphisms

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.047 PHASE I/II STUDY OF CARBOPLATIN PLUS GEMCITABINE FOR ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER: WEST JAPAN ONCOLOGY GROUP TRIAL (WJTOG 2905)

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Background: Monotherapy with a third generation anticancer agent has been regarded as the standard therapy for elderly patients with advanced non-small-cell lung cancer (NSCLC). However, it is unclear whether elderly patients with a good performance status can tolerate platinum-doublet chemotherapy like younger patients.
Methods: A combination phase I/II study was conducted in chemo-naive elderly patients with NSCLC to establish the toxicity and maximum tolerated dose (MTD) and to investigate the antitumor activity of carboplatin (CBDCA) plus gemcitabine (GEM). GEM was infused on days 1 and 8, and CBDCA on day 1 every 3 weeks.
Results: Seventy-five patients (phase I study; 26 patients) were enrolled. The most frequent toxicities were hematological, especially thrombocytopenia. Three of three patients experienced a dose-limiting

toxicity at dose level 3:1000 mg/m^2 GEM with AUC 5 CBDCA (MTD), three of eight at dose level 2b: 800 mg/m^2 GEM with AUC 5 CBDCA, and one of seven patients at level 2a: 1000 mg/m^2 GEM with AUC 4 CBDCA (recommended dose). In the phase II study, the overall response rate was 22.2% and the median overall survival time was 14.2months.
Conclusion: Although the recommended dosage is restricted to a lower level compared to younger patients, combination therapy using CBDCA with GEM is tolerable and promising for elderly patients with advanced NSCLC.
Keywords: phase I/II study, Carboplatin, gemcitabine, elderly patients

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P3.048 CAN WE PREDICT TOXICITY IN PATIENTS OVER 70 YEARS OLD TREATED WITH CHEMOTHERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)?

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Background: A recent randomized trial showed that patients over 70 years old with advanced lung cancer achieved superior survival but experienced more hematologic toxicity with platinum doublet therapy compared to single-agent therapy (Quoix et al., ASCO 2010). Clearly, not all elderly can tolerate this treatment. We need metrics to identify appropriate patients for doublet chemotherapy. A cancer-specific geriatric assessment (CGA) is in development (Hurria et al., ASCO 2010), but no definitive predictive metric has been established and none has been studied in specific sub-populations. To help refine and tailor a metric for prospective study in lung cancer, we retrospectively evaluated the ability of a modified version of the CGA derived metric to predict toxicities among elderly patients who received first-line chemotherapy for metastatic NSCLC.
Methods: We reviewed records for 70 consecutive patients age 70 or older with metastatic NSCLC treated at our center from January 2008 through December 2009 with first-line cytotoxic chemotherapy. The CGA-derived 11-item metric was modified to 9 items (age >72, pre-existing anemia, creatinine clearance <34, full dose chemotherapy planned, combination chemotherapy planned, falls, needing assistance with medications, impaired hearing, and difficulty walking) for which most data were available for our cohort. Scores were generated and risk categories were recalibrated based on our modifications.
Results: Patient characteristics: median age 75 (range 70-92); median Karnofsky performance status (KPS) 80% (range 60-90%); dependent in activities of daily living (ADLs) 6% and instrumental ADLs (iADLs) 9%. Treatment: 80% doublet therapy (64% platinum doublet); 40% completed 4 cycles without dose reduction. Toxicity: 44% hospitalized; 6% grade 4 hematologic toxicity; 39% grade 3/4 non-hematologic toxicity. KPS was not associated with toxicity or hospitalization. Dependence in ADLs and dependence in iADLS were associated with shorter survival ($p<0.001$, $p=0.02$). Doublet therapy had a higher risk of hospitalization ($p=0.02$) while platinum doublets had improved median survival (11 vs 8 months, $p=0.005$), but this is confounded by patient selection. Metric scores designated 22 low-, 35 intermediate-, and 13 high-risk patients. The incidence of grade 3 hematologic toxicity (18%, 31%, 46%), grade 4 hematologic toxicity (5%, 6%, 8%), and grade 4 non-hematologic toxicity (0%, 6%, 15%) increased across the risk groups, although non-significantly. Hospitalization (55%, 34%, 38%) and the inability to complete 4 cycles of treatment without dose reduction did not (59%, 57%, 69%).
Conclusion: Many in this cohort experienced significant toxicity and 44% required hospitalization, but others tolerated therapy well and possibly derived benefit from platinum treatment. The modified CGA-derived metric used in this analysis showed trends towards a predictive effect for some relative rates of toxicities but not for others in this retrospective cohort. This is likely because the metric was derived from patients with a wide spectrum of malignancies in various stages of their treatment and, therefore, may not be as accurate for this specific group of patients. Therefore, we plan to prospectively assess a version of the CGA in metastatic lung cancer patients to identify the factors most predictive of chemotherapy doublet tolerance in this population.

Keywords: Non-small cell lung cancer, geriatric, Chemotherapy

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P3.049 QUALITY OF LIFE AFTER TREATMENT FOR BRAIN METASTASES: INTERIM DATA FROM THE MRC QUARTZ CLINICAL TRIAL.

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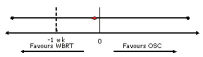
Background: QUARTZ addresses the longstanding clinical question; what is the role of whole brain radiotherapy (WBRT) in the treatment of patients with non-small cell lung cancer (NSCLC) and inoperable brain metastases. All patients receive steroids and optimal supportive care (OSC), and are randomised to WBRT or not. The trial's primary endpoint is quality adjusted life years (QALYS), reflecting the importance of quality of life (QoL) as well as survival in this very poor prognosis patient group. It is designed to assess whether OSC alone is non-inferior to OSC+WBRT, with a non-inferiority margin of 1 week in QALYS seen as clinically important. Recruitment started in March 2007 with a target of 534 patients. Despite widespread support from 76 UK and Australian centres, recruitment was slower than anticipated and the trial was under threat of closure. An issue contributing to the poor recruitment was thought to be the lack of preliminary data supporting the question being evaluated.
Methods: The Trial Steering Committee agreed to a data release relating to the first 151 randomised patients. They were unaware of the results at the time, Data were analysed and presented to participating centres, in order to provide investigators with further information upon which to base trial decisions and discussions.
Results: 60% of patients were male, the median age was 67 years (range 38 years - 85 years), 50% had good performance status (KPS >70), and 39% had a solitary brain metastasis on a CT or MRI scan. At baseline, whilst 22% of patients reported no moderate or severe problems, the remaining 78% reported a wide range of problems, most commonly tiredness (47%). 80% of patients received the full course of WBRT, though 11 (15%) patients experienced rapid progression and did not begin WBRT. The average daily dose of dexamethasone throughout the study was 6 mg in both arms. The average QALY was 30 days in the OSC alone group, and 31 days in the OSC+WBRT group. Median survival was 7.3 weeks for patients receiving OSC alone, compared to 7.0 weeks for those receiving OSC+WBRT. Treatment with WBRT did not appear to have an obvious effect on QoL.



Conclusion: These data provide preliminary evidence that omitting WBRT is not detrimental to this group of patients. They are not definitive results but provide a strong rationale for the trial continuing, to answer this longstanding clinical question. Recruitment is improving since the data release.
Keywords: supportive care, Non-small cell lung cancer, Whole Brain radiotherapy, Quality Adjusted Life Years

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P3.050 DO BETA-BLOCKERS ALTER DYSPNEA AND FATIGUE IN ADVANCED LUNG CANCER? A RETROSPECTIVE ANALYSIS.

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Background: Most patients with advanced lung cancer will suffer from dyspnea but there are multiple causes and the treatment options are limited. Cachexia, muscle weakness, and increased muscle receptor (ergoreceptor) feedback could increase ventilatory drive and thus contribute to both dyspnea and fatigue. The sympathetic component of this ventilatory pathway might be usefully interrupted by

beta-blockers. This retrospective review assessed the association between beta-blocker use and dyspnea and fatigue in a regional tertiary cancer centre.
Methods: An ethics approved review was conducted of new patients with stage III-IV non-small lung cancer (NSCLC) or any small cell lung cancer (SCLC) seen from July 2007 to June 2008. Data were abstracted for clinical characteristics, comorbidity, beta-blocker use, and pre-treatment Edmonton Symptom Assessment System (ESAS) dyspnea and fatigue scores. Sample size was calculated to have an 80% power to detect a 1.5 point difference (0.5 standard deviations) on the 10 point ESAS scale using a two-sided, two-sample t-test.
Results: There were 348 patients screened and 202 eligible for inclusion. Reasons for ineligibility included: stage I-II NSCLC (n=52) and not having completed ESAS (n=94). Median age was 67, 55.4% of patients were female, 18.8% had chronic obstructive pulmonary disease (COPD), and 5.9% had active coronary artery disease. Median hemoglobin was 129. Thirty-eight patients (18.8%) were taking beta-blockers. Over 60% of patients scored 4/10 or higher on their dyspnea and fatigue scores. Mean dyspnea / fatigue scores were 5.05 / 5.24 for patients taking beta-blockers and 4.94 / 5.11 for patients not taking beta-blockers, which was not statistically different (p-value = 0.89 for dyspnea, 0.93 for fatigue). Dyspnea and fatigue were moderately associated (Spearman rho=0.38, $p < 0.001$). Multivariate models showed that COPD was associated with increased dyspnea and fatigue and anemia was associated with increased fatigue, but beta-blockers did not alter ESAS scores. Recorded dosages of beta-blockers were low; 29 of 38 patients taking a beta-blocker had their dosage recorded, and 28 of these were taking a dose representing less than half of the daily maximal dose.
Conclusion: Dyspnea and fatigue are common in our patient population at the time of first consultation. COPD and anemia appear to contribute to these symptoms. No association between beta-blocker use and dyspnea or fatigue scores was observed. Given the limitations of this retrospective study, prospective research into the impact of beta-blocker use is warranted.
Keywords: Lung cancer, dyspnea, fatigue, beta-blockers

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P3.051 PATTERS AND COST OF MANGEMENT OF METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) AFTER COMPLETION OF CHEMOTHERAPY WITH THE INTRODUCTION OF ERLOTINIB.

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Background: We previously published the population- based patterns and cost of management of metastatic NSCLC after completion of chemotherapy until death, prior to the introduction of erlotinib in the treatment of NSCLC (Lung cancer 2010, 70; 110). The current study was undertaken to investigate the above in patients who also received erlotinib.
Methods: Metastatic NSCLC patients, who were approved for erlotinib in Manitoba between June 2006 and March 2009, were selected. Manitoba cancer registry (MCR) and chart review were used to capture the information on treatment and clinical outcome. Service utilization information and direct cost information were extracted from the MCR, the Physicians Claims, the Hospital Discharge database, and the Drug Program Information Network.
Results: We identified 71 NSCLC patients treated with erlotinib in the study period. Of these patients, 54% were male, 14% were Asian, and 70% were either current or ex-smoker. Most of the patients received erlotinib as either second line (42%) or as third line (48%) treatment. The median survival was 40.1 weeks from the last date of the last cycle of chemotherapy (39.3 for males; 52.1 for females). Each person on average had 33.2 medical claims (29.8 for males; 36.2 for females) or 90 medical claims per 100 person week. Among males, those aged 65 years and older had the most claims (38.9), while among females, the most claims were observed in the age group less than 55 years old (40.0). The patient cohort had a total of 100 hospitalizations

and 2.7 hospitalizations per 100 person weeks as compared to 207 and 7.0 before the introduction of erlotinib respectively.
Conclusion: Patients who were treated with erlotinib utilized less medical services including hospital admission, which has major impact on the overall management cost as compared to our previous published study population (80% of $10, 805). This may offset the cost of erlotinib and may possibly lead to cost saving.
Keywords: erlotinib, targeted therapy, Lung cancer, Cost

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P3.052 INFLUENCE OF BASELINE INFLAMMATORY MARKERS ON THE RESPONSE TO TKI AND OVERALL SURVIVAL IN NSCLC

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Background: Mutations of the epidermal growth factor receptor (EGFR) gene have been identified in non-small cell lung cancer specimens from patients responding to EGFR tyrosine kinase inhibitors (TKI). However, clinical resistance to TKI is commonly observed regardless of mutation status. There is evidence that resistance can be caused by secondary mutations (EGFR T790M) and MET amplification. A more recently described mechanism involves inflammation-driven IL-6 overproduction. We hypothesize that CRP is a marker of impaired TKI sensitivity possibly through the TGF-β IL-6 axis pathway in EGFR mutation positive patients.
Methods: We retrospectively reviewed the charts of all NSCLC patients with an EGFR mutation newly diagnosed between December 2003 and June 2010. Patients with CRP measurements prior to treatment with TKI therapy in any line were included. Response was evaluated by chest CT using Recist 1.1 and categorized as progression (PD) or non-progression (NP). Patients were categorized based on CRP value as ≤10mg/L and >10mg/L. We investigated the association between baseline CRP and response to TKI, time to progression, and survival.
Results: 40 patients were enrolled. M:F 12:28, mean age was 60+/-12 years; ECOG PS for 35 patients was ≤1. All patients were staged 3B/4. All 40 patients had been treated with a TKI: 5 patients received gefitinib and 35 received erlotinib. 8 received TKI 1st line, 19 2nd line, and 13 3rd/4th line. There was no difference in CRP when stratified by line. Best response to TKI was NP in 21 patients and PD in 16 patients. The mean CRP value was 22.25 (SEM 5.96) among those who were NP and 56.6 (SEM 20) in those who had PD. Of the 21 patients who were NP, 11 had CRP ≤10mg/L and 10 had CRP >10mg//L. Of the 16 patients who had PD, 6 had CRP ≤10mg/L and 10 had CRP >10mg//L. Median time to progression on TKI was 13.2 mo for CRP ≤10mg/L, 2.1 mo for CRP >10 mg/L (p=0.006).

CRP: n=40	Median Survival (months) ±SE	95% CI	p-value
≤10mg/L (n=17)	30.9±6.5	18.3-43.6	0.005
>10 mg/L (n=23)	4.9.±3.5	0.0-11.7	
Overall	12.4±5.3	2.0-22.8	

Conclusion: In our retrospective analysis of patients with an EGFR mutation treated with TKI, elevated CRP was associated with a worse outcome in terms of median time to progression and median survival. Large prospective studies are required to confirm these results.

Supported by: The Mona Zavalkoff Fund for Pulmonary Oncology
Keywords: Response, NSCLC and EGFR, CRP, TKI

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P3.053 A PHASE I STUDY OF PACLITAXEL, CARBOPLATIN AND YM155 (SURVIVIN SUPPRESSOR) IN SUBJECTS WITH SOLID TUMORS

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Background: To determine the maximum-tolerated dose (MTD) and to assess the safety, pharmacokinetics, and preliminary evidence of antitumor activity of YM155 (Y), a small-molecule selective survivin suppressant, administered in

combination with carboplatin (C) and paclitaxel (P).
Methods: Patients with advanced malignancies who had received no more than one prior chemotherapy regimen received C (AUC6) and P (200mg/m^2) followed by escalating doses of Y administered as a continuous intravenous infusion (CIVI) over 72 hours in 21-day treatment cycles.
Results: Twenty two patients (19 lung, 1 adenoid cystic, 1 angiosarcoma, 1 carcinoma of unknown origin) received 98 cycles of Y at six different dose levels from 3.6 to 12mg/m^2 with standard doses of C and P. Treatment with Y was well tolerated, grade 3/4 toxicities consisted of grade 3 neutropenia (41%) and thrombocytopenia (14%) and grade 4 neutropenia (41%). Non hematological toxicities consisted of grade 3 hypophosphatemia (18%), hyponatremia (14%), hypokalemia (9%) and grade 4 hyponatremia (9%). Grade 3 amylase and grade 3 pneumonitis during cycle 1 were considered dose limiting at the 12mg/m^2 dose. The MTD was determined as 10mg/m^2 and the median steady-state concentration, clearance, volume of distribution, and terminal elimination half-life of YM155 were 16.2 ng/mL, 8.6 L/h/m^2, 226 L/m^2, and 17 hours, respectively. Of 16 evaluable patients, 5 (31%) achieved a partial response and 11 (69%) achieved stable disease.
Conclusion: The combination of Y (10mg/m^2/d 72 hours CIVI) administered with C and P every 3 weeks exhibited a favorable safety profile. A phase II trial as first line therapy in patients with stage IV non small cell lung cancer is ongoing.
Keyword: survivin

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P3.054 BIWEEKLY AND CARBOPLATIN(CBDCA) AND PACLITAXEL(PTX) AS FIRST-LINE IS HOPEFUL THERAPY IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER: PRELIMINARY RESULTS OF A PHASE II STUDY

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Background: Incidence of elderly patients with advanced non-small cell lung cancer (NSCLC) is increasing, however the treatment for elderly patients is still waiting for the best answer. Although several studies had suggested the advantage of chemotherapy with platinum doublet for elderly patients with advanced NSCLC (e.g. Asco2010 abstract 2), the application of platinum doublet to the elderly is still controversial. To evaluate the efficacy and tolerability of combination chemotherapy with biweekly carboplatin (CBDCA) and paclitaxel (PTX) for elderly patients with advanced NSCLC, we conducted a multicenter non-randomized open label phase II trial.
Methods: Eligibility criteria were as follows; histologically or cytologically proven NSCLC, aged 70 years and older, ECOG performance status (PS) of 0 to 2, clinical stage IIIB and IV, chemotherapy naïve, and adequate organ function. Symptomatic brain metastases were not allowed. Patients received CBDCA (AUC=2.5) and PTX (90 mg/m2) on day 1 and 15 every 4 weeks for up to 6 cycles, until disease progression or intolerable toxicity. The primary endpoint was overall response rate (ORR), and the secondary endpoints were overall survival (OS), progression-free survival (PFS) and tolerability.
Results: 47 patients (median age 77 years old, range 70-85) were enrolled. 36 were male and 36 patients were stage IIIB. PS 0/1/2 were 19/26/2, respectively. The median number of treatment cycle was 3 (1-6). No complete response and 10 partial responses were observed, giving an ORR of 21.3% (95% CI: 9.6-33.0%). Twelve patients (25.5%) had stable disease and 14 (23.4%) had progressive disease as the best response and 11 had not evaluable (2 due to death, 3 due to adverse event, 5 due to withdrawal / missing). The overall disease control rate was 46.8% (95% CI: 32.5-61.1). Median PFS was 4.17 month (95% CI: 2.18-6.16). Grade 3/4 hematological toxicities were neutropenia (28%), leucopenia (19%), anemia (11%) and no thrombocytopenia. Grade 3 non-hematological toxicities were infusion reaction (2%), anorexia (2%), infection (13%), thrombosis (2%), fatigue (2%), diarrhea (2%) and gastrointestinal bleeding (2%). Although no grade 4 non-hematological toxicity was observed, one patient died probably due to treatment-related interstitial

pneumonitis. The adverse events were relatively mild and manageable.
Conclusion: The combination of biweekly CBDCA (AUC=2.5) and PTX (90 mg/m^2) was well tolerated and was effective for elderly patients with advanced NSCLC. (This study was registered at UMIN 000001328)
Keywords: paclitaxel, biweekly, elderly people, Carboplatin

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P3.055 INITIAL TOXICITY AND COMPLIANCE EVALUATION FOR CONSOLIDATION PEMETREXED FOLLOWING CONCURRENT CHEMORADIOTHERAPY (CCTRT) IN STAGE III NON-SMALL CELL LUNG CANCER (NSCLC): A PHASE II TRIAL.

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Background: cCTRT is the standard treatment for good performance status stage III NSCLC and is associated with 5 year survival of 20-25% . Strategies to improve on the efficacy of cCTRT with cisplatin/etoposide are required. Here we evaluate the compliance and acute toxicity of cCTRT followed by consolidation pemetrexed.
Methods: This was a single-institution phase II study. Treatment comprised cisplatin (50 mg/m^2 days 1, 8, 29, 36), etoposide (50 mg/m^2 days 1-5 and 29-33) and concurrent thoracic radiotherapy starting on day 1 chemotherapy (66 Gy in 33 daily fractions; 3D conformal radiotherapy or IMRT) followed by consolidation pemetrexed (500 mg/m^2 on days 71, 92 and 133). The primary endpoint was 1 year survival. Secondary endpoints were progression-free survival, acute/late toxicity (CTCAE v3.0), compliance and response to treatment.
Results: 35 patients were recruited between February 2008 and October 2010. Median age was 61 years (range 42-75) with 26% >65 years. M:F ratio was 23:12 and ECOG performance status was 0 (n=11) or 1 (n=24). Median predicted FEV_1 was 81% (41-94%). Tumour histologies comprised adenocarcinoma (n=7), squamous cell carcinoma (n=21), undifferentiated carcinoma (n=4) or was not specified (n=3). TNM staging (6th edition) at presentation was: T2N2=3 (9%), T2N3=2 (6%), T3N2=6 (17%), T4N0=12 (33%), T4N2=10 (29%), T4N3=2 (6%). Median planning target volume was 464.3 cm^3 (284.1-1064.3) and median V_{20} was 30% (10.5-35.3). All 35 patients received cCTRT: 33 patients (94%) received full dose concurrent chemotherapy and 32 patients (91%) received the planned dose of 66Gy (range 56-66 Gy). Number of patients who received pemetrexed: cycle 1=25 (71%), cycle 2=21 (60%), cycle 3=16 (46%). Reasons for omitting cycle 1 pemetrexed were as follows: 7 patients had not recovered from cCTRT-related adverse events, 2 patients withdrew and 1 patient died on study. Median duration from completion of cCTRT to cycle 1 pemetrexed was 32 days (19-41). Oesophagitis and pneumonitis were not assessable for one patient. 10 patients experienced grade 3 oesophagitis (29%) and 1 patient grade 4 (3%). Median duration grade 3/4 oesophagitis was 10 days (2-24). Median time from treatment commencement to onset of maximum grade oesophagitis was 36 days (8-82). 1 patient experienced grade 3 pneumonitis (3%), no grade 4. 8 patients experienced grade 3 fatigue (23%), no grade 4. Two patients suffered grade 4 venous thromboembolic events. 2 patients with central disease suffered grade 5 haemoptysis. The results of 1 year survival, progression-free survival and late toxicity are awaited.
Conclusion: The addition of consolidation pemetrexed following cCTRT for stage III lung cancer does not appear to worsen the incidence or severity of treatment-related pneumonitis or oesophagitis in a population of patients with large planning target volumes. However, the full dose of consolidation therapy was not feasible in half (54%) of the patients. This study highlights the challenges of adding further systemic therapy to cCTRT in locally advanced NSCLC, and will be of value to inform the design of future trials of consolidation treatment in this population.
Keywords: chemoradiotherapy, Non small cell lung cancer, Concurrent, NSCLC

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P3.056 RELATIONSHIP BETWEEN THE G-CSF AND BONE METABOLISM IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Although the granulocyte colony-stimulating factor (G-CSF) is widely used for neutropenia with cancer chemotherapy, the reaction of the neutrophil at the time of G-CSF medication, has large individual difference, and we cannot predict the reaction. The relation between myelosuppression with chemotherapy and bone density or bone metabolism is also unclear.
Methods: Stage IIIB or IV chemo-naive non-small cell lung cancer (NSCLC) patients were eligible. Patients received chemotherapy with platinum-based doublets. We measured serum bone metabolism markers (N-terminal telopeptide of type I collagen:NTx, bone alkaline phosphatase:BAP) before treatment and after each course of the chemotherapy. We measured lumbar-vertebrae bone mineral density (BMD) by dual-energy x-ray absorptiometry before treatment and after 3 courses of the chemotherapy. We evaluated the relation between BMD or bone metabolism markers, neutropenia with chemotherapy and G-CSF. Furthermore, the relation of glucocorticoids used with chemotherapy, and bone density or bone metabolism markers was also considered. At the time of neutropenia , G-CSF (filgrastim) was administered until recovering from myelosuppression . The cases required the radiotherapy to bone metastasis and treatment with bisphosphonates were excepted.
Results: Ten patients were enrolled in this study . Seven patients completed the treatment. The average of BMD before and after treatment were both 1.04±0.14 g/cm^2. The mean levels of NTX before and after treatment were 17.15±6.41 nmoL and 12.00±1.98 nmoL. The mean levels of BAP before and after treatment were 21.88±8.37 U/L and 20.95±6.58U/L. Chemotherapy had tendency to decrease serum NTX levels and did not reduce BMD. The early increases of NTX are reported in the glucocorticoid induced osteoporosis, however glucocorticoids used with chemotherapy for the purpose of anti-emesis and anti-allergy did not increase NTX levels in our study.
Conclusion: In this study, there was no correlation between the use of G-CSF with NSCLC chemotherapy, and bone density or bone metabolism markers. However, there was no increase in the risk of loss of BMD in NSCLC patients even if we repeated chemotherapy in a lung cancer patient.
Keyword: G-CSF BMD

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P3.057 PALLIATIVE MANAGEMENT IN LOCALLY ADVANCED/METASTATIC NON SMALL CELL LUNG CANCER IN NON SMOKER INDIANS.

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Background: Non small cell Lung cancer is a rare disease in Punjab state of North India. This is attributable to smoking constraints because of religious restrictions among Sikh community which accounts for fifty percent of state population. The prime occupation in the state is agriculture and the industries are few. Most of the patients belong to poor socioeconomic status and present at locally advanced and even metastatic stage.
Methods: 22 patients were treated during January 2009 to July 2010. All were non smokers with non squamous histopathology. 17 were male and 5 female in age group of 55-75 years. All had EGFR mutation . 16were locally advanced and 6 had metastatic disease at presentation. Palliative Radiotherapy for Haemoptysis, SVC obstruction and Pain in case of Pancoast tumors was given to 19 patients. 30Gy in 10 fractions @ five fractions per week. Oral gefitinib 250 mg OD was given to all patients.
Results: Results were evaluated at 3 months and 6 months. There was Partial response in 8 patients. 8 had stable disease. 6 patients had progression out of which 2 progressed at Ist evaluation and 4 at 2nd

evaluation. These were patients who presented with Metastatic disease. All the patients who had PR have had received palliative Radiotherapy.
Conclusion: Radiotherapy followed by Oral Gefitinib is an effective mode of palliation in locally advanced/ metastatic non squamous ,non smokers NSCLC .
Keyword: Gefitinib, Radiotherapy

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P3.058 INTRAVENOUS VINORELBINE (NVBIV) ON D1 SWITCH TO ORAL VINORELBINE (NVBO) ON D8 IN COMBINATION WITH CARBOPLATIN (CBDCA) AS FIRST LINE TREATMENT IN ADVANCED NON-SMALL LUNG CANCER (NSCLC) PATIENTS: FINAL RESULTS OF A PROSPECTIVE STUDY IN NONRANDOMIZED POPULATION

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Background: Lung cancer is the leading cause of cancer mortality in the Czech Republic. Approximately 80% of cases are NSCLC and 65% of patients have advanced disease at the time of diagnosis. For patients with advanced NSCLC and preserved functional status, the standard therapy is a double agent platinum-based chemotherapy. Most patients who receive first-line chemotherapy experience disease progression within 3 to 6 months of initiating therapy and the median survival time observed is 8 to 10 months. In this situation, there is a need to find effective therapeutic regimen with an administration as simple as possible and the most favorable toxicity profile. The purpose of this trial was to evaluate the activity and feasibility of CBDCA together with NVBiv and NVBo.
Methods: Patients with advanced NSCLC received NVBiv 25 mg/m^2 on D1 and NVBo 60 mg/m^2 on D8 combined with CBDCA AUC5 on D1 every three weeks. In stage III, chemotherapy was followed by external radiotherapy. The outcomes include following: response, median overall survival (mOS) and median progression free survival (mPFS). Response was assessed by imaging techniques after 4-6 weeks of treatment and was confirmed one month later by chest X-ray and/or CT scanning. The difference in response relative to baseline characteristics was determined using Pearson Chi-square test. Differences in OS and PFS relative to baseline characteristics were evaluated for significance using Log-rank test.
Results: 144 patients were treated: 117 men (81.2%) and 27 women (18.8%), median age 65 years. ECOG performance status at inclusion was PS 0 in 33 (22.9%) patients, PS 1 in 99 (68.8%) and PS 2 in 12 (8.3%) and patients. Most patients had stage IIIB 64 (44.4%) and stage IV NSCLC 76 (52.78%), only 4 (2.78%)pts were IIIA. Adenocarcinoma was confirmed in 32 patients (22.2%), squamous-cell carcinoma in 86 (59.7%) and other in 26 (18.1%). Complete response was confirmed in 1 (0.7%) patient, partial response in 68 (47.5%), stable disease in 47 (32.9%), 27 (18.9%) patients progressed, one patient (0.7%) was not evaluated. The regimen was well tolerated. Median cycles was 6, the dosage of NVB was without changes in 126 (87.5%) patients, the dosage of NVB was reduced in 14 (9.7%) and escalated in 4 (2.8%) patients. Major toxicities (Grade 3-4) were neutropenia in 45 (31.2%%), leucopenia in 22 (15.9%), anemia in 5 (3.5%), and thrombocytopenia in 3 (2.1%) patients. Febrile neutropenia was observed in 3 (12.1%) patients. The mOS was 14.2 moths and the mPFS 10.5 months. The differences between groups of pts according to PS (0+1 vs. 2) were statistically significant ($p < 0.001$) better for patiens with PS 0+1.
Conclusion: In this group of 144 non-selected

patients with advanced NSCLC treated with NVB-CBDCA in first line, switching from NVBiv to NVBo allows a more convenient and well tolerated treatment with evidence of high antitumour activity. This combination was active in all groups patients according histology (mOS 14,2 and mDFS 10,5 months). Statistically significant better were the results in patients with PS 0+1.

Keywords: vinorelbin, Advanced NSCLC, First line treatment

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P3.059 ADVERSE EFFECTS IN COMBINATION THERAPY WITH BEVACIZUMAB IN ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER – RETROSPECTIVE STUDY

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Background: Bevacizumab improves response rate (RR) , progression free survival (PFS) and overall survival (OS) when added to first line paclitaxel/carboplatin and RR and PFS when added to first line cisplatin/gemcitabin for patients with advanced non squamous non-small cell lung cancer.

Methods: Retrospective analysis of data of patients treated for newly diagnosed advanced non-squamous non-small cell lung cancer with chemotherapy and bevacizumab at five institutions in Slovakia. Patients which began the treatment between 06/2007 and 03/2010 were considered for this analysis.

Results: Included in the study were sixty one patients, median of age was 58(33-77) years, male were 34 (55.7%) female 27 (44.3%). Chemotherapy consisted of platinum (cisplatin or carboplatin) and another agent (gemcitabin, paclitaxel, pemetrexed, vinorelbin or docetaxel): cisplatin 37 (60.7%) pts, carboplatin 24 (39.3%) pts, gemcitabin 40 (65.6%) pts, paclitaxel 11(18.0%) pts, vinorelbin 6 (9.8%) pts, pemetrexed 3 (4.9%) pts, and docetaxel 1 (1.6%). Bevacizumab dose was 7.5mg/kg in 37 (60.7%) pts and 15mg/kg in 24(39.3%) pts. The median of administered cycles of bevacizumab was 8 (1-30). Median OS was 18.3 months (11.1-24.3 months 95% CI), median TTP was 8.4 months (6.6 – 11.2 months 95% CI). Objective response rate: CR 2(3%), PR 31 (53%), SD 23 (39%), PD 3 (5%). Grade 3/4 adverse events included neutropenia in 13 (21.3%) pts, leukopenia in 7 (11.5%) pts, thrombocytopenia in 6 (9.8%) pts and anemia in 9 (14.8%). Grade 3/4 non hematologic adverse events included hypertension in 14 (23%) pts, gastrointestinal perforation in 1 (1.6%) pt, cardiac ischemia after 24 cycles of B which required surgical bypass in 1 (1.6%) pt, arterial thrombosis in 1(1.6%) pt. In one patient pneumothorax grade 3 was observed due to cavitation of tumor after carboplatin, paclitaxel and B 15mg/kg. Cerebrovascular ischemia (stroke) was suspected in one patient, which died after first cycle with disease progression. Common grade 1/2 adverse events included leukopenia, neutropenia, anemia, fatigue, hypertension, and epistaxis. We briefly refer a case of two subsequent gastrointestinal perforation in patient treated with cisplatin/carboplatin + docetaxel + B 7.5mg/kg and discuss the possible reasons.

Conclusion: Adverse events in our local retrospective study were acceptable, the profile was similar to that in large studies E 4599 and AVAIL. From the more rare adverse events we have observed two subsequent GI perforations in one patient, cardiac ischemia after 24 cycles of B which required surgical bypass in one patient and pneumothorax due to tumor cavitation in one patient.

Keywords: gastrointestinal perforation, adverse events, bevacizumab

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P3.060 BRAIN METASTASIS REVEALING LUNG CANCER

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Background: To study epidemiological, clinical and therapeutic profile of lung cancer revealed with brain metastasis.
Methods: During the period 1993-2006, twenty two patients having lung cancer revealed with brain metastasis were treated in Habib Bourguiba's Universital Hospital of Sfax (Tunisia). The discovery of brain metastasis had incited to check up the disease extension and to start cerebral radiotherapy and chemotherapy.
Results: The age of patients varied from 34 to 73 years with a median age of 57.4 years. The sex ratio was 10. Symptoms revealing the disease were headache (20.5%), epileptic crisis (23.07%), hypertension syndroma (12.8%) and neurologic deficit (23.07%). All patients had radiological exploration (CT or MRI). Described lesions were numerous in 13 cases and single in 9 cases The diagnosis of lung cancer was based on anatomopathologic exam after metastasectomy (50%), radiological appearance of brain lesions (36.3%) and on chest radiography before anesthesia (13.6%). Lung cancer was adenocarcinoma in 41% and epidermoid in 32% of cases. Metastasectomy followed by radiotherapy have been realized in 54.5% of patients, 46.5% of patients had radiation alone Radiotherapy protocol was 30 Gy in 10 fractions (59%) or 18 Gy in 6 fractions (40.9%) Chemotherapy was administrated in 9 cases Average survival was 5 months after diagnosis (1 to 29 months)
Conclusion: Brain metastasis constitutes a frequent circumstance of discovery of the lung cancer. Therapeutic decision must be taken within a multidisciplinary committee considering performance statute of the patient, his co morbidities and disease prognostic. Brain radiotherapy is standard treatment chemotherapy is controversial. Metastasectomy is reserved to single metastasis. The best survivals are observed in cases of single metastasis and using metastasectomy, brain radiotherapy and chemotherapy. In other cases the prognostic is very poor.
Keyword: brain metastasis,lung cancer
A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.061 INDUCTION PEMETREXED AND CISPLATIN FOLLOWED BY MAINTENANCE PEMETREXED VS CARBOPLATIN-PACLITAXEL PLUS BEVACIZUMAB FOLLOWED BY MAINTENANCE BEVACIZUMAB: MULTICENTER RANDOMIZED PHASE III STUDY IN PATIENTS WITH ADVANCED NON-SQUAMOUS NON SMALL-CELL LUNG CANCER (NSCLC). PRELIMINARY DATA OF A QUALITY OF LIFE ORIENTED PHASE III TRIAL OF THE GOIM (GRUPPO ONCOLOGICO ITALIA MERIDIONALE)

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Background: In metastatic NSCLC, the role of chemotherapy has essentially a palliative approach with substantial similarities in terms of treatment efficacy and survival emerging over the years between the different systemic chemotherapy regimens used. More recently, other topics such as histotype, maintenance therapy and quality of life (QoL) have been explored to ameliorate this plateau. Cisplatin (C) plus Pemetrexed (P) and Carboplatin (Cb) in combination with Paclitaxel (T) and Bevacizumab (Be) represent two standards of care in patients (pts) with advanced Non Small-Cell Lung Cancer (NSCLC) and Non-Squamous histotype (NS). P maintenance after chemotherapy (CT) confers further advantage in NS-NSCLC with respect to placebo. Quality of Life (QoL) may influence the therapeutic choice if one of the

associations showed to be better tolerated and favoured an amelioration of QoL. its effect on symptom relief and QoL is of the utmost importance Thus, we propose a study comparing CP followed by P maintenance versus CbTBe followed by Be maintenance.
Methods: Since January 2010 chemonaive pts with NS advanced NSCLC, age ≤ 70 years, stage IIIB/IV according 7th TNM Edition, ECOG PS 0-1, adequate bone marrow reserve, renal , hepatic and coagulative function and at least 1 uni-dimensionally measurable lesion according RECIST criteria were enrolled. Pts were allocated 1/1 to the following arms: (A) C 75 mg / m^2 d1 plus P 500 mg / m^2 d1 q3 wks for 6 cycles followed by P 500 mg / m^2 q3 wks, until PD or unacceptable toxicity if SD or PR, (B) Cb AUC 6 d1 plus T 200 mg / m^2 d1 plus Be 15 mg / kg q3 wks for 6 cycles followed by Be 15 mg / kg q3 wks, until PD or unacceptable toxicity in SD/PR pts. The primary objective of the study is to evaluate the difference in terms of QoL between treatment arms. together with Co-primary endpoints represented by the EQ5D questionnaire total score and the EQ5D visual analog scale. Secondary objectives: evaluation of QOL across time, treatment activity and tolerability.
Results: Sample size and statistical design: Null hypothesis (H0): no minimal interesting difference (MID) (i.e. a difference of clinical interest) between arms at 12 weeks of maintenance. A sample of 49 patients per arm (not progressing during initial CT and having undergone maintenance therapy for at least 12 weeks) will have a 91% chance to demonstrate a MID in terms of EQ5D and VAS when H0 is not-true, and a 87% chance to demonstrate a MID in terms of EQ5D total score, when H0 is not-true. It is assumed that about 20% of randomized patients experienced a PD before the time of evaluation of the primary endpoint, with no significantly difference between arms. The study sample will then be increased to 118 patients [(49 +49) +20%)]. From january 2010 sixty six patients were recorded. Median age 49 years (range 39-70), M/F: 75%/25%, PS 0/1: 76%/24%, stage IIB/IV: 16%/84%.
Conclusion: The trial is actually recruiting and results are eagerly awaited.
Keywords: Chemotherapy, non-squamous advanced NSCLC, EQ5D questionnaire, Quality of Life

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P3.062 RANDOMISED EVALUATION OF STENTS TO OPEN RESTRICTED AIRWAYS IN PATIENTS WITH CENTRALLY PLACED NON-SMALL CELL LUNG CANCER (RESTORE - AIR)

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Background: A common cause of breathlessness in patients with lung cancer is malignant central airway obstruction. The deployment of an endobronchial stent can restore airway patency and improve breathlessness. This pilot RCT aimed to determine whether the deployment of a stent improves breathlessness and functional ability compared with standard palliative anticancer therapy alone in patients with advanced NSCLC.
Methods: Patients with central airway obstruction were randomised to either an intervention group (rigid bronchoscopy and endobronchial stent insertion plus palliative anticancer therapy) or to a control group (palliative anticancer therapy alone). The primary endpoint of the study was the proportion of patients achieving a 50% improvement in the 6-minute walk distance (6MWD) at 2 weeks compared to their baseline assessment. Exploratory endpoints included change in 6MWD at day 15 and 3 months, change in visual analogue scale (VAS) for breathlessness at day 15 and median survival. For the primary endpoint a 5% level of significance was used. For the exploratory end points a 1% level of significance was used.
Results: See Tables 1 and 2 for the clinical characteristics and results of the patients in the two treatment groups. Table 1: Clinical Characteristics in Treatment Groups

Characteristic	**Intervention arm N=10**	**Control arm N=11**
Age		
Mean (Range)	66 (58,73)	66 (57, 75)
Sex		
M:F	7:3	6:5
Histology		
Adenocarcinoma	1 (10%)	3 (27%)
Squamous cell	7 (70%)	6 (55%)
Undifferentiated carcinoma	2 (20%)	2 (18%)

Performance status		
1	6 (60%)	7 (64%)
2	4 (40%)	4 (36%)
Treatment		
Lines of anti-cancer therapy prior to randomisation. Mean (Range)	1 (0,3)	0.8 (0,2)
Line of anti-cancer therapy post randomisation. Mean (Range)	0.9 (0, 2)	1.4 (1,2)
Serious Adverse Events (adverse event requiring hospital admission or death within 30 days of admission)	6	1

Table 2: Change in 6MWD, VAS and Survival in Treatment Groups

Characteristics	**Intervention arm N=10**	**Control arm N=11**	**p value**
6MWD			
50% improvement from baseline	0/10	0/11	
Change from baseline at day 15 Median (Range)	36 (-203.5 to 156) n=8/10	10.25 (-109 to 65) n=8/11	p=0.372 (Mann-Whitney test)
Change from baseline at 3 months Median (range)	98.5 (45 to 139) n=4/10	-90 (-149.5 to -39) n=4/11	p=0.021 (Mann-Whitney test)
VAS			
1.5 point fall in VAS at day 15	40% (4/10)	18% (2/11)	p=0.234 (Fisher's exact test)
SURVIVAL			
Median survival (95% CI)	4.1 (1.1, 7.1)	6.2 (0, 18.6)	p=0.05 (Log Rank)

Conclusion: There was a trend toward towards improvement in 6MWD. This was most marked at 3 months (p=0.021, 1% significance). The number of patients in the study was small and only 3 out the 10 patients in the intervention arm actually received a stent, 4 others received laser therapy, dilatation or debulking procedures. Three patients received no procedures. Median survival was shorter for the intervention group than for the control group. This may be explained by two early (within 30 days) deaths in the intervention group. Further studies on the benefit of endobronchial stenting should select patients with a predicted life expectancy of 3 months.
Keywords: NSCLC, Bronchial Stents, 6 Minute Walking Distance, Airway Obstruction

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P3.063 THE EFFECT OF BODY WEIGHT LOSS ON THE PROGNOSIS OF ADVANCED LUNG CANCER PATIENTS

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Background: In patients with lung cancer, weight loss is common at presentation and a frequent cause of patient concern. The prognostic effect of weight loss has been reported repeatedly and confirmed by several retrospective studies. Weight loss is considered to be a specific symptom of cancer cahexia, which may be a new treatment target in combination with the apetite enhancer development like a ghrelin. In this study, we analyzed the relationship of weight loss and prognosis in advanced lung cancer patients in recent years.
Methods: A total of 206 patients confiremd as advanced lung cancer between 2002 and 2008 were reviewed retrospectively. The prognostic effect of weight loss on the overall survival was analyzed using logrank test statistically.
Results: Demographic characteristics of patients were: median age 67 years (33 to 86 years); M/F 148/58, Histology Ad/Sq/Sm/Others 101/41/47/17 Stage III/IV/Recurrence 55/143/8 Patient >5%weight loss/>10% weight loss 58%/36%; Timing of the weight loss after admission to the hospital <6m/6-12m/12-18m 37%/10%/4% MST in the patients with <5% or >=5% weight loss were 370 and 314 days, respectively (p=0.3234) MST in the patients with <10% or >=10% weight loss is 370 days and 289 days, respectively (p=0.0026).
Conclusion: Body weight loss (>5%) in the advanced lung cancer are observed in 58% during the entire cinical course, and associated with a marginal effect on worse prognosis. Weight loss >10% is correlated with shorter survival, and is a prognositic factor clearly. The body weight loss start during 6 months after first admission to the hospital.
Keywords: weight loss, Lung cancer, cahexia

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P3.064 EVALUATION OF THE EFFICACY AND SAFETY OF BEVACIZUMAB IN COMBINATION WITH PLATINUM -BASED CHEMOTHERAPY FOR ADVANCED NONSQUAMOUS NON-SMALL CELL LUNG CANCER.

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Background: Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF), has been associated with improved survival and response rates when combined with platinum-based chemotherapy in patients with non-small cell lung cancer (NSCLC). The aim of this retrospective study was to evaluate the efficacy and safety of platinum-based chemotherapy plus bevacizumab in patients with advanced nonsquamous NSCLC in our hospital.
Methods: Patients received platinum-based chemotherapy, including cisplatin (75mg/m2) plus pemetrexed (500mg/m2), carboplatin (area under the curve of 5) plus pemetrexed (500mg/m2), and carboplatin (area under the curve of 5) plus paclitaxel (200mg/m2) in combination with bevaciuzmab (15mg/kg) every 3 weeks. After 4-7 courses of chemotherapy, maintenance bevacizumab was continued until disease progression or intolerance to treatment.
Results: A total of 17 patients received this treatment. Base line characteristics : male/female 12/5, all patients are stage4 adenocarcinoma, ECOG PS0/1:13/4; median age:62.8yr. Of the patients evaluated for efficacy(n=14), the overall response rate was 71.4%; stable disease was observed in another 21.4%. Hematological toxicities of grade ≥3 included leucopenia in 23.5%, neutropenia in 35.3%, anemia in 5.9%, and thrombocytopenia in 17.6%, respectively. Neither febrile neutropenia nor neutropenic infection was observed. Common non-hematological toxicities were gastrointestinal toxicities, such as nausea, constipation, anorexia, and vomiting, although toxicities of grade ≥3 were not observed. There were no treatment-related deaths.
Conclusion: This combination treatment followed by maintenance therapy with bevacizumab was effective with acceptable toxicity in patients with advanced nonsquamous NSCLC.
Keywords: nonsquamous, bevacizumab, NSCLC

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P3.065 A RANDOMIZED TRIAL OF 1ST LINE DOCETAXEL AND CISPLATIN AT 75/60 VS 60/60 MG/M2 FOR PATIENTS WITH STAGE IIIB OR IV NON-SMALL CELL LUNG CANCER AND CYP3A5 GENOTYPE

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Background: Combinations of Docetaxel(D) and Cisplatin(P) are one of the standard regimens for the treatment of advanced non-small cell lung cancer (NSCLC). However, there have been concerns about toxicity of using a D regimen at 75mg/m^2 3-weekly dosage in an Asian population. The primary objective of this study was to prove non-inferiority of response rate of 60mg/m^2 dose of docetaxel with 60mg/m^2 cisplatin compared to 75mg/m^2 dose of docetaxel with 60mg/m^2 cisplatin as a first line treatment for NSCLC.
Methods: In this randomized, phase III clinical trial, we compared response rates and toxicity profile of two combination regimens of DP - 75/60 vs 60/60 mg/m^2/3week in patients with stage IIIB or IV NSCLC. Patients were stratified according to ECOG PS 0,1 vs 2, weight loss in the previous 6 months < 5% vs > 5% and Stage IIIB vs IV or Relapsed. The non-inferiority margin was set at -15%. A total of 264 patients were required to provide the study with 80% power with a 5% type 1 one-sided error rate. Secondary objectives included progression free survival and safety. Genotyping of CYP3A4, CYP3A5 and ABCB1 were performed and correlated with toxicities.
Results: From September 2007 to September 2009, 132 patients were enrolled. After a pre-planned interim analysis, this study was closed early as it met primary end point. The patients were randomly assigned to 75/60 (n=65) or to 60/60 (n=67). Response rates were 38.5% in 75/60 group and 40.3% in 60/60 group. The 95% CI for the difference in response rate was -14.9%~18.5%. There was no significant difference in number of cycles (3.42 vs. 3.57), time to progression (4.9 vs. 4.7m) between the two groups. However, the dose reduction rate

(53.8% vs 22.4% p<0.01), incidences of grade 3-4 leukopenia and neutropenia were significantly higher in 75/60 compared to 60/60 group. The incidence of neutropenia was significantly higher in non-expressing genotype (GG) compared to AG or AA genotypes of CYP3A5.
Conclusion: We conclude that D 60mg/m^2 in combination with P 60mg/m^2 was non-inferior to D 75mg/m^2 with P 60mg/m^2 in response rate and time to progression, while providing patients with a better safety profile in Asian population.
Keywords: Docetaxel, Cisplatin, Non-small cell lung cancer, CYP3A5

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P3.066 EFFECT OF PEMETREXED ON BRAIN METASTASES IN 45 PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER

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Background: Pemetrexed is a multitargeted antifolate inhibitor used as a standard agent in patients with advanced non squamous cell non small cell lung cancer (NSCLC). Some cases reported in the literature showed that it was effective on the brain metestasis in NSCLC. The purpose of this study was to evaluate the efficacy of Pemetrexed in the treatment of NSCLC patients with asymptomatic brain metastases.
Methods: NSCLC Patients with brain metastases from Nov 2007 to Dec 2010 in our department who received Pemetrexed were analyzed. SPSS version 12.0 software was applied to perform the statistical analysis.
Results: A total of 45 NSCLC patients were enrolled into this study with a median age of 57 years (range 35-76), M/F: 25/20, Smoker/ Nonsmoker: 19/26, single/ multiple lesion: 12/33, adenocarcinoma: 42. 32 patients received whole brain radiotherapy (WBRT) before the chemotherapy and 6 patients received Pemetrexed as a first-line agent. The median cycles of chemotherapy was 3 (range 1-7 cycles). No severe side effect was observed. Local cerebral response assessment showed that 17 patients (37.8%) got a partial response (PR), 20 (44.4%) had a stable disease (SD) and 8 (17.8%) were disease progressed (PD). General lesions assessment presented that 5(11.1%), 16(35.5%) and 24(55.6%) patients got a PR, SD and PD respectively. The disease control rate (DCR) was 82.2% in local cerebral disease, which was significantly higher than 46.6% in general lesions (P=0.004). As for patients who didn't previously receive radiotherapy, the ORR was 46.2% and DCR was 84.6% in local cerebral disease, while in general disease, 7.6% and 61.5% only.
Conclusion: Pemetrexed demonstrated a higher efficacy on cerebral metastases than general lesions in NSCLC, which could warrant further investigation to guide the clinical practice.
Keywords: asymptomatic brain metastases, Non small cell lung cancer, Pemetrexed

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.067 THE IMPACT OF EPIDERMAL GROWTH FACTOR RECEPTOR GENE MUTATIONS ON SKELETAL-RELATED EVENTS IN PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA

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Background: Bone metastases cause significant pain and morbidity leading to skeletal-related events (SREs), including a requirement for radiation or surgery of the bone, pathologic fractures and spinal cord compression. Recent reports suggested non-small cell lung cancer (NSCLC) patients with characteristics such as male sex, poor performance status and ever-smoking were more likely to have SREs. However, the relationship between EGFR gene mutation status

and SREs has not yet been assessed.
Methods: To assess the impact of EGFR gene mutations on SREs, we retrospectively examined the clinical records of patients with advanced lung adenocarcinoma who were evaluated EGFR mutation status and treated with Gefitinib or platinum-based chemotherapy as initial systemic treatment at Shizuoka Cancer Center between January 2008 and March 2010.
Results: A total of 138 patients were included in this study. The median age was 64 years (range, 33-80 years). Fifty patients (36%) were female, and 50 patients (36%) were never-smokers. The PS and EGFR mutation status were as follows: 41 patients with PS 0, 73 patients with PS 1, 24 patients with PS 2-4; 91 patients (66%) with wild type EGFR, 47 patients (34%) with EGFR mutations. Most patients had exon 19 deletions or the exon 21 point mutation termed L858R. The median follow-up time was 19.4 months (range, 10.3-36.8 months). The median overall survival for patients with wild type EGFR and EGFR mutations were 10.8 and 25.8 months, respectively ($p<0.01$). A total of 72 patients (52%) were diagnosed with bone metastases at the time of diagnosis, and 82 patients (59%) were found to have bone metastases during their clinical course; 52 patients (57%) of the 91 patients with wild type EGFR and 30 patients (64%) of the 47 patients with EGFR mutations. Among the 82 patients with bone metastases, 52 patients (63%) developed at least one SRE and 17 patients (21%) had multiple SREs. In patients with wild type EGFR, 33 patients (63%) developed at least one SRE and 8 patients (15%) had multiple SREs. In patients with EGFR mutations, 19 patients (63%) developed at least one SRE and 9 patients (30%) had multiple SREs.
Conclusion: Advanced lung adenocarcinoma patients with EGFR gene mutations have a longer survival, and are more likely to have multiple SREs.
Keywords: bone metastases, EGFR mutation, Adenocarcinoma

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P3.068 CLINICAL OUTCOMES OF LEPTOMENINGEAL METASTASIS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER IN THE MODERN CHEMOTHERAPY ERA

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Background: We intended to analyze the patterns of treatment and clinical outcomes of leptomeningeal metastasis (LM) in patients with non-small cell lung cancer (NSCLC) in the modern chemotherapy era.
Methods: We retrospectively reviewed the data of NSCLC patients who were diagnosed with LM from 2003 to 2009 in Seoul National University Bundang Hospital.
Results: Of the 50 patients with cytologically proven LM, 25 were male (50%), 14 (28%) had ECOG performance status (PS) ≥3, and the median age was 62.5 years (34-81). The patients were diagnosed with LM after median 10.4 month (0-86.8) from the initial diagnosis of metastatic NSCLC. LM presented in 11 patients at the time of initial diagnosis. The median overall survival (OS) after the diagnosis of LM was 4.3 months (95% CI 1.5-6.7). Forty-eight patients (96%) received intrathecal chemotherapy and cytological response rate was 52%. The median survival was 5.5 months in cytologic responders and 1.4 months in nonresponders ($p=0.075$). The median OS in patients with ECOG PS 1-2 was longer than in those with ECOG PS 3-4 (5.5 vs. 0.7 months, $p<0.001$). Twenty-two patients (44%) underwent systemic cytotoxic chemotherapy or EGFR tyrosine kinase inhibitor (TKI) after being diagnosed with LM. These patients showed prolonged survival (11.5 vs. 1.4 months, $p<0.001$), and in 15 patients (30%) who received EGFR TKI, the median OS was 19.2 months. In patients with ECOG PS 1-2, patients who received further systemic chemotherapy showed improved survival (11.5 vs. 2.1 months, $p<0.001$).
Conclusion: NSCLC patients with LM showed diverse clinical outcomes rather than uniformly poor prognosis. Systemic chemotherapy, especially EGFR TKIs, in addition to intrathecal chemotherapy might confer survival benefit.
Keywords: systemic chemotherapy, NSCLC, leptomeningeal metastasis, EGFR TKI

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P3.069 THE USE OF BEVACICUMAB IN ADVANCED NON-SMALL CELL LUNG CANCER, EXPERIENCE FROM A SINGLE INSTITUTION IN DENMARK

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Background: Bevacizumab, a humanized monoclonal anti-VEGF antibody, has demonstrated significant clinical benefit in the first-line treatment of advanced nonsquamous non-small cell lung cancer [1,2]. However there are several exclusion factors limiting the proportion of patients eligible for bevacizumab. The department of oncology Hillerød Hospital is to our knowledge the only institution in Denmark who routinely has treated patients with advanced NSCLC with bevacicumab since 2008. In the following study we will evaluate the exact proportion of patients with advanced adenocarcinoma of the lung, who were eligible for treatment with bevacicumab and characterize the reasons for exclusion or inappropriate usage of bevacizumab.
Methods: A retrospective review of all new patients with advanced non-small cell lung cancer at the department of oncology Hillerød Hospital from January 2009 through December 2010 will be conducted. Only adenocarcinomas will be recorded. With permission from the Danish Data Protection Agency and the National Board of Health, data will be abstracted from the patients electronic medical records. Bevacizumab eligibility criterias, at our instition, are in accordance with the SAIL study MO19390 [3] . Exclusion criterias are squamous or mixed adenosquamous histology, a history of significant haemoptysis (≥2·5 mL red blood per episode), uncontrolled hypertension, a history of thrombotic or haemorrhagic disorders. Radiological evidence of tumour invading or abutting major blood vessels and major surgery within 28 days before start of treatment. Patients with untreated brain metastasis are, in accordance with the European Medicines Agency, considered eligible for treatment with bevacicumab since march 2009.
Results: At the World conference 2011 we will be presenting results of the study of bevacicumab eligibility in above mentioned population.
The results will be correlated to a number of demographic variables including stage, age, race, sex and PS etc.
Conclusion: Our institution is the only oncology department in Denmark, who rutinely has been using bevacicumab for patients with advanced adenocarcinoma of the lung. This study evaluates the exact proportion of patients, who were eligible for treatment with bevacicumab and characterize the reasons for exclusion or inappropriate usage of bevacicumab. References cited:
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Keywords: Bevacicumab, eligibility, advanced adenocarcinomas of the lung

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P3.070 QUALITY OF LIFE ASSESSMENTS IN LUNG CANCER AND MESOTHELIOMA. A COMPARISON OF QUESTIONNAIRES AND PHYSICIAN CONSULTATION – A POOR WORKMAN ALWAYS BLAMES HIS TOOLS?

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Background: Lung cancer and mesothelioma patients often have poor Quality of Life (QoL). Validated QoL questionnaires are used in clinical trials, and should be useful in routine practice. This study aimed to identify the most effective questionnaire as a QoL tool for routine clinical use in thoracic malignancies.
Methods: Three QoL questionnaires were evaluated (EORTC QLQ C30+LC13, FACT-L, and PSALC)

in 3 separate time periods over the course of 3 years (April 2006-April 2009) in Oncology outpatients, Royal Marsden Hospital, Sutton. Newly diagnosed NSCLC, SCLC or mesothelioma patients completed a paper-based questionnaire before seeing the doctor; this was collected but not used during the consultation. The consultation continued as normal with a clinic letter dictated onto the Electronic Patient Record (EPR). Only questionnaire items reported as significant or important ('Quite a bit' or 'Very much' on each questionnaire scale) by >25% of patients were included in the analysis. For each questionnaire item, we assessed whether it was identified during the consultation or on the completed questionnaire. Questionnaire completion rate and number of missing responses were documented.

Results: The study patient population consisted of 33 NSCLC, 34 SCLC, and 31 Mesothelioma. The median age was 65.9 (45 – 84 yrs) with 58 male and 40 female patients. EORTC, FACT-L, and PSALC were completed by 36, 31, and 31 lung cancer and mesothelioma patients respectively. The number of symptoms/issues identified as significant or important by >25% of patients were as follows: 15 / 45 for EORTC, 19 / 37 for FACT-L, and 5 / 9 for PSALC questionnaires. The table shows cumulative percentage scores for each domain, comparing issues reported by: i) questionnaire alone and ii) within the consultation.

EORTC			FACT-L		
Effect on:	Occasions significant issue reported in questionnaire alone	Occasions issue reported in consultation	Effect on:	Occasions significant issue reported in questionnaire alone	Occasions issue reported in consultation
Physical function	16 (44%)	11 (31%)	Physical wellbeing	55 (25%)	29 (13%)
Role function	26 (72%)	4 (11%)	Functional wellbeing	80 (37%)	10 (5%)
Cognitive function	20 (56%)	1 (3%)	Lung Cancer Subscale	20 (56%)	1 (3%)
Emotional function	28 (78%)	5 (14%)	Emotional wellbeing	51 (27%)	2 (1%)
Social function	26 (72%)	2 (6%)	Social wellbeing	23 (11%)	0 (0%)

No patient refused to complete a questionnaire. With the EORTC, 18/540 responses were missing (3%). With the FACT-L, 34/589 responses were missing (6%). The PSALC questionnaire had no missing responses.

Conclusion: This study has shown the EORTC questionnaire to be the most effective QoL instrument to use during our routine clinical practice to improve QoL issues identification, and was associated with fewer missing responses than FACT-L. Discrepancies between the 2 modes of information gathering were greatest for non-physical symptoms and, therefore, questionnaires would serve as a tool for further discussion. However, all three questionnaires showed discrepancies in physical symptoms detection, potentially affecting assessment of a patient's true performance status (PS). Use of routine QoL tools can help focus questioning.

Keywords: Quality of Life, NSCLC, SCLC, mesothelioma

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P3.071 PHASE I STUDY OF E7080, A MULTI-TARGETED TYROSINE KINASE INHIBITOR, IN COMBINATION WITH CARBOPLATIN PLUS PACLITAXEL IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: E7080 is an orally administered receptor tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFR and KIT. In Phase I studies of E7080 monotherapy, a manageable toxicity profile and anti-tumor activity have been observed in patients with advanced solid tumors.

Methods: This was an open-label, dose-escalation study of E7080 administered twice daily (bid) in combination with carboplatin (C) (AUC 6 mg/mL/min, Day 1) and paclitaxel (P) (200 mg/m^2, Day 1) in chemotherapy-naïve patients with advanced NSCLC. After the initial 7-day run-in phase of E7080 monotherapy, patients received E7080 with CP every 3 weeks for a maximum of 6 cycles. Patients were allowed to continue E7080 monotherapy after the completion of CP. The initial dose level of E7080 was 6 mg bid in the dose-escalation cohort. Primary endpoint was the maximum tolerated dose (MTD) of E7080 in combination with CP. Patient accrual was expanded

to 22 patients at the MTD level in the expansion cohort to further evaluate safety and efficacy.
Results: Twenty-eight patients were enrolled. Patient backgrounds were: median age 58 years (range 38-73); males 75% / females 25%; performance status (PS) 0=68% / 1=32%; stage IIIB 29% / IV 71%; and histology subtype, adenocarcinoma 82% / squamous 7% / others 11%. In the dose-escalation cohort, 6 patients received 6 mg bid of E7080 with CP. Two dose-limiting toxicities (DLTs) were observed in 2 patients (febrile neutropenia and infection each) in the first cycle. Another patient discontinued E7080 monotherapy during the 7-day run-in phase due to deterioration of PS. In the next cohort, the dose of E7080 with CP was decreased to 4 mg bid and no DLT was observed in 6 patients. In the expansion cohort, 16 patients were enrolled at the MTD level of 4 mg bid. In 22 patients at the 4 mg level, the common toxicities included thrombocytopenia (100%), leukopenia (95%), neutropenia (95%), arthralgia (95%), peripheral sensory neuropathy (95%) and alopecia (95%). The common grade 3/4 toxicities were neutropenia (95%), leukopenia (50%), hypertension (36%), thrombocytopenia (27%) and febrile neutropenia (23%). The pharmacokinetic analyses of E7080 with C and P suggested no apparent interaction among the three drugs. In all 28 patients, the response rate (RR) was 60.7 % with 1 complete response and 16 partial responses, and the median progression-free survival (PFS) was 9.0 months. The RR and median PFS for 22 patients at the 4 mg level were 68.2% and 9.0 months, respectively. Biomarker analysis indicated that longer PFS in the 4 mg level was correlated with lower baseline levels of plasma stromal cell-derived factor (p=0.011).
Conclusion: The MTD of E7080 in combination with CP is 4 mg bid. Combination therapy shows an encouraging anti-tumor activity with manageable toxicity profile in patients with advanced NSCLC and warrants further evaluation.
Keywords: E7080, Non-Small-Cell Lung Cancer, Carboplatin, paclitaxel

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P3.072 PROGNOSTIC SCORE FOR SECOND-LINE CHEMOTHERAPY OF ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC): EXTERNAL VALIDATION IN A PHASE III TRIAL COMPARING VINFLUNINE WITH DOCETAXEL

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Background: Prognostic index for patients eligible for second-line chemotherapy of NSCLC was previously developed, based on individual patient data (IPD) of 9 randomized trials (Table 1) [Di Maio et al, Eur J Cancer 2010; 46: 735-743]. In this study, we aimed to validate the prognostic score, with the use of an external dataset.
Methods: We analyzed IPD of patients enrolled in a non-inferiority phase III trial comparing vinflunine vs. docetaxel in second-line treatment of advanced NSCLC. Primary endpoint of this validation was overall survival (OS). The following variables were considered for survival analysis and score calculation: gender, performance status (PS), extent of disease, tumor histotype, type of first-line treatment, response to first-line treatment. Cox model, stratified by treatment arm, was used for multivariate analysis. Individual prognostic scores were derived according to our scoring system, and patients were divided into 3 categories according to the score: <5 (best), 5-9 (intermediate), >9 (worst).
Results: All 551 patients enrolled in the trial had complete information for prognostic score calculation. Median OS in the whole study population was 6.9 months, with similar efficacy in the two study arms. At the multivariate survival analysis, there was no heterogeneity between the results obtained in the validation dataset and the results obtained in the previous dataset where the score was produced. Sixty patients (11%) were in the best category, 427 (77%) were in the intermediate category and 64 (12%) were in the worst category. Median OS was 12.9, 6.9 and 3.8 months for the best, intermediate and worst categories, respectively.

Cox model analysis showed a significant effect for intermediate vs. best category comparison (Hazard Ratio 1.79, 95%CI 1.31-2.47, p=0.0003) and for worst vs. best category comparison (Hazard Ratio 3.25, 95%CI 2.18-4.83, p<0.0001). The C-index of the model was high (0.926), indicating a good discrimination according to the proposed risk categories.

Conclusion: Prognostic ability of our score for candidates to second-line treatment in advanced NSCLC was successfully validated. Subgroups of patients with more vs. less favorable prognosis were identified. Prognostic score could be useful in clinical practice.

Table 1. Scoring system

	Points			
	0	**1**	**2**	**7**
Gender	Female	Male		
ECOG PS	PS 0		PS 1	PS 2
Tumor stage	IIIb (locally advanced)	IV (metastatic)		
Histologic type	Adenocarcinoma	Squamous	Other	
Type of first-line	Without platinum		Platin-based	
Objective response to first –line	Yes	No		

Keywords: Prognostic score, second-line chemotherapy, Advanced NSCLC, phase III randomized trial

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P3.073 CISPLATIN AND IRINOTECAN COMBINATION CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER PATIENTS ATTENDING A TB HOSPITAL IN INDIA

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Background: Lung cancer is the most commonly diagnosed malignancy and the leading cause of cancer related death. In absolute numbers, non small cell lung cancer (NSCLC) accounts for about 80% of all lung cancer cases. The combination of weekly Irinotecan (CPT-II) and monthly Cisplatin has shown promising result in advanced cases of NSCLC in Phase I and II studies. Earlier, we have presented our experience of using this combination, particularly, keeping in view the cost factor. This study was undertaken to evaluate the efficacy and safety profile of a combination of our weekly CPT-II and Cisplatin in patients with advanced NSCLC attending to a TB hospital.

Methods: Patients with chemotherapy naÏve stage III B or IV NSCLC were treated with repeated cycles of therapy comprising four weekly treatments with both Cisplatin and CPT-II for 6 cycles. The starting doses of CPT-II and cisplatin were 70 and 50 mg/m^2, respectively. Treatment was continued until the occurrence of disease progression, unacceptable toxicity, or the completion of sic chemotherapy cycles. Solid tumour response evaluation was determined using Modified Response Evaluation Criteria in Solid Tumour (RECIST) Criteria. 8 patients received external radiotherapy in addition.

Results: Of 137 patients registered at Lung Cancer Clinic 121 (88.32%) had NSCLC. Of these 40 (33.1%) met the eligibility criteria and were enrolled into study after taking consent (study group, n-40). Of these 40 patients, 5 (12.5%) were lost in follow up after one cycle and thus excluded from final analysis. Of 68 (56.2%) patients not given any chemotherapy, 49 did not meet the inclusion criteria. Remaining 19 (15.7%) patients, meeting th3 enrolment criteria, but refusing for any chemotherapy served as our control group to whom best supportive care (BSC) was offered and subsequently followed up. The median age of enrolled group (40 patients) was 59 years (range, 44-79). Eastern cooperative Oncology Group (ECOG) performance status was 0, 1 and 2 in 4 (10%), 25 (62.5%) and 11 (27.5%) patients respectively. Stage IIIB and IV disease was found in 27 (67.5%) and 13 (32.5%) respectively. The objective tumour response was seen in seven (26%) patients of whom 1(3.7%) had complete response (CR) and 6 (22.2%) had partial response (PR) while 15 (55.6%) had stable disease (SD). Five (18.51%) patients had progressive disease (PD). The median survival, the 1- year survival rate and the median progression free survival were 57 weeks (95% CI, 49.52 to 64.48 weeks), 53% and 27 weeks (range of 5 to 54 weeks) respectively, in 27 patients who completed six cycles of chemotherapy. The median survival for control group was 11 weeks (95% Confidence interval, 5.96 – 16.04 weeks) [log ran test, P<0.001] while all patients of this group expired by end of 35 weeks.

Grade ¾ non haematological toxicities included vomiting (12%) and diarrhoea (26%) where as grade 3/4hematological toxicities comprised of anaemia (14%), neutropenia (26%), and thrombocytopenia (14%).

Conclusion: Four weekly combined administrations of CPT-II and cisplatin achieved a promising overall response rate, median time to tumour progression, and median survival in patients with stage IIIB/IV NSCLC.

Keyword: RECIST Criteria, ECOG, BSC, NSCLC, Irinotecan (CPT-II) and Cisplatin

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P3.074 RESPONSE RATES TO CARBOPLATIN AND PEMETREXED IN NON-SQUAMOUS NON-SMALL CELL LUNG CANCER – A SINGLE CENTRE AUDIT

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Background: Cisplatin and Pemetrexed has become standard chemotherapy in the management of advanced non-squamous non-small cell lung cancer. For logistical reasons, including lack of capacity and long infusion times with Cisplatin, the preferred combination of chemotherapy in our centre is Carboplatin and Pemetrexed. This audit examines response rates and toxicity profile in our patient population.

Methods: All patients with non-squamous non-small cell lung cancer who received chemotherapy using Carboplatin and Pemetrexed between August 2009 and August 2010 were included. A total thirty nine patients underwent treatment and data were analysed from the patient notes and chemotherapy record. Patients received Carboplatin AUC5 and Pemetrexed 500mg/m^2 every 21 days with a CT scan after 3 cycles and a further 3 cycles given if response or stable disease was seen. Responses were taken from CT scan assessments and were divided into Good or Partial response, Stable disease, Disease progression or treatment discontinued due to toxicity. Formal tumour measurements such as RECIST were not taken.

Results: 23/39 (59.0%) of patients achieved a good or partial response. 7/39 (17.9%) achieved stable disease and 9/39 (23.0%) had progressive disease or unacceptable toxicity. The commonest toxicity reported was anaemia requiring transfusion 7/39 (17.9%) followed by fatigue 5/39 (12.9%). Febrile neutropenia occurred in 3/39 (7%) and platelet transfusion was needed in 2/39 (5%).

Conclusion: The use of carboplatin as a platinum agent in patients with non-small cell lung cancer is relatively controversial. It is believed by many people that response rates and survival are less with carboplatin compared to cisplatin and this is the subject of a large clinical trial which is due to report later this year (the BTOG2 trial). Additionally, carboplatin is more myelosuppressive than cisplatin, leading to concerns when given in combination with other myelotoxic drugs. Cisplatin is nephrotoxic and requires long pre and post treatment hydration schedules leading to difficulties in delivery of this treatment in the outpatient setting. Cisplatin is contra-indicated in patients with impaired renal function, and carboplatin has been safely used in this group as dose is adjusted according to renal function. We have found in our centre that patients prefer carboplatin over cisplatin and this audit shows that the toxicity of carboplatin in combination with pemetrexed is manageable. The response rate was very high compared to trial data, suggesting significant activity of this combination of chemotherapy, although our population was highly selected, non-randomised and tumour assessments were subjective. Our results suggest that further research is warranted to investigate whether carboplatin has superiority over cisplatin when given in combination with pemetrexed.

Keywords: Non-small cell lung cancer, Chemotherapy, Carboplatin, Pemetrexed

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P3.075 ERLOTINIB AFTER FAILURE OF GEFITINIB THERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) WITH OR WITHOUT EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION

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Background: EGFR tyrosine kinase inhibitors (EGFR-TKI), gefitinib and erlotinib, are effective in the treatment of patients with advanced NSCLC, especially those harboring EGFR mutations. Although both EGFR-TKIs may be affected by the same resistance mechanism, erlotinib is given at a higher biological dose than gefitinib and may confer some clinical benefit after failure of gefitinib therapy. Several studies evaluated the effects of erlotinib after gefitinib failure in patients with advanced NSCLC. However, the numbers of patients were small and EGFR mutational status was not examined in all patients. To clarify the role of erlotinib after gefitinib failure in patients with advanced NSCLC in association with EGFR mutational status and response to prior gefitinib treatment, we conducted this retrospective analysis.
Methods: Patients with advanced NSCLC with or without EGFR mutation who were treated with erlotinib after gefitinib failure and had the presence of measurable or evaluable lesion(s) were eligible. Erlotinib was started at the dose of 150 mg daily and was given until disease progression or unacceptable toxicity. Tumor response was evaluated with computed tomography of the chest or chest radiography.
Results: Twenty Japanese patients were collected from 9 institutions. Thirteen patients (65%) were female and 15 patients (75%) were non-smokers. Eighteen patients (90%) had adenocarcinoma and one patient each had squamous cell carcinoma and NSCLC not otherwise specified. Seventeen patients (85%) harbored sensitive EGFR mutations (exon 19 deletions in 7, the L858R substitution in 10). In gefitinib therapy, 14 patients achieved partial response (PR) and five had stable disease (SD) with a response rate of 70% and disease control rate of 95%. In erlotinib therapy after failure of gefitinib therapy, two patients achieved PR and 13 had SD with a response rate of 10% and disease control rate of 75%. The median progression-free survival time and median overall survival time (both from start of erlotinib therapy) were 13.7 weeks and 54.3 weeks, respectively. The response rate, disease control rate and progression-free survival time were 12%, 76% and 13.3 weeks, respectively, for the EGFR mutant group (N=17) and 0%, 67% and 24.3 weeks, respectively, for the EGFR wild type group (N=3). The response rate, disease control rate and progression-free survival time were 14%, 79% and 19.3 weeks, respectively, for patients who had achieved PR with gefitinib (N=14) and 0%, 80% and 11.9 weeks, respectively, for patients who had had SD with gefitinib (N=5).
Conclusion: Erlotinib appears to have some clinical benefit after failure of gefitinib therapy. There was no significant difference in disease control rate according to EGFR mutational status and response to prior gefitinib therapy. Patients who had achieved partial response with gefitinib tended to have longer PFS with erlotinib.
Keywords: EGFR mutation, gefitinib, erlotinib, Non-small cell lung cancer

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P3.076 PHASE Ⅰ/Ⅱ TRIAL OF S-1 PLUS DOCETAXEL (DTX) FOR PREVIOUSLY TREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): KANTO RESPIRATORY DISEASE STUDY GROUP.

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Background: S-1, a novel oral fluoropyrimidine, is active in the treatment of NSCLC. Previous studies investigating a combination of S-1 plus DTX showed promising efficacy but clinically problematic emesis. We conducted a phase I study to find the maximum tolerated doses (MTD) of bi-weekly administered DTX with oral S-1 for one week, and a phase II study to evaluate the efficacy and toxicity.

Methods: Previously treated pts with NSCLC were included. Other eligibility criteria were performance status of 0-1, measurable lesions, age < 75 years, and adequate organic functions were eligible. Pts received S-1 on days 1-7 and DTX on day 1 of each 14-day cycle.
Results: Doses of S-1/DTX (mg/m^2) in the phase I study portion were escalated as follows: 80/30, 80/35, and 80/40. In the phase I, MTD among 13 patients were S-1 80 mg/m^2 with DTX 40 mg/m^2. The dose limiting toxicity (DLT) was febrile neutropenia. The recommended doses for the phase II study were S-1 80mg/m^2 and DTX 35 mg/m^2. A total of 34 pts from 5 institutions were enrolled from Oct. 2009 to Nov. 2010. The overall responses were CR 0; PR 9; SD 12; PD 10 and NE 3, resulting in a response rate of 26.5% (95% confidence interval [CI], 11.6-41.3%). The overall disease control rate was 61.8% (95% CI, 45.4-78.1%). Hematologic grade 3/4 toxicities were neutropenia (29.4%), febrile neutropenia (2.9%) and thrombocytopenia (2.9%). In non-haematologic toxicities, 4 patients with grade 2 interstitial pneumonitis were observed. Nine patients experienced grade 1 nausea only for short durations, and there were no grade 2 nausea.
Conclusion: The combination of one week S-1 with biweekly DTX is an active regimen with low-emesis and low myelotoxicities for previously treated advanced NSCLC.
Keywords: Non-small cell lung cancer, phase I/II study, Docetaxel, S-1

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P3.077 IMPACT OF ANEMIA DURING PACLITAXEL-CARBOPLATIN THERAPY ON SURVIVAL OF PATIENTS WITH ADVANCED NON-SMALL- CELL LUNG CANCER: A RETROSPECTIVE ANALYSIS OF A PHASE II TRIAL (LOGIK0403) BY THE LUNG ONCOLOGY GROUP IN KYUSHU, JAPAN

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Background: Anemia is frequently observed in cancer patients undergoing chemotherapy. No large-scale epidemiologic study evaluating the incidence of chemotherapy-induced anemia in cancer patients has been conducted in Japan. The LOGIK0403 was a phase II randomized trial comparing biweekly and weekly administration of paclitaxel-carboplatin therapy in advanced non-small-cell lung cancer (NSCLC). We retrospectively determined the prevalence and incidence of anemia throughout treatment for each group, risk factors for the development of anemia, and the impact of anemia during chemotherapy on treatment outcome including overall survival (OS) using these data.
Methods: Previously untreated NSCLC patients enrolled in the LOGIK0403 trial (n=140) and having at least one hemoglobin value recorded during chemotherapy were included in the analysis. The Wilcoxon rank-sum test was used to examine the association between baseline variables and hemoglobin grades. Median survival times for the different worst grades of hemoglobin during chemotherapy were calculated using the Kaplan-Meier method. Univariable and multivariable Cox proportional hazards regression analyses were performed to assess the impact of anemia during chemotherapy on OS.
Results: A total of 135 patients were included in this analysis. Fifty-six percent of the patients had hemoglobin of grade 1 (between the lower limit of normal and 10 g/dL) and 4% had grade 2 (10-8 g/dL) prior to chemotherapy. Patients in the weekly group had more severe anemia during chemotherapy

compared to the biweekly group. More than 50% of the patients in the weekly group had hemoglobin of grade 2-4 (< 6.5 g/dL) as the worst grade. Pre-chemotherapy hemoglobin grade and treatment regimen were associated with the worst grade of hemoglobin during chemotherapy (P < 0.001). A statistically significant difference was seen in terms of OS among the worst grades of hemoglobin (P = 0.02), whereas no significant differences were seen in relative dose intensity, objective response rate, or progression-free survival. Multivariable Cox regression analysis demonstrated that the worst grade of hemoglobin was an independent prognostic factor after adjustment for relevant variables such as sex, performance status, and histology (anemia during chemotherapy was associated with poorer survival).

Table. Cox regression analysis for the association between overall survival and worst grade of hemoglobin during chemotherapy.

	Univariable Analysis		Multivariable Analysis	
Variable	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Hemoglobin Grade				
Grade 0/1	1 (Referent)		1 (Referent)	
Grade 2	1.50 (0.98, 2.28)	0.06	2.04 (1.31, 3.17)	0.002
Grade 3/4	2.08 (1.21, 3.56)	0.008	2.38 (1.31, 4.32)	0.004
Sex				
Male	1 (Referent)		1 (Referent)	
Female	0.36 (0.23, 0.56)	<0.001	0.29 (0.18, 0.48)	<0.001
Performance Status				
0	1 (Referent)		1 (Referent)	
1	2.33 (1.59, 3.44)	<0.001	2.26 (1.51, 3.38)	<0.001
Histology				
Adenocarcinoma	1 (Referent)		1 (Referent)	
Others	1.36 (1.10, 1.68)	0.004	0.99 (0.78, 1.25)	0.90

Conclusion: Anemia that occurred during paclitaxel-carboplatin therapy was associated with poorer survival of patients with advanced NSCLC. Further studies are required to investigate the detailed role of anemia during chemotherapy in a prospective study design.

Keywords: Lung cancer, survival, anemia, Chemotherapy

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P3.078 PEMETREXED MONOTHERAPY FOR JAPANESE PATIENTS WITH PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER (NSCLC).

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Background: Pemetrexed monotherapy would be considered one of the standard second-line treatments for pretreated and relapsed NSCLC. Since pemetrexed was approved for NSCLC in May 2009 in Japan, there has been little evidence in clinical practice to assess the efficacy and safety of pemetrexed in Japanese patients with advanced NSCLC. Our objects are to assess the outcome and adverse events of pemetrexed monotherapy for Japanese patients with advanced NSCLC at the Yokohama Municipal Citizen's Hospital.
Methods: We retrospectively reviewed advanced NSCLC patients who received pemetrexed monotherapy at our hospital. Pemetrexed 500 mg/m2 was administered every 3 weeks with oral folic acid and vitamin B12 i.m. supplementation. Patients also received dexamethasone i.v. day 1 to reduce toxicity. Chemotherapy was repeated unless disease progression, unacceptable toxicities or patient refusal was occurred.
Results: From May 2009 to December 2010, a total of 53 Japanese patients with stage III and stage IV disease were evaluable for the analysis. Patients characteristics were as follows: median age 68 years, 32% (n=17) female, ECOG PS 0-1/2 were 49 (92%)/4 (7.5%), Stage III/IV were 16 (30%)/ 37 (70%), adenocarcinoma histology/ others were 49 (93%)/4 (7%), and EGFR mutation positive/negative/unknown were 9/28/16. Second line chemotherapy/3rd/>4th were 18/17/18 and median administered cycles was 3 (range 1-19). Previous use of platinum were given in 42 (79%). Gr 3/4 hematologic toxicities were neutropenia 8/1 patients, thrombocytopenia 0/0, anemia 3/0 and febrile neutropenia 2/0. Gr 3/4 non-hematologic toxicities were pneumonitis 4/0 patients and syncope 1/0. All four patients (7.5%) with Gr 3 pneumonitis were male and ex or current smokers. Although all pneumonitis were recovered by steroid

therapy, two of four patients needed home oxygen therapy at discharge. All other hematologic and non-hematologic toxicities showed Gr 2 or less and no treatment-related deaths occurred. The overall response rate was 5.7% and disease control rate was 60% (PR/SD/PD/NE: 3/29/19/2). The median progression free survival time was 3.4 months (95% CI 2.52~4.28): female 6.1 months (95% CI 3.11~9.02), male 2.6 (95% CI 1.28~3.92) and median overall survival time was 13.6 months (95% CI 8.49~18.78). Based on the multivariate analysis using Cox proportional hazard model, only poor prognostic factor was PS 2 (HR: 4.65, 95%CI: 1.25-17.3, p=0.022).
Conclusion: Results of this retrospective study suggest that pemetrexed monotherapy in Japanese patients with previously treated NSCLC has promising efficacy, especially in disease control rate and overall survival. However, because our study was reported by single institution and had small sample size, it is unclear whether pneumonitis is more eventful in Asian peoples, especially in Japanese. Since it is expected to increase in use of pemetrexed worldwide, further investigations are warranted
Keywords: NSCLC, Pemetrexed, monotherapy, single agent

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.079 CLINICAL EXPERIENCE USE GEFITINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER WITH A MUTATION EGFR.

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Background: 35th Congress of the European Society of Medical Oncology (ESMO) in Milan, Italy, a late-breaking abstract provided final overall survival (OS) results from the IPASS study (IRESSA Pan-Asia Study), which compared gefitinib to platinum-based chemotherapy for the treatment of first-line advanced Non-Small Cell Lung Cancer (NSCLC). This study contributes to the discussion and debate about the role of EGFR mutation testing as part of the standard clinical work-up for patients presenting with NSCLC.
Methods: Of the 13 patients examined with a diagnosis of non small cell lung cancer, 8 patients had histology: adenocarcinoma. 4 of them were identified a mutation in 19 exon EGFR. All patients were women, Ñaucasians, never smokers, aged 59, 65, 65 and 70 years with comorbidity . All patients at the time of initiation of therapy were 4 stages of the disease with lung metastasis (4 pts) and bones (1 pts) , the overall state ECOG 1-3. All patients received gefitinib as first-line therapy at a dose of 250 mg. Duration of therapy from 1 month to 14 months.
Results: One patient a month later, while taking gefitinib, marked progression of the disease. One patient died of a heart attack after 4 month. Two patients continued to receive gefitinib between 3 and 14 months. They noted the stabilization process. All patients noted diarrhea 1-2 degrees, pustular rash of 1 degree, does not require a dose reduction and withdrawal of therapy.
Conclusion: All patients with non-small cell lung cancer should be tested for EGFR mutation for the correct choice of therapy. Gefitinib was well tolerated and can be assigned to elderly patients with comorbidity and performance status greater than 2.
Keyword: gefitinib, NSCLC,

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.080 CLINICAL SIGNIFICANCE OF EPIDERMAL GROWTH FACTOR RECEPTOR GENE MUTATIONS ON PROGRESSION OF BRAIN METASTASES IN PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA

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Background: Recent reports suggested a lower risk of central nervous system (CNS) progression in patients with advanced non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR) initially treated with EGFR-targeted agents (gefitinib or erlotinib). However, the relationship between EGFR gene mutation status and development of CNS progression has not yet been fully assessed.
Methods: To assess the impact of EGFR gene mutations on progression of brain metastases (BM), we reviewed the clinical records of patients with advanced lung adenocarcinoma who were evaluated EGFR mutation status at Shizuoka Cancer Center between January 2008 and January 2010.
Results: A total of 141 patients were included in this retrospective study, and 47 patients (33%) were positive for EGFR gene mutations. The most common mutations observed were exon 19 deletions (28 patients) and the exon 21 point mutation termed L858R (19 patients). Two patients had both an exon 19 deletion and L858R. Fifteen (32%) of the 47 patients with EGFR mutations, and 25 (27%) of the 94 patients with wild type EGFR had BM at the time of diagnosis. The median follow-up time was 14 months. The median progression-free survival for patients with EGFR mutations and wild type EGFR were 8.3 and 5.9 months, respectively ($p = 0.048$). The median overall survival for patients with EGFR mutations and wild type EGFR were 25.3 and 10.1 months, respectively ($p<0.001$). The 1- and 2-year actuarial rates of BM progression in patients with EGFR mutations were 30% [95% confidence interval (95% CI), 18-45] and 58% (95% CI, 39-75), respectively, compared with corresponding rates of 30% (95% CI, 20-42) and 37% (95% CI, 25-51) in patients with wild type EGFR ($p = 0.403$). BM at the time of diagnosis was associated with an increased risk of BM progression in both patients with EGFR mutations ($p = 0.022$) and wild type EGFR ($p<0.001$). Of the patients with BM at the time of diagnosis, the median BM progression-free survival for patients with EGFR mutations and wild type EGFR were 15.9 and 10.0 months, respectively ($p = 0.203$). Of the 47 patients with EGFR mutations, 13 patients (28%) were initially treated with EGFR-targeted agents (gefitinib or erlotinib). Initial treatment with EGFR-targeted agents was not associated with a decreased risk of BM progression in patients with EGFR mutations ($p = 0.923$).
Conclusion: There was not a significant relationship between the cumulative risk of BM progression and the EGFR gene mutations in patients with advanced lung adenocarcinoma.
Keywords: EGFR mutation, Brain Metastasis, Adenocarcinoma

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P3.081 EGFR TYROSINE KINASE INHIBITOR : CLINICAL EFFICACY IN ADVANCED NON SMALL CELL LUNG CANCER IN OUR SETUP

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Background: To evaluate Progression Free Survival (PFS), efficacy and tolerance of single agent Gefitinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, as up-front therapy for advanced non-small cell lung cancer (NSCLC) in elderly patients.
Methods: 30 patients, aged between 65 and 80 years, smokers or non-smokers, who were unfit for chemotherapy, received oral Gefitinib 250 mg daily as first-line up-front therapy for the treatment of advanced NSCLC at our institution. Patients had stage IIIB or stage IV NSCLC and Eastern Cooperative Oncology Group (ECOG) performance status 0-2 and adequate hematologic, renal, and hepatic functions. Measurable disease as assessed by Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Palliative local radiotherapy was used in those patients who had painful metastasis.
Results: Out of 29 evaluable patients, 14 had adenocarcinoma, 12 had squamous cell carcinoma, 2 had large cell carcinoma and 1 had bronchioloalveolar carcinoma. There was significant increase in PFS with 1-year survival over 60%. The partial response (PR) plus stable disease (SD) rate by ECOG performance status (PS) was 8/9 for PS 0 patients; 9/18 for PS 1-2 patients. Two patients discontinued therapy due to toxicities; both had severe liver dysfunction. A correlation between rash and antitumor activity was noted.
Conclusion: We found encouraging response and PFS results with Gefitinib as first-line up-front treatment in selected patients with advanced NSCLC. The treatment is also cost effective, with oral therapies scoring over cost of hospitalization and

IV drug administration. Moreover, the compliance is more because of convenience of being on a pill. Gefitinib monotherapy should undergo further evaluation as first-line therapy in advanced NSCLC.
Keywords: gefitinib, EGFR Tyrosine Kinase Inhibitor, Advanced Non-Small Cell Lung Cancer

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P3.082 A RANDOMIZED DOUBLE-BLIND STUDY OF N-ACETYLCYSTEINE TO PREVENT NEUROTOXICITY INDUCED BY PLATINUM CONTAINING CHEMOTHERAPY IN PATIENTS TREATED FOR (NON) SMALL CELL LUNG CANCER AND MALIGNANT MESOTHELIOMA. A PRE-LIMINARY REPORT.

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Background: Neurotoxicity is a common side effect of cisplatin. Peripheral neuropathy occurs in the majority of patients receiving cumulative doses of cisplatin. Another frequently occurring dose-dependent side effect is ototoxicity, affecting 30-70% of patients. These side effects pose an important clinical problem as they can be dose-limiting and reduce quality of life. Both peripheral neuropathy and ototoxicity are caused by cisplatin induced formation of reactive oxygen species. N-acetylcysteine (NAC), a cysteine-analog with strong anti-oxidant capacity, has shown a protective effect against cisplatin induced neurotoxicity in animal studies. In patients antioxidants have also demonstrated protective effects in studies with oxaliplatin (NAC) and cisplatin (vitamin E). This study investigated whether NAC can prevent cisplatin induced neurotoxicity.
Methods: Patients receiving at least four cycles of cisplatin (80 mg/m^2 per cycle) in the treatment of (non) small lung cancer or malignant mesothelioma were randomly assigned to receive either intravenous NAC 40 mg/kg 6 hours after completion of the cisplatin infusion or placebo. Patient with pre-existent polyneuropathy or uncontrolled metastasis in the central or peripheral nervous system were excluded. Before start of the treatment, after the 3rd cycle and 2 months after the last cycle, neurotoxicity was assessed by EMG including clinical examination and/or audiometry. Primary endpoints consisted of the modified Total Neuropathy (TNP) score for peripheral neuropathy. For ototoxicity CTCAE criteria and the intergroup AR medulloblastoma protocol (A9961) were used.
Results: Until September 2010 45 patients had been included. A pre-defined safety-analysis was then performed. Assessment of peripheral neurotoxicity, using the modified TNP score, could be done for 26 patients who had undergone measurements at baseline and after the 3rd cycle, and for 13 patients who had completed the whole study. Disease progression was the mean reason patients couldn't complete the study. No significant changes between the groups concerning modified TNP score were found so far. Mean modified TNP scores increased in the placebo group from 5.3 (baseline) to 7.0 (after 3rd cycle) to 8.0 (end of study). The intervention group showed increase from 2.7 (baseline) to 4.0 (after 3rd cycle) to 6.9 (end of study). The incidence of any ototoxicity after the 3rd cycle showed no significant difference between the groups. No difference in tumour response was observed.

Ototoxicity CTCAE (after 3rd course)					
	incidence n(%)	grade 1	grade 2	grade 3	grade 4
Placebo	3(27)	1	2	0	0
NAC	5(42)	5	0	0	0
Ototoxicity AR medullablastoma protocol (after 3rd course)					
	incidence n(%)	grade 1	grade 2	grade 3	grade 4
Placebo	2(18)	0	2	0	0
NAC	3(25)	2	0	0	1

Conclusion: This interim analysis shows that application of N-acetylcysteine seems safe in patients receiving cisplatin based chemotherapy as no negative effect on tumour response was observed. However NAC hasn't shown a protective effect in cisplatin induced neurotoxicity so far.
Keywords: Lung cancer, Cisplatin, N-acetylcysteine, neurotoxicity

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P3.083 CLINICAL OBSERVATION OF COMPOUND MATRINE INJECTION IN COMBINATION WITH CHEMOTHERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Compound Matrine Injection is an effective anti-cancer drug. Recent clinical study shows that it can alleviate the symptoms, improve the quality of life, and reduce adverse effects of chemotherapy in patients with advanced NSCLC. The purpose of this study was to evaluate the therapeutic effect and safety of Compound Matrine Injection in combination with chemotherapy in the treatment of advanced (NSCLC).
Methods: A total of 60 patients with lung cancer in our hospital were randomly assigned to 2 groups,30 people in each group. The trial group received common chemotherapy for 6 weeks plan in combination with Compound Matrine Injection for the first 10 to 14 days, while the control group received common chemotherapy only. The therapeutic efficacy on solid tumor, immunological function, improvement of life quality and the adverse reaction were compared between the two groups.
Results: The short term therapeutic efficacy on solid tumor , improves patients'immune function, improvement of life quality and the adverse reaction and side effects of the treatment group was much better than that of the control group. There were significant difference in theses indexes compared with control group ($P<0.05$).
Conclusion: Compound Matrine Injection has synergism and attenuation action on chemotherapy in patients with advanced lung cancer, enhance cellular immune function, improving quality of life, which is thus worthy of being recommended in clinical practice.
Keyword: Compound Matrine Injection; NSCLC; Chemotherapy

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P3.084 EARLY CLOSURE OF A CLINICAL TRIAL OF DICHLOROACETATE IN PATIENTS WITH PREVIOUSLY TREATED, ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) AND BREAST CANCER

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Background: Dichloroacetate (DCA) is a highly bioavailable, small molecule that inhibits pyruvate dehydrogenase kinase, promoting glucose oxidation and reversing the glucolytic phenotype in cancer tissues in preclinical studies. DCA has been used for decades in the symptomatic treatment of mitochondrial disorders and lactic acidosis. DCA is undergoing evaluation in early phase trials in solid tumors and a recently completed phase Ib trial in glioblastoma multiforme.
Methods: A clinical trial was conducted at UCLA with collaborators at the University of Alberta. The study was an open label trial of DCA 6.25 mg/kg orally twice daily in patients with previously treated stage IIIB/IV NSCLC or stage IV breast cancer. The NSCLC cohort was to enroll 29 patients. The breast cancer cohort was to enroll 18 patients with expansion to 43 patients if 3 responses were seen among the 18 patients. Normal organ function was required. ECOG PS 0-2 was initially allowed, but this was restricted to 0-1 during the study.
Results: Seven patients were enrolled, six had NSCLC and one had breast cancer. All patients had been previously treated, most with multiple previous therapies. The breast cancer patient, who had known brain metastases, had stable disease after eight weeks, but then developed progressive brain metastases shortly thereafter. Two patients had disease progression after approximately six to eight weeks. Two patients withdrew within a week of enrollment, one after an unrelated grade IV pulmonary embolism (PE) and the other enrolled in a hospice program and died within 30 days of study enrollment. One patient died suddenly

after approximately one week on study. The cause of death was not identified, as the family refused further investigation. A cerebrovascular accident was suspected based on symptoms. One patient developed lethal PE after one week on study. Although the relation of these deaths to DCA was uncertain, the UCLA Data Safety and Monitoring Board decided to close the study. This decision is supported by recent evidence that oral DCA therapy requires several months to reach sustained therapeutic serum levels; suggesting that during this time, patients are vulnerable to early disease progression. Grade III or higher peripheral neuropathy was not observed. Although this is a potential adverse effect of DCA, it typically appears a few months into therapy.
Conclusion: Patients with previously treated advanced NSCLC are likely to develop disease progression before therapeutic serum levels can be achieved with oral DCA therapy. Further development of DCA should be in alternate settings, including less advanced disease or in combination with standard therapies in advanced disease. This study generated insufficient data to draw conclusions regarding the role of DCA in previously treated metastatic breast cancer patients. This study was supported by the Lincy Foundation, the Aljian Family Trust in Memory of James Aljian and the Hecht Foundation.
Keyword: Dichloroacetate

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P3.085 RANDOMIZED PHASE II TRIAL OF ERLOTINIB WITH OR WITHOUT PF-3512676 (CPG 7909, A TOLL-LIKE RECEPTOR 9 [TLR9] AGONIST) IN PATIENTS WITH ADVANCED RECURRENT EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: PF-3512676 is a TLR9 agonist that can activate innate and adaptive immune responses. This phase II study was conducted to assess the efficacy and safety of PF-3512676 in combination with EGFR tyrosine kinase inhibitor erlotinib in patients with EGFR-positive advanced NSCLC after failure of at least 1 prior chemotherapy regimen.
Methods: Patients were randomized 1:1 to treatment with PF-3512676 (0.20 mg/kg injected subcutaneously once weekly) plus erlotinib (150 mg daily) or erlotinib alone. Randomization was stratified by Eastern Cooperative Oncology Group performance status and smoking history. Efficacy was evaluated every 6 weeks. The primary endpoint was progression-free survival (PFS); secondary endpoints included objective response rate, overall survival (OS), safety, and detection of specific immune activation biomarkers.
Results: A total of 43 patients were randomized to the study, but only 39 patients received treatment with PF-3512676 and erlotinib (n=18) or erlotinib alone (n=21). Patient characteristics were well balanced between the 2 arms. Median duration of erlotinib treatment was 6 weeks (range, 1 - 81 weeks) in combination with PF-3512676 and 7 weeks (range, 0 - 29 weeks) when used as monotherapy. The study was halted because of slow enrollment and an unplanned interim analysis indicating that a large improvement in PFS with the addition of PF-3512676 would be unlikely even if additional patients were enrolled. In the PF-3512676 plus erlotinib and the erlotinib alone arms, median PFS was 1.6 and 1.7 months (HR 1.00; 95% CI: [0.49, 2.01]; P=.934), respectively; median OS was 6.4 months and 4.7 months (HR 1.30; 95% CI: [0.61, 2.79]; P=.493), respectively. There were 2 partial responses (PRs, 10%) and 2 patients with stable disease (SD) in the PF-3512676 plus erlotinib arm; there was 1 PR (5%) and 3 with SD in the erlotinib alone arm. Levels of immune activation biomarkers measured in patients treated with PF-3512676 and erlotinib demonstrated an increase in serum interferon-inducible protein 10 (IP-10) from mean 173 pg/mL to 841 pg/mL at 24 hours postdose

cycle 1 and remained elevated (mean, 445 pg/mL) through day 8; however, there were no detectable increases in interferon-alfa (IFN-α). Among 13 patients in the PF-3512676 plus erlotinib arm with tumor samples at baseline, 4 had EGFR mutations, and 2 of these 4 went on to have PRs. In the erlotinib arm, of the 17 available samples, 2 were positive for EGFR mutations, and only 1 of these had a PR. Salient grade 3 or 4 adverse events (AEs) reported in the PF-3512676 plus erlotinib/erlotinib alone arms were: diarrhea (5/0), dyspnea (5/6), fatigue (4/1), other flu-like symptoms (2/0), anemia (2/1), and lymphocytopenia (1/4). Injection-site reactions, decreased appetite, and flu-like illness were common AEs considered related to PF-3512676, but these were mostly grade 1 or 2. There were no study-related deaths.

Conclusion: Addition of PF-3512676 to erlotinib did not show any potential for increase in PFS compared with erlotinib alone in patients with advanced recurrent EGFR-positive NSCLC. The combination of PF-3512676 plus erlotinib was tolerable and did not have a significant effect on immune activation biomarkers.

Keywords: PF-3512676, erlotinib, Non-small cell lung cancer, immunotherapy

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P3.086 ELDERLY PATIENTS WITH ADVANCED NSCLC IN PHASE III CLINICAL TRIALS: ARE THE ELDERLY EXCLUDED FROM PRACTICE-CHANGING TRIALS IN ADVANCED NSCLC?

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Background: Elderly patients constitute a large proportion of patients with advanced non-small cell lung cancer (NSCLC). The median age of newly diagnosed patients with lung cancer in the United States is approximately 70 years of age. Despite this, the elderly are significantly underrepresented in clinical trials in the treatment of advanced NSCLC. This has led to uncertainty as to the optimal treatment of older patients. Here we seek to determine the proportion of elderly patients in key phase III clinical trials in advanced NSCLC.

Methods: A literature search for all phase III randomized controlled trials of systemic therapy for advanced NSCLC between 1980 and the present was performed using Pubmed. The 100 most highly cited trials were then determined using the Web of Science application. The exclusion criteria and results of each of these studies were examined for the exclusion of elderly patients, median patient age and age range.

Results: A total of 238 trials were reviewed. Among the 100 most cited trials, 31% specifically excluded elderly patients in their trial design (age exclusion ranged from >65 to >75 years of age). The mean patient age in these trials was 60.8 years. The average age for trials that did not specifically exclude elderly patients was not significantly different at 62.2 (p=0.37).

Conclusion: Elderly patients are significantly underrepresented in key phase III clinical trials in advanced NSCLC. A significant percentage of these trials specifically excluded elderly patients. However, the median patient age in trials which allowed elderly patients is not dissimilar, and the mean patient age in all these trials is lower than that of the general advanced NSCLC population. Greater representation of elderly patients in phase III trials is required to better inform the optimal treatment of advanced NSCLC in the general population.

Keywords: NSCLC, Elderly, systemic therapy

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P3.087 PEMETREXED COMBINED WITH PLATINUM AS FRONT LINE TREATMENT IN NON SQUAMOUS NSCLC: AN INDIAN PERSPECTIVE

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Background: The management of NSCLC has seen a paradigm change in the last two years. In particular, there is plethora of options available in the treatment of Non squamous NSCLC. In 2009, Pemetrexed Platinum combination became the standard of care in the first line treatment of adenocarcinoma. We undertook this study to evaluate the efficacy of this regimen in the first line treatment of non squamous NSCLC.

Aim: 1) To evaluate the efficacy & safety

of Pemetrexed platinum based combination chemotherapy in the 1st line treatment of advanced Non squamous NSCLC 2) To compare the efficacy of Pemetrexed based chemo in EGFR wild type vs EGFR mutant population

Methods: Chemotherapy naïve patients with histologically/ cytology proven Non squamous NSCLC with at least 1 measurable disease site, ECOG performance status <2, were included. Patients with brain metastases, Inadequate bone marrow reserve or deranged renal function tests were excluded. EGFR mutation test were performed in all the patients where Biopsy specimen were available Patients were treated with Inj Pemetrexed 500 mg/ m2 & Cisplatin 75 mg/m2 or Carboplatin AUC 5 q 3weekly after Folic acid, Vit B12 & Dexamethasone premedication. Patients were evaluated every 3 cycles with CT scans. A maximum of 6 cycles of combination chemotherapy were given.

Results: 50 patients were analyzed. The Demographic details and efficacy analysis are mentioned as below:

Median Age	62 years
Male : female	65:35
Smoking status	35 smokers, 15 never smokers
ECOG PS 0,1	40
ECOG PS 2	10
EGFR mutation present	11/50
Complete Response	2/50
Partial response	20/50
Stable disease	13/50
Progression Free survival	5.2 months
Median no of cycles	5

Safety analysis: The combination chemotherapy was well tolerated with only 4% of patients developing Grade III/ IV hematological toxicity. Dose delays & modifications were also infrequent <5%. Efficacy in EGFR mutation positive patients: In 11 patients who were mutation positive, 2 patients had CR while 4 patients had partial response.

Conclusion: Pemetrexed Platinum combination is highly active in Non squamous NSCLC with good efficacy & safety profile. In patients who are EGFR mutant, Pemetrexed based combination chemotherapy was highly active which raises the question whether this subtype of patients have inherent good prognosis. However the number of patients in this study are too low to reach any definite conclusions.

Keywords: Pemetrexed, NSCLC, First line treatment

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P3.088 PRELIMINARY REPORT OF A RANDOMIZED TRIAL OF COMPUTER-ASSISTED QUALITY OF LIFE ASSESSMENT IN ADVANCED NSCLC PATIENTS

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Background: Maximizing health-related quality of life (QoL) is a fundamental goal in the systemic treatment of advanced non-small cell lung cancer (NSCLC). However, the routine assessment of QoL in clinical practice has been complicated by lengthy questionnaires, and the inability to access results in a timely manner. The 9-item Lung Cancer Symptom Scale (LCSS) has been developed in electronic form using a hand-held pocket personal computer (eLCSS-QL). With equivalent feasibility, reliability, and validity to the LCSS paper version, the electronic version permits instant data transfer in an easy-to-use graphic format with trends for clinician use. Using a randomized trial design, we explored the impact of using the eLCSS-QL on treatment patterns in patients with advanced NSCLC receiving first-line chemotherapy. Primary endpoints include palliative care referral rates and duration of systemic therapy; secondary endpoints include the use of supportive interventions and QoL during treatment.

Methods: Eligible patients are required to: have a diagnosis of incurable (M1a or b) NSCLC; be scheduled for first-line chemotherapy outside of a clinical trial; performance status (PS) 0-3; be literate in one of English, French, Portuguese, Spanish, Italian, or Chinese; and be able to provide informed consent. Patients are excluded if unable to complete the eLCSS-QL independently, or if they do not start chemotherapy. Patients, stratified by oncologist and planned treatment (platinum doublet vs. single agent), are randomized either to have the oncologist receive their eLCSS-QL data in real time (Arm A), or not (Arm B, usual care). All patients complete the eLCSS-QL at baseline, at the beginning of

each cycle of chemotherapy, and at follow up visits until disease progression (initiation of subsequent therapy).

Results: To date, 101 potentially eligible patients have been enrolled; 1 was not randomized (clinical deterioration). Six did not begin chemotherapy as planned (5 Arm A, 1 Arm B), and are not included in outcome analyses. Of the 94 remaining eligible patients, 43 were randomized to Arm A, 51 to Arm B; 13 remain on chemotherapy. Characteristics are similar between the groups. Median age of the sample is 65 years (range 39 to 80), 56% are male, 7%/55%/32%/5% are PS 0/1/2/3. 44% are stage M1a. Of those enrolled, 85% received single agent therapy, and 15% a platinum doublet. Baseline LCSS scores are similar between the groups, although numerically higher in Arm B (control). Referral rates to palliative care during first-line therapy trended higher in Arm A, 44% versus 35% in Arm B, although not significantly different in this number of patients (p=0.38). The median duration of chemotherapy was 4 cycles in both groups. Additional data on secondary endpoints of supportive interventions used and QoL over time in both arms will be presented.

Conclusion: Computer-assisted QoL assessment is feasible in clinical practice, and has the potential to demonstrate the impact of supportive and palliative care interventions in advanced NSCLC. Larger trials may be required to demonstrate statistically significant differences in outcomes with the routine use of QoL assessment.

Keywords: Lung Cancer Symptom Scale, Advanced NSCLC, Quality of Life, randomized trial

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P3.089 OUTCOMES OF GERIATRIC ASSESSMENT FOR OLDER LUNG CANCER PATIENTS FROM A DEDICATED GERIATRIC ONCOLOGY PROGRAM

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Background: The ageing population in Australia is leading to increased numbers of elderly patients referred to medical oncologists for the management of lung cancer. Studies have demonstrated that geriatric assessment and intervention may improve outcomes of the elderly with cancer and guide treatment decisions for older patients with lung cancer. Therefore, understanding the profile and outcomes of elderly patients with lung cancer are important for creating personalised treatment plans. We set out to describe the characteristics and outcomes of elderly patients with lung cancer referred to the geriatric oncology program at the Royal Adelaide Hospital Cancer Centre (RAHCC).

Methods: Patients aged 70 years and older with lung cancer treated at the RAHCC during the period between Jun 2008 and Jun 2010, were asked to complete a self administered questionnaire covering co-morbidities, medications, physical function, social supports, exhaustion, nutrition, cognition and psychological wellbeing. Based on their questionnaire, patients were classified as fit, vulnerable or frail. The patients continued to receive standard care as deemed appropriate by their treating physicians. A retrospective chart review identified demographics, diagnosis, treatment regimes and mortality.

Results: One hundred and twenty patients were seen in this period (mean age 75.6 years, male 65%). One hundred and three patients (86%) were diagnosed with NSCLC (13 (12.6%) early stage, 34 (33%) locally advanced and 56 (54%) metastatic), and 17 (14%) with SCLC (4 (24%) limited stage and 13 (76%) extensive stage). The Charlson co-morbidity score was ≤2 in 80%, with 37% having >3 co-morbidities. Significant weight loss (>10%) was seen in 33% of patients. Sixty percent of patients lived with partners, 26% lived alone, 11% lived with children and 2% lived in other accommodation (no data on 4 patients). Patients were categorised into three groups: fit 29 (24%), vulnerable 74 (62%) and frail 17 (14%). As a result of the assessment, 91 (75%) patients had referrals made, most commonly 24 to dietetics, 18 to social work, 17 to palliative care team, 13 to geriatrics, and 10 to occupational therapy. Seventy-seven patients (47% of frail, 66% of fit and 68% of vulnerable patients) were treated with chemotherapy. The majority of the fit (74%), vulnerable (70%) and frail (62%) patients completed the planned cycles of chemotherapy. Seventeen percent of the frail group proceeded onto second line chemotherapy. After a median follow-up of 19 months, the frail patient group had a significantly

higher mortality (94%) as compared to the other two groups (fit 55%, vulnerable 67%).
Conclusion: The preliminary analysis demonstrates that this elderly group of patients have a wide variation in functional status and social situations. A similar proportion of fit, vulnerable and frail patients received treatment, but there was no survival benefit for frail patients. Proper geriatric oncology assessments may help deliver appropriate treatment to the right person and avoid potentially toxic treatments.
Keywords: older lung cancer patients, geriatric oncology

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P3.090 THE EFFICACY AND THE SAFETY OF ERLOTINIB FOR THE PATIENTS WHO WERE DIAGNOSED WITH POSTOPERATIVE RECURRENCE OF NON–SMALL-CELL LUNG CANCER (NSCLC)

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Background: Although BR.21 trials revealed that erlotinib can prolong survival in patients with stage IIIB or IV non–small-cell lung cancer (NSCLC) after first-line or second-line chemotherapy, little is known about the efficacy and the safety of erlotinib for the patients who were diagnosed with postoperative recurrence of NSCLC.
Methods: Twenty seven patients received erlotinib treatment at a dose of 150 mg daily between June 1, 2008 and December 31, 2010 and ten patients (37%) had been diagnosed with postoperative recurrence. The patients' characteristics, response rate, toxic effect and survival were investigated retrospectively. The response rate was evaluated on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) by means of computed tomography and tumor markers (if available). The toxic effects were assessed according to National Cancer Institute Common Toxic Criteria (NCI-CTC).
Results: The median age of the ten patients was 73 years (range 44-80); seven males and three female; seven adenocarcinomas, two squamous cell carcinomas and one large cell neuroendocrine carcinoma; seven patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1 and three with PS 2. One patient had the sensitive mutation of epidermal growth factor receptor (EGFR), one had negative mutation and other eight had unknown status. Ninety percent had received more than one prior chemotherapy regimen, 80 percent had received platinum-based chemotherapy, and 30 percent had received prior gefitinib treatment. Erlotinib was given as a first-line therapy in one patient, second-line in three patients, third-line in three patients, fourth-line in one patient, and fifth-line in two patients. The response rate was 30 percent (three PR and two SD); the median duration of the exposure and the median overall survival were 5 months and 8.5 months, respectively. At the time of data cut-off, one patient continued erlotinib treatment; four patients received chemotherapy and five patients received best supportive care after termination of erlotinib. Eight deaths had occurred but two patients were alive at the time of analysis. The patient who continued erlotinib had the 24-months-survival and had the sensitive mutation of EGFR. Most frequent toxic effect was rash (70 percent); liver dysfunction was shown in one patient and stomatitis was shown in one patient.
Conclusion: Erlotinib treatment was selected as a second-line therapy or later and its side effects were acceptable. As compared with BR.21 trial, response rate was 30 percent (8.9 percent in BR.21); median progression free survival was 5 months (2.2 months in BR.21); median overall survival was 8.5 months (6.7 months in BR.21). In conclusion, erlotinib was the safe and effective option for the patients who were diagnosed with postoperative recurrence of NSCLC.
Keywords: erlotinib, postoperative recurrence, non–small-cell lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.091 PLASMA HOMOCYSTEINE LEVELS ARE ASSOCIATED WITH THE HEMATOLOGICAL TOXICITY OF PEMETREXED EVEN WITH FOLATE SUPPLEMENTATION

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Background: Systemic folic acid and vitamin B_{12} supplementation is necessary for pemetrexed treatment, because severe toxicities of pemetrexed treatment without folate supplementation were observed in patients who had high levels of plasma homocysteine (Hcy) in early clinical trials. However, it was not examined whether the plasma Hcy levels would still associated with the hematological toxicity of pemetrexed in patients receiving folate supplementation. The purpose of this study was to examine the relationship between the pretreatment plasma Hcy levels after folate supplementation and the hematological toxicity of pemetrexed monotherapy in advanced non-small cell lung cancer (NSCLC).
Methods: From June 2009 to November 2010, 58 NSCLC patients received pemetrexed monotherapy (500mg/m2, every 3 weeks) and also received oral folic acid (0.5mg) daily and a vitamin B_{12} injection (1mg) every 9 weeks, beginning 1 to 2 weeks before the first dose and continuing until 3 weeks after the last dose of the study treatment. The plasma Hcy levels before the first dose of pemetrexed were measured. Complete blood cell counts were measured at least once a week during first cycle of pemetrexed monotherapy. The relationship between the plasma Hcy levels and hematological toxicities during the first cycle of pemetrexed monotherapy were evaluated.
Results: The patient characteristics were as follows: male/female: 26/32; median age: 65 years(34-79); histology, adeno/large: 56/2; PS, 0/1/2/3: 30/25/2/1. The mean pretreatment plasma Hcy was 8.73μmol/ml (3.5-34.6μmol/ml). The pretreatment plasma Hcy significantly correlated with the nadir of the absolute leukocyte counts (r=-0.374 p=0.004), the nadir of the absolute neutrophil counts (r=-0.286 p=0.028), and the nadir of the absolute thrombocyte counts (r=-0.324 p=0.012). In addition, the pretreatment plasma Hcy significantly correlated with the decline rates of leukocytes (r=+0.378 p=0.003), neutrophil (r=+0.335 p=0.009) and thrombocytes (r=+0.363 p=0.005).
Conclusion: Plasma Hcy levels are associated with hematological toxicity of pemetrexed monotherapy with folate supplementation.
Keywords: Pemetrexed, Homocysteine, folate supplementation, Hematological toxicity

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P3.092 ADVANCED NON-SMALL CELL LUNG (NSCLC) IN YOUNG PATIENTS (≤ 40 YEARS) : TREATMENT AND CLINICAL OUTCOMES.

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Background: NSCLC is rarely diagnosed in patients (pts) ≤ 40 years, however in this case it is usually considered as a distinct disease, with younger pts having a better prognosis compared to older pts. In the last decade, the introduction of third generation drugs and targeted therapies enhanced survival in pts with IIIB/IV stage, with a median survival (MS) of 12-14 months. Some studies have reported small series of young pts with NSCLC but the age cut-offs varied among studies and most of them did not specifically address the clinical outcomes of the IIIB/IV stage pts. The present report specifically addresses the treatment and the clinical outcomes of pts ≤ 40 years with IIIB/IV stage NSCLC treated after 2000 in our institutions.
Methods: We reviewed all pts referred for NSCLC from 2000 to 2010 to our Institutions and selected a consecutive series of 97 pts ≤ 40 years older. Eleven pts with early stages were excluded and 86 with IIIB/IV NSCLC were assessed. Pts characteristics: male/female 58%/42%; median age 36 years (range 21-40); stage IIIB/ IV 8%/92%; histological type: adenocarcinoma 71 %, squamous 9 %, other 20 %. Metastatic sites of these pts were lung in 50%, liver in 15%, lymph nodes in 43%, brain in 24%, bone in 28%, pleural in 20%, and adrenal in 8%.
Results: All but 4 pts received systemic treatment for their IIIB/IV disease: 41% received only one line,

26% two lines, 19% three lines, and 14% four lines. Seventy pts received as first-line a platinum-based doublet (among them 46 were treated with cisplatin + gemcitabine and 5 received bevacizumab too), 4 a platinum-based triplet, 8 a single-agent therapy. The response rate was 28% (3 CR + 21 PR). Forty seven pts received a second-line treatment (consisting of non cross resistant chemotherapy in 30 pts and of TKIs in 17), 26 a third-line (15 chemotherapy, 11 TKi) and 11 a fourth-line treatment (2 received chemotherapy, 9 TKi) . The MS is 19 mos with a 62.8% 1-y OS.

Conclusion: Our experience confirmed that ≤ 40 years IIIB/IV NSCLC pts presented survival outcomes better than expected in the overall population. An ancillary study is ongoing to evaluate possible biomarkers as prognostic factors on available tumor samples.

Keywords: NSCLC, young patients

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P3.093 A POOLED ANALYSIS OF ADVANCED NONSQUAMOUS NSCLC PATIENTS WITH STABLE TREATED BRAIN METASTASES IN TWO PHASE II TRIALS RECEIVING BEVACIZUMAB AND PEMETREXED AS SECOND-LINE THERAPY

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Background: The efficacy of angiogenesis inhibition has been established in the treatment of several tumor types, including advanced non-small cell lung cancer (NSCLC). However, approximately 30% of patients with advanced NSCLC will develop brain metastases, and this subset of patients was excluded from initial trials of bevacizumab due to the theoretical risk of CNS hemorrhage.

Methods: Two open-label phase II studies investigated the safety and efficacy of bevacizumab and pemetrexed as second-line therapy after a platinum doublet in advanced nonsquamous NSCLC with brain metastases. In one study, this combination was used exclusively. (Stanford study). The other trial included both first and second-line combinations; bevacizumab and pemetrexed in combination was one of several options for second-line use at the investigator's discretion (PASSPORT study). In the Stanford study, patients were eligible if their CNS disease was radiographically stable at least one month after radiation or surgery and they no longer required steroids. In PASSPORT, patients were eligible 3 months after CNS surgery or 1 week after completion of radiation alone provided imaging within 1 week of treatment initiation showed no CNS progression or hemorrhage. Though cytotoxic treatment could start 1 week after radiation, bevacizumab was withheld until at least 4 weeks after radiation was completed. Patients on both studies were treated with pemetrexed 500mg/m2 and bevacizumab 15mg/kg on day 1 of each 3 week cycle until progression or discontinuation for symptoms or adverse events. The primary endpoint was safety, specifically CNS hemorrhagic events. Secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Results: 16 patients were accrued on the Stanford study (2 centers), and 22 on the second-line pemetrexed arm of PASSPORT (13 centers) for a total of 38. The median age for all patients was 60 (range 33-74). 66% had adenocarcinoma, 13% had large cell carcinoma, and 21% had other pathology. Patients received a median of 6 cycles of therapy (range 1-42). There were no CNS bleeding events in either study. Two grade 5 (acute renal failure and respiratory distress) and three grade 4 adverse events (neutropenia, severe fatigue and pneumonia) were observed. There were 2 thromboembolic events requiring anticoagulation. Median PFS was 7.2 months (95% CI 5.5-9.0, mean 10.2), and median OS was 14.8 months (95% CI 9.4-20.1, mean 16.6). On the Stanford study, a partial response was observed in 4 patients (25%), and 14 (88%) demonstrated at least stable disease; these data were not collected in PASSPORT.

Conclusion: The combination of pemetrexed and bevacizumab is a relatively safe and well-tolerated

treatment for second-line use in advanced NSCLC patients with stable treated brain metastases. No CNS hemorrhage events were noted in either study. PFS and OS compare favorably to those of other second-line treatments in this setting, exceeding those observed in the registration trial for pemetrexed alone. Larger multiple-arm studies will be required to assess the comparative effectiveness of such regimens, but these data suggest bevacizumab need not be withheld from appropriately selected patients with brain metastases.

Keywords: cns, Metastatic, Pemetrexed, bevacizumab

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P3.094 CLASSIFICATION AND REGRESSION TREE ANALYSIS OF CLINICAL PATTERNS THAT PREDICT SURVIVAL IN 127 CHINESE PATIENTS WITH ADVANCED NON - SMALL CELL LUNG CANCER TREATED BY GEFITINIB

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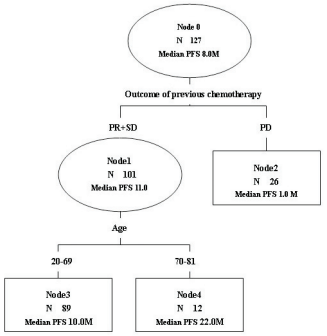
Background: Gefitinib produce tumor regression only 10–20% in heavily pretreated unselected NSCLC as second and third line setting, and responses are more common in female, never smokers, adenocarcinoma, and Asian population. Nevertheless, it's hard to find such a patient with all about clinical characteristics, and need to identify subgroups of patients who will be likely to obtain differant survival time before using gefitinib in our clinical practice.

Methods: The clinical and follow up data of 127 Chinese NSCLC patients referred to the Cancer Hospital & Institute, Chinese Academy of Medical Sciences from March 1, 2005 through March 30, 2010 were analyzed. Multivariate analysis of progression free survival (PFS) was performed using recursive partitioning referred to as classification and regression tree (CART) analysis

Results: The median PFS of 127 eligible Chinese NSCLC patients was 8.0 months(95%CI, 5.8-10.2 m). CART was performed with an initial split on outcomes of first line chemotherapy, and second split on age of the patients. Three terminal subgroups were formed, and the median survival time of the three subsets ranged from 1.0 month (95%CI, 0.8-1.2 m) for those with progression disease outcome after first line chemotherapy subgroup, 10 months (95%CI, 7.0-13.0 m) in patients with partial response or stable disease in first line chemotherapy, and younger than 70 years old, to 22.0 months (95%CI, 3.8-40.2 m) for the patients obtaining partial response or stable disease in first line chemotherapy at age of 70~81.



Conclusion: Partial response, Stable disease in first line chemotherapy and age ³ 70 is correlated closely with long term survival treated by gefitinib as second or third line setting in Chinese advanced NSCLC patients. CART can be used to identify previously unappreciated patient subsets and is a useful method for dissecting complex clinical situations and identifying homogeneous patient populations in clinical practice.

Keyword: Classification and Regression tree, Non - Small Cell Lung Cancer, Gefitinib

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Poster Session 3 – NSCLC – Advanced Stage Wednesday, 6 July 2011 12:15-14:15

P3.095 COST-EFFECTIVENESS OF TREATMENT WITH NEW AGENTS IN ADVANCED NON-SMALL-CELL LUNG CANCER: A SYSTEMATIC REVIEW

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Background: Over the past decades, research focusing on new chemotherapeutic agents for patients with inoperable NSCLC have reported only modest gains in survival. These health gains are achieved at considerable costs, but economic evidence on superiority of one of the agents in terms of cost-effectiveness is lacking. The objective of this systematic review is to assess fully published cost-effectiveness studies comparing the new agents docetaxel, paclitaxel, vinorelbine, gemcitabine and pemetrexed, and the targeted therapies erlotinib and gefitinib among each other.
Methods: PubMed, EMBASE.com and Economic Evaluations (via the Cochrane Library, Wiley) were systematically searched for fully published studies from the past ten years. Studies were screened by two independent reviewers according to a priori inclusion criteria. The methodological quality of the included studies was evaluated by two independent reviewers using standardized assessment tools.
Results: 222 potential studies were identified. 11 cost-effectiveness and cost-utility studies were included. The methodological quality of the full economic evaluations was fairly good. Transparency in costs and resource use, details on statistical tests and sensitivity analysis were points for improvement. In first-line treatment, there were indications that gemcitabine-cisplatin is cost-effective compared to platinum-based regimens containing either paclitaxel , docetaxel or vinorelbine (range of incremental life years: 0.04-0.13; range of incremental costs: US$ -926-US$ -5 686). In one study pemetrexed-cisplatin was cost-effective compared to gemcitabine-cisplatin in patients with nonsquamous cell carcinoma (ICER per life year gained: US$ 83 537). In second-line treatment, docetaxel was cost-effective compared to BSC (range of ICERs per life year gained: US$ 22 190-US $32 133). Erlotinib was cost-effective compared to placebo (ICER per life year gained: US$ 33 728). Docetaxel and pemetrexed were dominated by erlotinib.
Conclusion: We found indications for superiority in terms of cost-effectiveness of gemcitabine-cisplatin in a first-line setting and for erlotinib in second-line setting.
Keyword: Cost-effectiveness

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P3.096 ESTIMATION OF QUALITY-ADJUSTED PROGRESSION FREE SURVIVAL (QA-PFS) OF FIRST LINE TREATMENTS IN EGFR MUTATION-POSITIVE ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS IN THE NETHERLANDS

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Background: Gefitinib, a tyrosine kinase inhibitor, is an effective treatment for patients with advanced NSCLC with an activating mutation in the epidermal growth factor receptor (EGFR M+). Randomised clinical trials showed a benefit in progression free survival (PFS) for gefitinib versus doublet chemotherapy in EGFR M+ patients (Mok,2009, Mitsudomi,2010, Maemondo,2010). From a patient perspective, not only PFS itself is important but also their health-related quality of life (QoL). Therefore Quality Adjusted Progression Free Survival (QA-PFS) of gefitinib versus relevant chemotherapy (paclitaxel/carboplatin (Pac/Carb); gemcitabine/ cisplatin (Gem/Cis); pemetrexed/cisplatin (Pem/Cis); was evaluated from a Dutch health care perspective in patients with EGFR M+ stage IIIB/IV NSCLC. PFS rather than overall survival (OS) was evaluated since OS may be largely influenced by subsequent treatment lines.
Methods: Mean PFS for Pac/Carb was obtained by extrapolating median PFS as reported in the Iressa-Pan-Asia Study (IPASS; Mok, 2009). Network meta-analysis was used to estimate the mean PFS for the therapies of interest relative to Pac/Carb. Adjustment for QoL was done by incorporating utilities for the Dutch population, obtained by converting FACT-L data using the Lamers algorithm (2007). FACT-L data collected during progression-free state from EGFR M+ patients in IPASS treated with either gefitinib or Pac/Carb were used. The utility of the other doublet chemotherapy regimens was assumed

similar to the utility of Pac/Carb. Finally the specific utilities were multiplied by the mean PFS for each treatment arm to determine the QA-PFS.
Results: The estimated mean PFS with getitinib (10.52 months; 95% confidence interval [CI]: 8.87-12.53 was significantly higher than that for the doublet chemotherapies (Table). In IPASS, the FACT-L derived utility at start of study treatment was 0.736±0.1059 for all EGFR M+ patients in both arms. In the gefitinib arm, the utility in the PFS period increased by 0.0528±0.0095, whilst no change in utility was observed for the Pac/Carb treatment arm. Combining the utilities with the mean PFS resulted in a QA-PFS for gefitinib of 8.32 months (95%CI: 7.01-9.91). In comparison with Pac/Carb, Gem/Cis and Pem/Cis, gefitinib increased the QA-PFS by more than 3 months (Table). Progression free survival (PFS) and Quality Adjusted PFS (QA-PFS) in months (mean and 95% confidence intervals)

	Pac/Carb	Gem/Cis	Pem/Cis	Gefitinib
PFS	6.65 (5.90; 7.40)	6.98 (6.11; 7.89)	7.15 (6.17; 8.21)	10.52 (8.87; 12.53)
QA-PFS	4.91 (4.36; 5.51)	5.14 (4.52; 5.83)	5.27 (4.56; 6.07)	8.32 (7.01; 9.91)
Δ QA-PFS	3.41 (2.35; 4.79)	3.17 (2.01; 4.58)	3.04 (1.91; 4.41)	

Conclusion: In the Dutch health care setting, the PFS benefit of first line gefitinib in advanced NSCLC EGFR M+ patients in comparison to standard doublet chemotherapy is further supported by the QA-PFS, which takes account of the additional QoL benefits for gefitinib over doublet chemotherapy.
Keywords: EGFR tyrosin kinase inhibitor, Progression free survival (PFS), EGFR mutation, Quality of life (QoL)

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P3.097 IMPORTANCE OF EGFR STATUS IN HIV INFECTED PATIENTS WITH NON SMALL CELL LUNG CANCER

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Background: Non small cell lung cancer (NSCLC) incidence is higher in HIV-infected people, even adjusted to the smoking history. Patient's characteristics differ from the general population by a younger age and a worse prognosis. Chemotherapy is particularly toxic because of drug interactions with the antiretroviral therapy. Mutations of the epidermal growth factor receptor (EGFR) are a favorable prognostic factor in NSCLC and predict responsiveness to EGFR tyrosine kinase inhibitors. KRAS mutations are mutually exclusive with EGFR mutations and might be a negative prognostic factor. No data are available on the prevalence of EGFR and KRAS mutations in NSCLC of HIV positive patients.
Methods: Tissue of 41 consecutive HIV infected patients with NSCLC were assessed for EGFR and KRAS mutations by direct sequencing.
Results: Thirty five patients were male (85%), median age was 49 years (range 37-70) and most were Caucasians (n=39, 95%). All patients had a smoking history, current (n=32, 78%) or former (n=9, 22%). Eighteen patients (44%) had stage I-IIIA disease and 23 patients (56%) had stage IIIB-IV disease. The major histological subtype was adenocarcinoma (58.5%). The median CD4 lymphocyte count was 420/μl (range, 3-1070). KRAS mutations were detected in the tissue of 4 patients (11%). Tumor EGFR mutations were identified in 2 patients (5.5%) with two exon 19 deletions. These two patients were male, Caucasian, smoker or previous smoker, with stage IV adenocarcinoma. EGFR inhibitor (erlotinib) was administrated as second line therapy in both patients with an excellent tumor response and a time to progression of 15 months and 14 months, respectively. They are still alive at 33 and 23 months of the diagnosis, whereas the median overall survival of EGFR wild type patients with stage IIIB-IV NSCLC (n=20) was only 4.7 months (CI 2.2-8.1; p=0.011).
Conclusion: Prevalence of EGFR and KRAS mutations are similar in NSCLC among HIV-positive patients than in the general population. EGFR mutations are a strong prognostic factor of survival and are predictive for response to EGFR inhibitors in HIV patients.
Keywords: mutation Kras, HIV, non small cell cancer, mutation EGFR

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P3.098 THE PREFERABLE TIMING OF TREATMENT WITH EGFR-TKIS FOR NSCLCS WITH EGFR MUTATIONS.

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Background: Non-small cell lung cancers (NSCLCs) with sensitive mutations of the pidermal growth factor receptor (EGFR) gene are highly responsive to EGFR tyrosine kinase inhibitors (TKIs). Recent clinical studies revealed that first-line gefitinib, a EGFR-TKI, improved progression-free survival (PFS) for patients with EGFR-mutated NSCLCs, as compared with standard chemotherapies, but did not improve overall survival because of possible efficacy of gefitinib as second-line or later therapy for patients treated with first-line chemotherapy. Thus, the best timing of treatment with EGFR-TKIs for cases with EGFR mutations is still undetermined. To explore the preferable timing, we compared between efficacy of EGFR-TKIs as first-line and that as second-line in EGFR-mutated NSCLCs.
Methods: Thirty seven advanced NSCLC patients with sensitive mutations of the EGFR gene, who were treated at the Tottori University Hospital, Japan, from May 2007 to March 2010, were retrospectively evaluated response of therapy according to RECIST and progression free survival (PFS). The differences in response rate (RR) and median PFS (mPFS) between first- and second-line EGFR-TKIs were statistically analyzed. Median overall survival (mOS) for patients treated with first- and second-line EGFR-TKIs was also compared.
Results: The 37 patients with median age of 68 years included 14 men and 23 women. Among the patients, 15 patients were treated with EGFR-TKIs as first-line (group A), and 22 were treated with those as second-line (group B). RRs of EGFR-TKIs in group A and B were 44% and 57% respectively (p=0.86). mPFSs for group A treated with EGFR-TKIs as first-line was 8 months, and that for group B treated with EGFR-TKIs as second-line was 11 months (p=0.54). In group A, 44% of the patients were treated with second-line chemotherapies after first-line EGFR-TKIs. The other patients did not undergo any chemotherapy after treatment of EGFR-TKIs due to worsing their performans status. In group B, 94% of the patients were treated with second-line EGFR-TKIs after first-line chemotherapies. mOSs in group A and B were 21 and 43 months, respectively (p=0.07).
Conclusion: Although there was no difference in response of EGFR-TKIs between first- and second-line therapy in EGFR-mutated NSCLCs, overall survival for patients treated with second-line EGFR-TKIs tended to be longer than that for patients treated with first-line EGFR-TKIs. Since a considerable fraction of patients treated with first-line EGFR-TKIs could not be treated with second-line chemotherapies, the preferable timing of treatment of EGFR-TKIs might be second-line therapy.

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P3.099 STABLE DISEASE IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) - LACK OF RESPONSE TO CHEMOTHERAPY OR RELEVANT CATEGORY OF RESPONSE?

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Background: Stable disease is probably the most frequent category of response to chemotherapy in advanced NSCLC. It reflects, at some extent, the natural course of disease. Therefore, is it the failure of treatment or, it should be seen as a relevant response category as a part of disease control rate? This question is closely related to the relationship between response categories and survival in advanced NSCLC and prognostic aspects of particular categories.

Methods: 362 patients (318 males and 44 females), median age 57 years, were treated in four prospectively conducted clinical trials at one site, with platinum-based chemotherapy, with 120mg/m2 of cisplatin every 4 weeks or 500mg/m2 of carboplatin (later AUC 5). PS 0/1 had 60% patients (pts) and stage IIB/IV was recorded in 45%/55% of pts. Median number of received cycles was 4, median overall survival for the group as a whole was 7 months.
Results: Stable disease (SD) was recorded in 48% of patients, response rate (RR = complete + partial response) in 32% of pts and progressive disease (PD) in 20% of pts. Median number of cycles was 5 in RR pts, 4 in SD pts and 1 in PD ones and median survival times were 11 months, 7 months and 3 months, respectively. In Cox regression model for overall survival, SD category had 39% greater risk of death compared with RR patient [HR (95%CI): 1.39 (1.09-1.78); p<0.001], while PD patient had 4.1 times greater risk, compared with RR [HR (95%CI): 4.10 (3.03-5.55); p<0.001]. With landmark method on three months, this risk was even smaller for SD/RR pts [HR (95%CI): 1.32 (1.01-1.72); p=0.044], while for PD/RR pts hazard ratio was 2.12 [95%CI: (1.49-3.00), p=0.003].
Conclusion: Response category of stable disease seems to be closer to response rate than to disease progression in front-line chemotherapy in treatment of advanced NSCLC. This does not deny that response rate should be the most desirable short-term outcome, but confirms that platinum-based chemotherapy influences patients' outcome even in lack of response, and supports administering of chemotherapy in advanced NSCLC.
Keywords: stable disease, response to chemotherapy, advance non-small cell lung cancer

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P3.100 ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PHASE II/III STUDY IN CHEMONAïVE PATIENTS: EGFR-TARGETING CHIMERIC MONOCLONAL IGG-1 ANTIBODY CETUXIMAB ADDED EITHER TO GEMCITABINE FOLLOWED BY DOCETAXEL OR CARBOPLATIN PLUS GEMCITABINE. RESULTS OF THE PHASE II STUDY PART.

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Background: This randomized phase II/III trial is meant to assess the efficacy and safety of cetuximab in combination with two different chemotherapy regimens. Primary study endpoints: Clinical relevant toxicities (phase II) and overall survival (phase III).
Methods: Chemonaïve patients with histologically confirmed stage IIIB or IV NSCLC and performance status (WHO) 0–2 received cetuximab 400 mg/m² as loading dose and then 250 mg/m² weekly either combined with gemcitabine 1000 mg/m² days 1 + 8 for 2 cycles (3qw) followed by docetaxel 75 mg/m² day 1 for 2 cycles (q3w) (arm A) or carboplatin AUC5 day 1 and gemcitabine 1200 mg/m² days 1 + 8 for 4 cycles (q3w) (arm B). If patients did not progress single agent cetuximab was continued until tumor progression or unacceptable toxicity.
Results: TABLE 1: Toxicities per patient requiring clinical intervention.

Clinical relevant toxicities	Arm A		Arm B	"Maintenance"
	Cetuximab / gemcitabine n=173 (pts)	Cetuximab / docetaxel n=112 (pts)	Cetuximab / carboplatin/ gemcitabine n=172 (pts)	Single-agent cetuximab n=162 (pts)
Total number of cycles (3qw)	312	203	547	962
Median number of cycles per patient	2	2	4	4
Anemia + ≥ 1 blood transfusion	1%	4%	10%	-
Thrombopenia + ≥ 1 platelet transfusion	<1%	-	11%	-
Febrile neutropenia + IV antibiotics	<1%	6%	3%	-
Skin reaction (any/grade 3)	80%/6%	25%/6%	79%/9%	34%/6%

352 patients were enrolled equally in each treatment arm in the Phase II part. 345 patients received study medication (173/172 arm A/B). 2914 infusions of cetuximab combined with chemotherapy and 2666 infusions without chemotherapy were given. Toxicities per patient requiring clinical intervention

are shown below. 162 patients on single agent cetuximab received up to 39 cycles without significant toxicity (arm A: 75 patients, range 1-35 cycles, median 4, mean 5.9, and 13 patients ≥10 cycles; arm B: 87 patients, range 1-39 cycles, median 4, mean 6.0 and 12 patients ≥10 cycles). Under treatment with cetuximab in combination with chemotherapy, grade 3 or 4 hematological toxicity was more common in patients receiving carboplatin/gemcitabine (anemia 3%, leukopenia 17%, neutropenia 25%, and thrombopenia 2%, arm A versus anemia 10%, leukopenia 29%, neutropenia 38%, and thrombopenia 40%, arm B, respectively, all $p<0.01$, χ^2-test). Skin reactions were common and occurred in 79% of patients in both treatment arms. 32% of patients (arm A) and 42% (arm B) completed the protocol, and overall response rates were 19%/31% in arm A/B, respectively. Overall survival as a secondary aim of the Phase II part showed no statistically significant differences (hazard ratio 1.102, $p=0.4288$, χ^2-test).

Conclusion: Cetuximab in combination with single agent gemcitabine-docetaxel and with carboplatin/gemcitabine is well tolerated. Patients on weekly single agent cetuximab received up to 39 cycles. Toxicity signals were as expected with slightly higher toxicity in carboplatin/gemcitabine treatment as well as higher rates of completion of protocol and response. In overall survival no statistically significant difference is seen so far. The study continues as a Phase III trial with a total of 608 patients.

Keywords: safety, Overall survival, Non-small cell lung cancer, cetuximab

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P3.101 THE DIFFERENCE IN CHEMOTHERAPEUTIC EFFICACY BETWEEN ADVANCED NON-SMALL CELL LUNG CANCERS WITH AND WITHOUT EGFR MUTATIONS

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Background: Although non-small cell lung cancers (NSCLCs) with mutations of the epidermal growth factor receptor (EGFR) gene are more sensitive to EGFR tyrosine kinase inhibitors than those without the mutations, it is still unknown whether there is a difference in efficacy of systemic chemotherapies between the two subtypes of NSCLCs.

Methods: One hundred nineteen advanced NSCLC patients, who underwent systemic chemotherapies as a first-line therapy at the Tottori University Hospital, Japan, from April 2007 to August 2010, were retrospectively evaluated chemotherapeutic response according to RECIST and progression free survival (PFS). The differences in response rate (RR) and median PFS (mPFS) between NSCLC cases with and without sensitive EGFR mutations were statistically analyzed. The difference in efficacy between plutinum doublet chemotherapies (P) and non-plutinum chemotherapies (non-P) in EGFR-mutated cases or in non-mutated cases was also analyzed.

Results: Among the 119 cases, consisting of 90 adenocarcinomas, 27 squamous cell carcinomas and 2 large cell carcinomas, 26 cases (22%) had EGFR mutations. P were performed in 66 cases, including 13 with EGFR mutations and 53 without, and non-P were performed in 53 cases, including 13 with the mutations and 40 without. The P included 21 cisplatin-based regimens and 45 carboplatin-based ones. The majority (73%) of non-P regimens was combination of vinorelbine (VNR) and dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines (DIFs, i.e., UFT or S-1). RR in NSCLCs with EGFR mutations was significantly higher than that without the mutations (50% vs. 23%, $p<0.05$). There is no difference in mPFS between NSCLC patients with and without EGFR mutations (6.9 months and 4.3 months, respectively, $p=0.31$). In EGFR-mutated cases, RRs in NSCLCs treated with P and with non-P were 48% and 54%, respectively ($p=0.89$), and mPFS for patients treated with non-P was significantly longer than that for patients treated with P (10.0 months vs. 3.4 months, $p<0.01$). Such a difference was not found in NSCLC cases without EGFR mutations.

Conclusion: Systemic chemotherapies might be more effective in NSCLCs with EGFR mutations than in those without the mutations. In particular, non-plutinum chemotherapies, e.g., combination of VNR and DIF, might have long-term effects in EGFR-mutated NSCLCs.

Keywords: NSCLC, EGFR, DIF, Vinorelbine

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P3.102 EFFICACY OF ERLOTINIB ACROSS CLINICAL SUBGROUPS IN CHINESE PATIENTS AND A BROADER ASIAN SUBPOPULATION WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC): SUB-ANALYSIS OF THE TRUST STUDY

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Background: The epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib has proven efficacy in multiple treatment settings for advanced NSCLC (Shepherd et al, 2005; Cappuzzo et al, 2010; Zhou et al, 2010). The global, phase IV TRUST study provided the opportunity to gather clinical data on the efficacy and tolerability of erlotinib in patients who had progressed following first-line chemotherapy (or were unsuitable to receive such therapy). The results for the overall population and the Asian subpopulation of this study have been published (Reck et al, 2010; Mok et al, 2010). We carried out an additional sub-analysis to examine the efficacy of erlotinib across clinical subgroups in the Chinese and Asian subpopulations of TRUST, to determine whether clinical characteristics influenced outcomes with erlotinib in these patients.
Methods: TRUST was an open-label, non-randomised study. Eligible patients had stage IIIB/IV NSCLC and had either failed on or were unsuitable to receive chemo-/radiotherapy. Oral erlotinib 150mg/day was given until disease progression or unacceptable toxicity. This analysis reports progression-free survival (PFS) and overall survival (OS) outcomes in the Chinese subpopulation of TRUST by gender, histology and smoking status.
Results: The study included 519 patients enrolled in China, out of a total of 1242 patients in the Asian subpopulation and 6665 patients in the overall study population. The 6-month PFS rate for all Chinese patients was 50.5%; however, this rate rose to 59.9% in female never-smokers with adenocarcinoma histology (n=177). Median PFS and OS by clinical characteristics are reported in the table for the Chinese subpopulation. As shown, the PFS results are consistent with those of the wider Asian subpopulation in TRUST. Full multivariate subgroup analyses will also be presented. Reported adverse events in the Chinese subpopulation were consistent with those in the overall Asian subpopulation.

	Median PFS, mos		Median OS, mos
Clinical characteristic	All Chinese patients (n=519)	*All Asian patients (n=1242)*	All Chinese patients (n=519)
Histology			
Adenocarcinoma	8.05	*7.69**	15.67
Squamous-cell carcinoma	3.09	*2.76*	8.57
Bronchoalveolar carcinoma	13.34	–	21.75
Large-cell carcinoma	1.41	*4.24***	4.53
Other	3.34	–	15.69
Gender			
Male	4.8	*3.91*	13.3
Female	9.17	*8.94*	18.46
Smoking status			
Current/former smoker	4.14	*3.45*	11.99
Never smoker	9.2	*8.71*	18.76

*combined with 'bronchoalveolar carcinoma'; **combined with 'other'

Conclusion: Clinical characteristics such as adenocarcinoma/bronchoalveolar carcinoma histology, female gender and never-smoker status were associated with longer PFS and OS in the Chinese and Asian subpopulations of this open-label study of erlotinib. It is likely that these results can be attributed to the higher incidence of activating EGFR mutations in these clinical subgroups.
Keywords: Non-Small-Cell Lung Cancer, erlotinib, Asian patients, TRUST

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P3.103 EFFICACY OF CRIZOTINIB IN RETROSPECTIVE COMPARISONS WITH STANDARD-OF-CARE (SOC) REGIMENS FROM THREE PFIZER-SPONSORED CLINICAL TRIALS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Crizotinib is a potent, selective, ATP-competitive, small-molecule anaplastic lymphoma kinase (ALK) inhibitor. In an expanded cohort of an early clinical study in patients with advanced ALK+ NSCLC, crizotinib demonstrated clinical activity with a high response rate. Results of retrospective analyses comparing the efficacy of crizotinib in patients with advanced NSCLC with that of SOC regimens (paclitaxel/carboplatin or gemcitabine/cisplatin as first-line treatment and erlotinib as second-/third-line treatment) in three Pfizer-sponsored clinical trials are reported.
Methods: We conducted two types of analysis: (1) covariate-matched simulations of randomized controlled trials of crizotinib versus SOC for advanced NSCLC from control arms of the three Pfizer-sponsored trials to compare efficacy outcomes in patients with comparable baseline characteristics (adenocarcinoma histology, smoking classification, age, and race [Asian/non-Asian]), and (2) a covariate-adjusted modeling analysis to retrospectively predict the response rates of patients treated with crizotinib who had the same baseline characteristics (adenocarcinoma histology, smoking classification, age, race [Asian/non-Asian], gender, disease stage, ECOG performance status, and weight) as those treated with a SOC regimen from a control arm in the three Pfizer-sponsored trials. Information about ALK status was not available from the three control trials.
Results: Crizotinib therapy was associated with a higher objective response rate (ORR; 61%; 95% confidence interval [CI]: 52, 70%) than ORRs of the covariate-matched unselected historical controls from the three Pfizer-sponsored trials, ranging from 10% to 24%. Similar results were observed using the covariate-adjusted modeling approach with estimated ORRs for the standard regimens ranging from 15% to 21% after simultaneous adjustment for eight baseline characteristics. Overall, the estimated magnitudes of the ORRs generated for unselected controls using both approaches were at least 50% lower relative to the ORR of 61% observed with crizotinib. An assessment of the secondary endpoints, progression-free and overall survival (PFS; OS), produced similar results. The preliminary median PFS of crizotinib therapy was 10 months (95% CI: 8.2, 14.7 months) in heavily pretreated patients, which was longer than PFS reported in the covariate-matched unselected historical controls, ranging from 1.9 to 5.9 months. The hazard ratios for PFS of crizotinib versus each of the three control regimens ranged from 0.28 to 0.38. The median OS of crizotinib in the clinical trial has not yet been reached. However, the hazard ratios for OS of crizotinib versus the three control regimens ranged between 0.25 and 0.47.
Conclusion: There is supporting evidence that crizotinib treatment may provide clinical benefit for the treatment of patients with ALK+ advanced NSCLC in the context of SOC therapies in first- or later-line treatment settings.
Keywords: PF-02341066, Non-small cell lung cancer, Crizotinib

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P3.104 INDIRECT COMPARISON OF EFFICACY, SAFETY, AND COST: PEMETREXED/CISPLATIN VERSUS BEVACIZUMAB/GEMCITABINE/CISPLATIN IN PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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Background: Two regimens have recently been approved in several countries for the treatment of non-squamous advanced non-small cell lung cancer (NSCLC): (i) the doublet pemetrexed/cisplatin (PemC), and (ii) the triplet of bevacizumab (Bev) with gemcitabine/cisplatin (GC). In the absence of head-to-head evidence between the 2 regimens, they have been compared indirectly via a common comparator arm, GC, using data from the AVAiL and JMDB phase 3 studies. The AVAiL study had 3 arms comparing 7.5 mg/kg BevGC (7.5BevGC), 15 mg/kg BevGC (15BevGC), and GC.[1] The JMDB study compared PemC to GC.[2] Indirect comparison between BevGC and PemC is possible given similar characteristics of the trial design and patients. The results, only in terms of the progression free survival (PFS) hazard ratio (HR), have been previously reported (HR [7.5BevGC vs. PemC]=0.83, with no

confidence interval [CI] or P value cited).[3] The aims of this study were to indirectly compare the regimens in terms of overall survival (OS), safety, and cost, plus to provide complete results for PFS. This may have important implications in decision making for clinical as well as economic reasons.
Methods: An indirect comparison of both regimens in the non-squamous NSCLC population was performed using the Bucher method. Analyses included OS as the primary endpoint, PFS, safety, and cost.
Results: The indirect comparison of the doublet PemC with the triplet BevGC for OS numerically favored PemC (HR [PemC vs. 7.5BevGC]=0.87, 95% CI: 0.69 - 1.10, p=0.242 and was statistically significant for HR [PemC vs. 15BevGC]=0.79, 95% CI: 0.62 - 0.99, p=0.042). In contrast, the indirect comparison for PFS numerically favored BevGC (HR [7.5BevGC vs. PemC]=0.83, 95% CI: 0.69 - 1.01, p=0.066 and HR [15BevGC vs. PemC]=0.94, 95% CI: 0.77 - 1.16, p=0.585). The percentage of patients suffering at least 1 severe adverse event (ie, ≥Grade 3) was significantly lower with PemC (odds ratio: OR [PemC vs. 7.5BevGC]=0.59, 95% CI: 0.39 - 0.89, p=0.013 and OR [PemC vs. 15BevGC]=0.46, 95% CI: 0.30 - 0.71, p<0.001). For PemC, rates of neutropenia (p<0.001), thrombocytopenia (p<0.001), and hypertension (p=0.009 and p=0.001 for 7.5BevGC and 15BevGC, respectively) were statistically significantly lower for PemC when compared to both doses of BevGC. A costing model developed for Russia, considering mean treatment cycles calculated from the trials and pharmacy drug costs, showed a savings of $11,100 USD with the PemC doublet, driven mostly by drug costs ($10,900 USD).
Conclusion: PemC produced at least comparable OS outcomes with significantly fewer toxicities and was cost-saving in non-squamous NSCLC patients. Based on this indirect comparison PemC should be considered the preferred regimen in this setting. References 1. Reck et al. J Clin Oncol. 2009;27(8):1227-34. 2. Scagliotti et al. J Clin Oncol. 2008;26(21):3543-51. 3. Nuijten et al. Lung Cancer. 2010;69 Suppl 1:S4-10.
Keywords: NSCLC, Pemetrexed, bevacizumab, cost analysis

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P3.105 POOR SLEEP QUALITY AND FATIGUE AMONG PATIENTS WITH LUNG CANCER

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Background: Poor sleep quality in patients with cancer may be the cause of the commonly described fatigue and sleepiness in these patients. Aim of this study was to assess the sleep quality of patients with lung cancer and to explore possible correlations with daytime fatigue and sleepiness.
Methods: Forty-eight recently diagnosed with lung cancer patients were initially enrolled. Eighteen of them were re-evaluated after 3 cycles of chemotherapy. Sleep quality was subjectively assessed by Pittsburgh Sleep Quality Index (PSQI), daytime sleepiness was assessed by Epworth Sleepiness Scale (ESS) and daytime fatigue by Fatigue Severity Scale (FSS).
Results: In all patients poor sleep quality (PSQI>5), as well as daily fatigue (FSS>4) was revealed. PSQI and FSS scores correlated in a statistically significant way (p=0.002), while ESS scores showed no correlation. Further analysis of the PSQI components revealed a significant correlation between FSS and Subjective Sleep Quality (p<0.001), Sleep Duration (p=0.011) and Daytime Dysfunction (p=0.016). Among the 18 patients who were reevaluated after chemotherapy, a significant correlation was found between FSS and Habitual Sleep Efficiency (p<0.001), Subjective Sleep Quality (p=0.027) and Sleep Disturbances (p=0.024).
Conclusion: Poor sleep quality is associated with daytime fatigue among patients with lung cancer, both at the diagnosis and during treatment.
Keywords: NSCLC, SLEEP DISTURBANCES, fatigue, SLEEP QUALITY

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P3.106 IMPACT AND SAFETY PROFILE OF ERLOTINIB TREATMENT IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER – A SMALL PROSPECTIVE STUDY

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Background: Erlotinib is a small molecule inhibitor of epidermal growth factor receptor tyrosine-kinase activity that has been shown to significantly increase survival for patients with previously treated advanced non-small cell lung cancer (NSCLC). We aimed to investigate the impact of erlotinib as a second or third line treatment in patients with advanced NSCLC and associated adverse events.
Methods: Seventeen patients with stage IIIB and IV NSCLC, previously treated with at least one regimen of platinum-based chemotherapy received 150 mg of erlotinib orally, once a day, till disease progression.
Results: Mean age of studied patients was 65.29 ± 10.90 (range 41-83, 95% CI 59.69-70.90). The disease control rate was 47.05%. Among studied patients, there was partial remission (PR) in 4 cases (23.52%), stable disease (SD) in 4 cases (23.52%), and progressive disease (PD) in 9 cases (52.94%). Median progression-free survival and overall survival times were 8.29 ± 5.10 months (range 2-19, 95% CI 5.66-10.92) and 21.63 ± 7.782 months (range 11-36, 95% CI 16.12-29.13), respectively. The 1-year survival rate was 52.94%. Among studied patients, 11 (64.70%) experienced erlotinib-related adverse events. Most of the patients experienced erlotinib-related rash (n=10, 58.82%); grade 1/2 in 6 cases (54.54%) and grade 3 in 4 cases. One patient developed grade 1 trombocytopenia. Dose reduction was registered in only 1 case of grade 3 rash.
Conclusion: Our study confirm the favorable efficacy and safety profile of erlotinib in patients with advanced NSCLC.
Keywords: erlotinib, advanced non-small lung cancer, disease control, safety profile

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P3.107 A PHASE II TRIAL OF PEMETREXED (P), GEMCITABINE (G), AND BEVACIZUMAB (BV) IN UNTREATED PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: P and G are active agents with acceptable toxicity profiles in the treatment of NSCLC. The addition of BV to chemotherapy has resulted in a significant improvement in survival for pts with non-squamous NSCLC. We conducted a phase II trial of P, G and BV on a novel every two week schedule in untreated pts with advanced NSCLC.
Methods: Advanced, non-squamous NSCLC pts with measurable/evaluable disease, no prior treatment for advanced disease, PS 0-1, adequate hepatic, renal and bone marrow function, treated brain metastases were eligible. No unstable hypertension, cardiac/vascular disease, hemoptysis, anti-coagulation, recent major surgery, no cavitation or close proximity of primary cancer to a major vessel were allowed. Pts received P 500 mg/m^2, G 1500 mg/m^2, and BV 10 mg/kg every 2 weeks for 12 cycles. Doses were reduced to P 400 mg/m^2 and G 1200 mg/m^2 when grade 4 neutropenia occurred in the first 2 patients. BV was continued until disease progression or toxicity. Primary endpoint was progression-free survival (PFS). Secondary endpoints were response rate (RR), toxicity, time to progression (TTP) and overall survival (OS).
Results: 39 pts were accrued. Median age 62 yrs, males 56%, stage IV 87%, adenocarcinoma 82%. 38 pts are response evaluable. 16 pts (42%) had a response (1 CR, 15 PR) (90% CI for RR is 0.30 - 0.55), and 12 had SD (32%) for a disease control rate of 74%. Currently the median treatment cycles for all pts are 7 (range 1-23, for P,G and 1-57, for

BV). All pts are evaluable for toxicity. Grade 3-4 toxicities: neutropenia 11, fatigue 7, elevated ALT/AST 4, dyspnea 4, leukopenia 3, pain 3, anorexia 2, hypertension 2, thrombocytopenia 1, lymphopenia 1, febrile neutropenia 1, nausea/vomiting 1, perforation 1, neuropathy 1, otitis media 1, PE 1, and DVT 1. One grade 5 hemoptysis occurred in a pt off treatment for progressive disease. All pts had a median PFS of 6.1 months (90% CI 3.6 months, 7.7 months) with a 1 year PFS rate of 18%. The median OS is 19.6 months (90% CI 12.5 months, 29.9 months) with a 1 year OS rate of 64%. The median TTP is 6.1 months (90% CI 4.2 months, 7.8 months).
Conclusion: The combination of P, G, and BV is a very active and tolerable treatment for NSCLC. Updated results will be presented at the meeting.
This research is supported by Lilly Oncology and Genentech.
Keywords: NSCLC, Pemetrexed, gemcitabine, bevacizumab

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P3.108 PHASE II TRIAL OF IMATINIB MESYLATE AND DOCETAXEL IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER.

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Background: Platelet-derived growth factor (PDGF) and receptor (PDGF-R) are co-expressed in many human cancers and are suspected to have a role in regulation of tumor vascular uptake of chemotherapy. Imatinib mesylate, inhibits both PDGF-R a and b; when it was combined with paclitaxel, an additive antitumor effect resulted preclinically, most likely through decreasing the interstitial fluid pressure by inhibiting PDGF-R, providing rationale for a phase II single arm trial in platinum-refractory NSCLC in combination with docetaxel.
Methods: Patients with metastatic NSCLC (any histologic subtype); platinum-refractory with ≤ 1 prior treatment, ECOG PS 0-2 were treated with intravenous docetaxel (60 mg/m2 every 3 weeks), and oral imatinib mesylate (400 mg daily) initiated on day 1 until disease progression. Consenting patients received perfusion CT scans for analysis of tumor perfusion at baseline and week 3 and had serum specimens analyzed for PDGF levels at baseline, week 3, week 6 and at the off-study time. Baseline tumor specimens were collected for immunohistochemical (IHC) analysis of CD117 (c-kit), PDGFR-a, PDGFR-b and PDGFRB gene copy number by fluorescence in situ hybridization.
Results: Twenty-two patients were enrolled onto the study, response was seen in one (4.5%) and was long –lasting (158 weeks), while disease control was achieved in 9 patients (40.9%). With a median follow up of 36 weeks, the median progression-free survival was 7.9 weeks, and overall survival was 35.6 weeks. The main adverse events were grades 1-2 diarrhea, neuropathy, and nausea/vomiting and grade 3 dyspnea, fatigue, and edema. Seven patients experienced at least one grade 3 adverse event and 10 patients experienced at least one grade 2 adverse event. Of 5 consenting patients with baseline serum PDGF levels, 3 had progression and 2 had stable disease, and no association of PDGF serum level with response, survival, or development of adverse events was seen. Of 14 patients with tumor specimens, all had CD117 analysis, 13 had analyses of the remaining markers. There was no association of any of the biomarkers with either patient demographics or clinical response, however any expression of PDGFR-a in stroma (p=0.04) and PDGFR-b (p=0.03) in tumor cytoplasm were both associated with a worse PFS, and PDGFR-a in the stroma, showed a trend towards a worse overall survival.
Conclusion: The clinical activity of decetaxel-imatinib in refractory NSCLC is modest. Expression of PDGFR-a in stroma, and PDGFR-b in tumor cytoplasm are potential negative predictiveand/or prognostic biomarkers. Further analyses of PDGFRB copy number in correlation with survival is underway.
Keywords: NSCLC, PDGFR, Imatinib, Docetaxel

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P3.109 GEFITINIB IN EGFR FISH POSITIVE/PHOSPHO-AKT POSITIVE AND/OR NEVER SMOKER NON-SMALL CELL LUNG CANCER (NSCLC), CLINICAL AND BIOLOGICAL EFFECTS.

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Background: Effectiveness of gefitinib, a tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR), in never smokers and/or EGFR FISH positive NSCLC patients has been evaluated only in retrospective studies and few data exist on the biological effects of gefitinib therapy in tumor samples.
Methods: This study has been designed to include 39 patients EGFR FISH positive/phospho-Akt (p-AKT) positive and/or never smokers with advanced or metastatic NSCLC. Gefitinib is given at the daily dose of 250 mg. When feasible, primary tumor biopsy was repeated immediately before therapy, during therapy and at progression. Specimens were evaluated for EGFR and HER2 gene copy number by FISH, EGFR gene mutation by DNA sequencing, and EGFR and p-AKT protein expression by immunohistochemistry.
Results: Data from the first 28 enrolled patients are available: median age was 60 years (range, 43–80); male/female: 7/21; stage IIIB/IV: 2/26; ECOG PS 0/1/2: 18/6/4; 25 patients had a diagnosis of adenocarcinoma and/or bronchioloalveolar carcinoma; 13 patients had brain metastases, and in 10 cases gefitinib was offered as first-line therapy. Twenty-four patients were never smokers and 19 were EGFR FISH positive. Overall response rate was 54%, including 1 complete and 14 partial responses. Median time to progression was 6.45 months, and median survival was not reached. Response to therapy was not influenced by previous therapies or presence of brain metastases. Toxicity was mild, and consisted in grade 1–2 skin rash (68%) and diarrhea (57%). One patient developed grade 3 diarrhea and another patient was hospitalized for acute interstitial lung disease. In patients exposed to previous chemotherapy, no difference in EGFR or HER2 FISH results were observed in specimens collected at the time of original diagnosis compared to specimens collected immediately before gefitinib therapy. In 14 cases primary tumor biopsy was repeated during gefitinib therapy.
Conclusion: These preliminary data indicate that gefitinib is highly effective in patients with trial characteristics.
Keywords: Non small cell lung cancer, EGFR, gefitinib

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P3.110 ERLOTINIB VS BEST SUPPORTIVE CARE AS THIRD-LINE TREATMENT OF ADVANCED NSCLC: A REAL-WORLD COST-EFFECTIVENESS STUDY

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Background: The British Columbia Cancer Agency (BCCA) began funding erlotinib as third-line treatment for advanced NSCLC in 2004. This study investigated the real-world cost-effectiveness of third-line erlotinib in patients treated across British Columbia, Canada.
Methods: This was a retrospective study of all BCCA patients who received 3rd line erlotinib compared to a historical group treated with 2nd-line docetaxel then no further active treatment (best supportive care – BSC). The primary endpoint was cost-effectiveness, measured as cost per years of life gained. The calculation of life years gained was based on the area under the Kaplan-Meier curve of overall survival, defined as days between end of second line chemotherapy and death or censoring. Analysis was performed from the perspective of the British Columbia Ministry of Health Services, and was included the costs of drugs, radiation, hospitalization, appointments, tests, and home/community care.
Results: A total of 78 erlotinib patients and 69 BSC patients were identified in our study. There was no significant difference in either survival or cost

between the two groups in the real-world setting. Results are presented in the table.

Parameter	Erlotinib N = 78	Best Supportive Care N = 69
Median OS – days (95% CI)	231 (26, 831)	138 (27, 428)
Mean OS – days (95% CI)	291 (233, 349)	181 (141, 222)
	Difference	110 days
Median PTD – days (95% CI)	114 (6, 807)	68 (7, 309)
Mean PTD – days (95% CI)	195 (148, 242)	105 (82, 129)
	Difference	90 days
1-year OS - %	33.3	10.1
Mean drug cost/patient (range); $	$7,823 ($1,166, $36,550)	$171 ($0, $6,959)
Mean radiotherapy cost/patient (range); $	$2,629 ($0, $16,273)	$1,901 ($0, $11,391)
Mean MSP-billable services; $	$2,363 ($74, $9,052)	$2,003 ($32, $8,921)
Mean PharmaCare cost/ patient; $	$4,276 ($0, $25,534)	$4,271 ($0, $46,273)
Mean HCC cost/patient; $	$107 ($0, $6,815)	$384 ($0, $11,223)
Mean hospital cost/patient; $	$17,127 ($547, $81,653)	$14,494 ($0, $60,821)
Mean overall cost/patient (range); $	$34,326 ($6,569, $99,370)	$23,224 ($1,095, $78,775)
	Difference	$11,102

An ICER of $36,838 was calculated based on the above results. More than 30% of a Monte Carlo sampling of 1000 probable ICERs dominated (cost less, were more effective than) BSC. No sampled ICERs were dominated by BSC.

Conclusion: Third-line erlotinib is cost-effective compared to best supportive care. Patients in the BCCA can expect an average of 110 days additional survival with erlotinib.

Keywords: health economics, erlotinib, retrospective trial, cost effectiveness

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P3.111 ANTITUMOR ACTIVITY OF BEVACIZUMAB IN COMBINATION WITH METRONOMIC CHEMOTHERAPY (MPEBEV REGIMEN) IN METASTATIC NON-SMALL CELL LUNG CANCER

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Background: Bevacizumab, is a humanized monoclonal antibody to vasculo-endothelial-growth-factor, with anti-cancer activity in non-small-cell-lung cancer (NSCLC) patients. Results from a previous dose/finding phase I study in advanced NSCLC patients, described the anti-angiogenic and toxicological effects of a newest bevacizumab combination with metronomic chemotherapy with cisplatin and oral etoposide (mPEBev regimen) and identified the bevacizumab dosage to use in future trials. We therefore, designed a phase II trial to evaluate in advanced NSCLC patients the antitumor activity of this metronomic dose/dense regimen.

Methods: 45 patients (36 males and 9 females), with a mean age of 54 years, an ECOG 2, stage IIIB/IV and NSCLC (34 adenocarcinoma, 10 squamous cell carcinoma, 1 undifferentiated carcinoma) were enrolled. They received every three weeks, cisplatin (30 mg/sqm, days 1-3), oral etoposide (50 mg, days 1-15) and bevacizumab (5 mg/kg, day 3). Responsive patients received maintenance therapy after 4 chemotherapy cycles with bevacizumab 5mg/kg every 3 weeks and daily erlotinib (150 mg). Kaplan Meier curves were used to estimate survival (OS) and progression free survival (PFS).

Results: Grade I-II hematological, mucosal toxicity and alopecia were the most common adverse events. The occurrence of severe infections (17%), thromboembolic episodes (4.4%) and severe mood disturbances (6.7%) were also recorded. There was a partial response in 31 (68.8%) patients, a stabilization in 8 (17.8%), and a progressive disease in 6 (13.3%) with a median PFS of 8.00 (95%CI;6.192-9.808) months and median OS of 15 months (95% 10.660-19.340).

Conclusion: Our bio-chemotherapy regimen resulted very active in advanced NSCLC however, the toxicity associated with the treatment will require strict selection of the patients to enroll in future studies.

Keywords: NSCLC, bevacizumab, metronomic-chemotherapy

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P3.112 GENETIC POLYMORPHISMS OF DRUG TRANSPORTER ARE ASSOCIATED WITH HEMATOLOGIC TOXICITIES IN KOREAN CANCER PATIENTS RECEIVING DOCETAXEL CONTAINING CHEMOTHERAPY.

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Background: Docetaxel (Taxotere) has been known as one of the most active anti-cancer drugs for breast, ovary, head and neck, prostate, and non-small cell carcinoma. Neutropenia is a frequent toxic reaction observed during its treatment. We carried out association study between docetaxel-related hematologic toxicities and genetic polymorphisms of CYP3A4, CYP3A5, ABCC2, and SLCO1B3. .
Methods: Clinical information was collected from 79 cancer patients who received docetaxel containing chemotherapy. We extracted genomic DNA from periphreal blood and genotyped CYP3A4 (CYP3A4*1B, CYP3A4*18, CYP3A4*3), CYP3A5(CYP3A5*2, CYP3A5*3), ABCB1 (C1236T, G2677T/A, C3435T), SLCO1B3 (rs11045585), ABCC2 (rs12762549) using direct sequencing and pyrosequencing.
Results: Mean age was 58.1 and sex ratio 59:20. Most of all pts was advanced non-small cell lung cancer (77%). Pts receiving over 60mg/m2 of docetaxel were 84.8%. Severe neutropenia(G3-4) occurred in 56pts (70.9%). And, mild-to moderate leucopenia, anemia and thrombocytopenia(G1-2) were observed in 48(60.8%), 75(94.9%) and 78(98.7%), respectively. Genetic variants of CYP3A4 (CYP3A4*1B, CYP3A4*18, CYP3A4*3) and CYP3A5*2 were not found. Allele frequency of CYP3A5*3, ABCB1(C1236T, G2677T/A, C3435T), SLCO1B3 (rs11045585), and ABCC2 (rs12762549) were 0.73, 0.36, 0.39, 0.62, 0.7, and 0.86, respectively. Statistically significant associations existed between G2677T/A and leucopenia (P=0.041) and between SLCO1B3 and neutropenia (P=0.038). Both G2677T(A) and C3435T genotype were correlated with leucocytes(P=0.011 and P=0.06), neutrophils(P=0.019 and p=0.059), hemoglobin(p=0.037 and p=0.01), hematocrit(P=0.04 and P=0.004) with statistical significance.
Conclusion: Taken together, our data suggest that G2677T/A (MDR1) and SLCO1B3 might be major pharmacogenomic predictors for severe leucopenia and neutropenia in the cancer patients who docetaxel containing chemotherapy is given.
Keywords: Docetaxel, SLCO1B3, toxicity, G2677T/A

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.113 EFFICACY OF ERLOTINIB AFTER THE FAILURE OF GEFITINIB IN PATIENTS WITH ADVANCED OR METASTASIS NON-SMALL CELL LUNG CANCER

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Background: Tyrosine kinase inhibitors (TKIs) is an active agent for advanced or metastasis non-small cell lung cancer. Unfortunately, resistant will appears unavoidably. The optimal treatment for patients with progressive non-small cell lung cancer who initially show a good response to TKI is not well known. This study is to evaluate the activity of erlotinib in patients who failure to gefitinib.
Methods: 40 Chinese patients who experienced treatment failure after achieving disease control with gefitinib (250mg daily) were analyzed retrospectively. 16 patients shifted to erlotinib (150mg daily) immediately, the other 24 patients received chemotherapy first and thereafter erlotinib (150mg daily).
Results: In all population, the disease control rate

for erlotinib was 52.5% (21/40) while the objective response rate was only 10.0% (4/40). The median progression free survival (PFS) and the overall survival (OS) were 3.0 months and 12 months, respectively. However, no statistically difference was observed in disease control rate between two treatment groups (56.3% for erlotinib group and 50.0% for erlotinib following chemotherapy, respectively, p=0.755). The median PFS and the OS were similar (4 months vs. 2months for PFS, p=0.768; 12months for OS in both groups, p=0.51).
Conclusion: Erlotinib could be considered either immediately after gefitinib failure or following chemotherapy after gefitinib failure in progressive non-small cell lung cancer patients who initially got benefit from gefitinib.
Keyword: Erlotinib, Gefitinib, non-small cell lung cancer

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P3.114 LONG-LASTING DISEASE CONTROL WITH GEFITINIB IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) LACKING THE CLASSICAL PREDICTIVE FACTORS: REPORT FROM AN EXPANDED ACCESS PROGRAM (EAP)

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Background: According to literature for pretreated, unselected pts with advanced NSCLC the median duration of treatment with gefitinib was 2 to 3 months. Single case reports indicate that gefitinib may lead to sustained disease control in pts lacking the classical molecular and clinical predictive factors (EGFR mutation, asian background, female gender, never-smoking and adenocarcinoma). The aim of our study was to characterize long-term survivors in an unselected Caucasian population of pts with NSCLC treated with gefitinib.
Methods: The Swiss Expanded Access Program (EAP) was open between Nov 2000 and Apr 2004 to provide pts with locally advanced and/or metastatic inoperable NSCLC access to gefitinib on a compassionate use basis before marketing authorization. Eligible pts received 250mg of gefitinib daily until disease progression or unacceptable toxicity. Patients were registered in an anonymized way, including the date of the first and the last drug order by the treating physician. The reporting of SAEs was requested. For the current study, we selected pts with a minimum of 2 years therapy with gefitinib, and retrospectively collected age, gender, smoking status, tumor histology, tumor stage, sites of metastases, and EGFR mutation status if available.
Results: 464 pts were registered to the Swiss EAP, and 430 received at least one order of gefitinib, corresponding to 3 months of therapy. The median and mean duration of treatment was 3 months and 6 months, respectively (range 0.1 to 84+ months). Treatment was well tolerated in the overall population; drug-related SAEs were reported in 21 (4.9%) of the 430 pts. In this genetically unselected population, 36 (8.4%) pts received gefitinib for longer than 1 year and 18 (4.2%) pts for 2 years or more (up to 7 years and therapy ongoing). Clinical characteristics were available for 10 of the 18 long-term survivors. Three pts were male and 7 were female, age at diagnosis was 35 to 76 years. Seven pts were active smokers (up to 40 pack years). Performance status (PS) was PS0/1 in 8 pts and PS2 in 2 pts. Six pts had received prior chemotherapy and 3 pts prior radiotherapy. Tumor EGFR mutation status was available for 4 pts, 3 pts had activating EGFR mutations and one pt had wild type EGFR. In the 18 long-term survivors, treatment was well tolerated. One cardial SAE was reported, which was unrelated to gefitinib. Two pts had diarrhea, and three pts had skin rash.
Conclusion: Gefitinib can lead to long-lasting disease stabilization in individual pts, and long-lasting gefitinib therapy appears to be well tolerated. Unexpectedly, the group of long-term survivors

included patients lacking the classical predictive factors, including several active smokers, and at least one pt with wild type EGFR.
Keywords: gefitinib, caucasions, EGFR-mutation, long-term tolerability

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P3.115 FUNCTIONAL DECLINE IN PATIENTS WITH ADVANCED STAGE NON-SMALL CELL LUNG CANCER

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Background: The functional decline that is seen in patients with lung cancer is a complex issue. It is well recognised by treating clinicians that patients with advanced NSCLC decline physically over time; however this has been poorly studied to date. This study aimed to quantify the physical function and health-related quality of life (HRQoL) of patients with advanced non-small cell lung cancer (NSCLC).
Methods: A descriptive cohort study was performed. Patients with stage III and IV NSCLC were recruited within one month of starting treatment and completed assessments bi-monthly to six months or until they became too unwell to participate. HRQoL and functional status data were collected using the EORTC QLQ-C30, the 6-minute walk distance (6MWD) and timed up and go test (TUG). Preliminary results from the study are presented.
Results: 36 patients with a mean age of 62 years (18 males) had a mean 6MWD at baseline of 416.7m, significantly lower than predicted for age, sex and height (562.6m). This significantly declined from baseline to 2 months (n=22) by a mean of 35.8m (95%CI:14.7 to 56.9; p=0.02), with a significant decline from baseline to 4 months (n=16) of 53.8m (95%CI:17.3 to 90.4; p=0.007). Time taken to complete the TUG increased (worsened) significantly from baseline (mean 7.7 seconds) by a mean 0.83 seconds (95%CI: 0.56 to 1.11; p<0.05) at 2 months (n=22) and a mean of 1.04 seconds (95%CI: 0.7 to 1.39; p<0.05) at 4 months (n=16). Despite the decline in physical function, self-reported global HRQoL had a non significant improvement from baseline to 2 months, followed by a decline in global HRQoL from 2 to 4 months that was not statistically significant.
Conclusion: Patients with advanced NSCLC have clinically significant lowered physical function at commencement of treatment. Function continues to decline significantly over time, despite improvements in self-reported HRQoL from baseline to 2 months. Future interventional studies are needed to address this issue. Funding for this study was provided by a NHMRC Palliative Care Grant
Keywords: Physical function, Health-related quality of life, Advanced NSCLC

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P3.116 LUNG CANCER PATIENTS ACCEPT POTENTIALLY RISKY PROCEDURES PERFORMED SOLELY TO DETERMINE OPTIMAL TREATMENT

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Background: Some novel treatments for lung cancer require analysis of biopsy material that is in excess of that needed just to define the tumour histologically. Obtaining this added material may create risks, discomfort or inconvenience for patients and the attitudes of actual patients to this are unknown. There is added the risk that the test will be considered futile if the result most desired is not generated.
Methods: Patients living with lung cancer were presented with a construct not relating directly to their own care. It stated that, in order to determine whether a novel but potentially highly effective treatment might be suitable for them, additional testing would be needed. The procedures were a blood test (no risk), core needle node biopsy. excision of a cervical node and mediastinoscopy. Test yield was stated as 25% and treatment response rate 95%. Procedural discomforts were described as was mortality for each procedure. Patients were asked to mark on a 100mm VAS score line, how likely it is that they would agree to have the procedure. 0mm was 'I would definitely have the

procedure' and 100mm was ' I would definitely not have the procedure'.
Results: 24 patients were enrolled; 20 male with median age 73. All stages were represented and experience of treatment included all modalities. Results are summarised in the table

	Stated mortality	VAS - mean (SEM)	Subjects with VAS >50mm
Blood test	0	5(1.0)	0
Core needle biopsy	0.1%	4(0.9)	0
Surgical node excision	0.4%	8(1.6)	0
Mediastinoscopy	1.0%	14(3.0)	2

Conclusion: There is a high level of acceptance of supplementary procedure that could generate access to an effective treatment. This is seen even when risks are somewhat overstated and the likelihood is that the procedure will be a negative result. In determining appropriate investigative pathways for lung cancer, the high level of willingness of patients to have such procedures with inconvenience, discomfort and potentially grave risk should be considered.
Keywords: gene testing, personalised medicine, patients beliefs

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P3.117 THE THERAPEUTIC OUTCOMES OF ERLOTINIB AFTER FAILURE OF GEFITINIB FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Erlotinib (E) has been approved for use on patients (pts) with metastatic/advanced non-small cell lung cancer (NSCLC) who had received chemotherapy since December 2007 in Japan. There has been some controversy about whether E is effective even for the pts who had already been treated with gefitinib (G). The aim of this study is to investigate the therapeutic outcomes of E after failure of G at our hospital, retrospectively.
Methods: Pts with metastatic or advanced NSCLC who had built up a resistance to prior G were eligible. Other prior chemotherapeutic regimens and the lines of treatment were not included in the criteria. Pts received 150 mg of E orally every day.
Results: From February to November 2007, 10 pts who had experienced PD or relapse in the treatment with G received E. All 10 pts had adenocarcinoma, median age was 60.5 (range 41-74), 9 were women and 5 were smokers. Five of the 10 pts were examined for EGFR mutation status and all 5 pts had EGFR mutation. The response rate and the disease control rate were 20 % and 80 %, respectively. Five pts were given E in the third or fourth line treatment. The other 5 pts were given E in the fifth or later line treatment. The effects of E were similar in both groups of pts. Two pts had received G for more than one year and were expected to respond well to E judging from prior reports. Contrary to our expectations, the therapeutic results of E were PD in both pts.
Conclusion: E is a possible option for pts who show resistance to G, and could be given as the third, fourth or later line treatment. However, a long duration of response to G is not necessarily a predictive factor of the responder to E.
Keywords: erlotinib, gefitinib, NSCLC

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P3.118 PROGRESSION FREE SURVIVAL MORE THAN 12 MONTHS UNDER THE TREATMENT OF ERLOTINIB IN PATIENTS WITH NSCLC ST III/IV: A RETROSPECTIVE STUDY OF PATIENT HEALTHCARE UTILIZATION, TOXICITIES AND OUTCOME

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Background: Erlotinib was approved by the US FDA on November 2004 for Patient with advanced or metastatic NSCLC. Clinical trial have shown response rate of less than 10% to Erlotinib and

progression free survival of 2 months in second line treatment with Erlotinib. We present a review of 41 patient with prolong survival, more than 12 months, under the treatment of Erlotinib. The goal of this study was to analyze epidemiological factors, tissue histology and side effect in this group of patient with prolong progression free survival.
Methods: Patients with stage IIIB or IV NSCLC cancer were treated in Meir medical centre and received treatment with Erlotinib more than 12 months. Data were collected on age, gender, performance status, smoking status, length of treatment, toxicities profiles, Progression Free Survival (PFS), overall survival (OS) and analyses were carried out.
Results: A number of 41 patients with stage IIIB/IV disease were analyzed. Of them, 73% (30) were female with mean age of 65 and 27% were male with mean age of 68. Performance status (PS) average was 1 and improved during the first half of the year of treatment. Over 91% (37) of the patients had previous chemotherapy. About 10% (4) had stage III disease with malignant pleural effusion. About 90% (37) had stage IV disease and of them, 68% (28) of all the patients had only lung metastasis. Patients treated with Erlotinib had an average PFS of 128 weeks, and OS of 178 weeks. Over 75% (31) of the patients did not smoke. The PFS among smoker was 121 weeks and PFS among non-smokers was 130 weeks. The patients who had skin toxicities had an average PFS of 121 weeks, in contrast to patients without skin toxicities that had an average PFS of 81 weeks. The most common reasons for dose reduction were skin toxicities 52% (21).
Conclusion: The data above represent our site experience with Erlotinib. The results represent an extraordinary PFS and OS among those patients. The correlation between response rate, toxicities profiles, and other contributing factors (non smoking, female) support the major data from clinical study in this field. In contrast, the actual response rate is significantly higher than reported in those clinical trials. In the future, a Molecular factor should be further investigated in this group of patients.
Keyword: NSCLC, OS, PFS, US FDA

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P3.119 PARTIAL RESPONSE TO FIRST-LINE GEFITINIB FOR ADVANCED PULMONARY ADENOCARCINOMA HARBORING BOTH SYNCHRONOUS EGFR MUTATION AND EML4-ALK FUSION: REPORT OF TWO CASES

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Background: The fusion of the anaplastic lymphoma kinase (ALK) with the echinoderm microtubule-associated protein-like 4 (EML4) and epidermal growth factor receptor (EGFR) mutations are reported mutually exclusive. Advanced non-small cell lung cancer (NSCLC) patients with EML4-ALK did not benefit from EGFR tyrosine kinase inhibitors (TKIs).
Methods: Multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) followed by sequencing was performed for EML4-ALK fusion status detection. EGFR and KRAS mutations were determined by direct DNA sequencing. Positive results of EML4-ALK fusion were also confirmed by RACE-coupled PCR sequencing.
Results: From March 2010 to August 2010, two female patients with advanced pulmonary adenocarcinoma were found to harbor both synchronous EGFR mutation (exon19 deletion and exon21 L858R respectively) and EML4-ALK fusion (Variant 6 and Variant 1 respectively). Being relatively young (aged 44 and 56 respectively), both patients were never smokers. They were also found to have wild type KRAS. 122 and 36 days respectively after receiving first-line EGFR TKI gefitinib, they achieved partial reponse.
Conclusion: Advanced NSCLC patients harboring synchronous EGFR mutation and EML4-ALK fusion are sensitive to gefitinib. Whether they could also benefit from ALK inhibition after failure to gefitinib warranted further investigation.

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P3.120 IS THERE A ROLE FOR CHEMOTHERAPY RE-CHALLENGE IN NON SMALL CELL LUNG CANCER?

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Background: Chemotherapy re-challenge (CTR) is an established and recommended clinical practise in some solid tumours in particular ovarian and small cell lung cancers, based on a presumed sensitivity of cancer cells to specific cytotoxics. Considering the limited treatment options in non small cell lung cancer (NSCLC), it would be worth exploring the incidence and impact of CTR.
Methods: Medical records of 2150 patients (pts) diagnosed with NSCLC and treated with chemotherapy (CT) at our institution, between 2003-2011, were screened. We identified pts treated with CTR during the course of their disease. We examined patients' clinical and treatment data.
Results: 9/2150 pts (0.4%) were offered a CTR regimen. Male:female ratio was 6:3 and median age 56 years (range 51-76). The histological subtypes were adenocarcinoma (A) (4 pts), squamous cell carcinoma (3 pts) and not specified (NS) (2 pts). All patients were of good Performance Status (0-1), and the majority without any comorbidities (6/9). All pts were treated with a platinum agent combined with either pemetrexed (5pts), taxane (3 pts) or gemcitabine (1 pt). 3/9 pts had initially received CT in the adjuvant setting and rechallenge on relapse, whereas 6 pts were treated for advanced/metastatic disease. In the later 6 pts, partial response (PR) as best response was observed in 5 (83.3%). The median time to progression (TTP) after the first chemotherapy course was 10 months (range 3.6-37.5). Best responses following CTR were PR in 2 (22%), stable disease (SD) in 3 (33%) and disease progression (PD) in 4 (44%), whereas median TTP after CRT was 3 months (2.5-12). The 2 pts with PR after CTR (1 A, 1 NS) had both demonstrated PR after the initial CT with platinum-pemetrexed and TTP of 9 and 17 mo respectively.
Conclusion: CTR is rarely observed in NSCLC, and has a limited role and unlike success. In selected though patients with a very good initial response and satisfactory TTP (>9 mo) it might be a reasonable option.
Keyword: Lung cancer, Chemotherapy, Re-challenge

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P3.121 SEVERITY OF ANXIETY AND DEPRESSION AMONG LUNG CANCER PATIENTS USING THE HAMILTON RATING SCALE

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Background: Trend for lung cancer cases is rising in both male and female Indonesian. Previous study shown that around 51% of lung cancer patients had psychiatric disorder ranging from adjustment disorders to severe depression. We did a collaborative study to detect any psychiatric disorder in lung cancer patients.
Methods: Subject of the research were recruited consecutively after informed consent given. All subjects were interviewed by using Hamilton Anxiety and Depression Scale Questionnaire. We analyzed the data to find the incidence, severity of psychiatric disorder and its correlation with other factors (gender, age, level of education and socio-economic).
Results: We recruited 64 lung cancer patients which comprise of 77% male and 23% female. The mean age was 56 years old. Most of the patients were in advanced stage of adenocarcinoma. In regards of anxiety, we found that in 31 out of 64 patients (48.4%) suffers anxiety, of which 20 out of 31 (64.5 %) were categorized as mild anxiety. In terms of depression, we found that 29 out of 64 patients (45.3%) suffers depression with 25 out of 29 (86.2%) were categorized as mild depression. All of those patients with depression were also diagnosed to have anxiety as well. The incidence of anxiety had a significant correlation with gender (OR, 3; 95% CI, 1.62 to 11.06) and education (OR, 2.98; 95% CI, 1.89 to 10.18). However, only level of education had significant correlation with depression (OR, 3.43; 95% CI, 1.02 to 11.96) which was analyzed by multivariate analysis.
Conclusion: Anxiety and depression are common among lung cancer patients, and physician should be aware of these conditions for the better management

of lung cancer.
Keyword: lung cancer, anxiety, depression, the Hamilton Rating Scale.

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P3.122 REASON: A REGISTRY FOR THE EPIDEMIOLOGIC AND SCIENTIFIC EVALUATION OF EGFR MUTATION STATUS IN NEWLY DIAGNOSED NSCLC PATIENTS STAGE IIIB/IV IN GERMANY

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Background: Lung cancer is the leading cause of cancer deaths worldwide. In Germany alone, each year approx. 33,000 men and 13,200 women are newly diagnosed with lung cancer and approx. 41000 die of the disease. 70-80% of patients present with non-small-cell lung cancer (NSCLC). Studies have shown in recent years that somatic mutations in the EGFR gene predict for sensitivity to EGFR tyrosine kinase inhibitors (TKI) in patients with advanced NSCLC. Certain clinico-pathological characteristics are associated with a positive EGFR mutation status (i.e. adenocarcinoma histology, Asian origin, non-smoking history, female gender), however, most of this information arises from Asian studies. The REASON study was set up to investigate the prevalence of EGFR mutations in German patients with advanced NSCLC and the association with clinico-pathological parameters, thus generating data from a predominantly Caucasian population.
Methods: REASON is an AstraZeneca sponsored registry (ClinTrials ID: NCT00997230). It is planned to include 4000 subjects with stage IIIB/IV NSCLC and for whom EGFR mutation testing is planned, at approx. 130 sites (100 hospital-based, 30 office-based) throughout Germany. The primary aim is to collect epidemiological data on the EGFR mutation status in the German patient population and to correlate the EGFR mutation status with clinico-pathological characteristics (e.g. smoking status, gender, histology, etc.). As secondary objectives, real-life clinical outcome data of all EGFR mutation positive patients (i.e. PFS, OS, DCR), clinical management and pharmaco-economic data (such as resource use) associated with the diagnosis and treatment of EGFR mutation pos. patients with advanced NSCLC will be collected.
Results: Between Nov 2009 and Jan 2011, 3504 patients have been registered into REASON with enrolment ending March 2011. Methods and first data on the frequency of EGFR mutations in German patients with stage IIIB/IV NSCLC will be presented.
Conclusion: REASON is a German registry aiming to provide the largest data base yet on baseline epidemiological and clinico-pathological characteristics of patients with newly diagnosed stage IIIB/IV NSCLC in a predominantly Caucasian population. In addition, real-life information will be collected on treatment patterns of patients with stage IIIB/ IV EGFR mutation positive NSCLC, pharmaco-economic parameters (resource use, hospitalisations, etc.), and clinical outcomes.
Keywords: locally advanced or metastatic NSCLC, EGFR mutation, newly diagnosed NSCLC

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P3.123 A PHASE II TRIAL OF LOW-DOSE METRONOMIC ORAL VINORELBINE COMBINED WITH BEVACIZUMAB IN PATIENTS WITH PRETREATED, ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC). PRELIMINARY RESULTS

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Background: Frequent administration of low doses of cytotoxic drugs (metronomic chemotherapy) has been suggested to suppress tumor growth possibly by inhibiting tumor angiogenesis. In a previous phase II trial from our group, metronomic oral vinorelbine showed promising activity as salvage treatment of NSCLC. We conducted a phase II trial to evaluate the antitumor activity and toxicity of metronomic oral vinorelbine combined with bevacizumb, a monoclonal antibody against vascular endothelial growth factor (VEGF), in pretreated patients with advanced or metastatic non-squamous NSCLC.
Methods: Patients (pts) with confirmed non-squamous NSCLC and measurable disease, pretreated with at least one chemotherapy regimen, were eligible. Oral vinorelbine was administered at a fixed dose of 50 mg three times a week, and bevacizumab was administered intravenously at a dose of 10 mgr/Kg every two weeks. Each treatment cycle consisted of 28 days. Treatment was administered until disease progression or unacceptable toxicity.
Results: Twenty eight patients, of the forty eight projected, have been enrolled. Median age was 57.5 years (range, 42-73), 75% were male, 96.4% had disease stage IV, and 89% had an ECOG performance status of 0-1. Treatment was administered as second-line in 6 (21%) pts and as ≥ third line in 22 (79%). All pts were evaluable for toxicity and response assessment. Grade 3/4 neutropenia was observed in 2 pts (7.1%), and grade 3 thrombocytopenia in 1 (3.6%). One patient (3.6%) died due to treatment-related febrile neutropenia. Non-hematologic toxicity included grade 2 neurotoxicity in 1 pt (3.6%), grade 2/3 fatigue in 5 pts (17.8%), grade 2 diarrhea in 1 pt (3.6%) and grade 2 constipation in 1 pt (3.6%). In an ITT analysis, 2 (7.1%) partial responses (PR) were recorded, 3 (10.7%) pts had stable disease (SD) and 23 (82.1%) progressed. Tumor growth control rate (PR + SD) was 17.8%. Median time to tumor progression (TTP) was 1.3 months (range, 0.8 - 10.1) and median overall survival (OS) 9.6 months (range, 1.0 - 23.4). The 1-year survival Kaplan-Meier estimate was 37.6%.
Conclusion: These preliminary results suggest that the combination of metronomic oral vinorelbine and bevacizumab is safe and demonstrates antitumor activity in a population consisting mostly of heavily pretreated pts with advanced NSCLC.
Keywords: metronomic vinorelbine, bevacizumab, NSCLC, phase II trial

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P3.124 COST-EFFECTIVENESS ANALYSIS (CEA) BETWEEN ERLOTINIB AND GEFITINIB FOR PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) IN THAILAND

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Background: Both Erlotinib and Gefitinib are registered in Thailand for treating advanced NSCLC. All advanced NSCLC patients who were treated with TKIs are required to register with the Central Health Informatics (CHI) for reimbursement. There is no data on the economic analysis of these two drugs. This study compared the cost-effectiveness between Erlotinib and Gefitinib which will be translated to other healthcare systems.
Methods: This is a retrospective cohort study of Thai patients who were diagnosed with advanced NSCLC and treated with EGFR TKIs during January 2006 to December 2010. The clinical benefits of TKIs were evaluated over the duration of the TKIs' treatment. The cost-effectiveness analysis adopted the healthcare system perspective which was measured in terms of cost per-life-day-gained and costs included all direct drugs costs for treatment.
Results: Seven hundred and seventy-eight consecutive cases were available for analysis. According to the comparative results shown in the Table, the incremental survival and duration of clinical benefits were 74 days and 59 days respectively in favor of Gefitinib which result in cost-saving of 1,078.5 baht and 1,352.7 baht per-life-day gained.

	Gefitinib	Erlotinib
No. of patients	301	477
Duration of clinical benefits (days)	281.8	222.7
Direct medical costs during TKIs (baht)	595,424.1	674,923.5
Overall survival (days)	455	381
Mean total direct medical costs (baht)	717,819	797,639

(Exchange rates in February 2011: US dollar $1=30.77 Thai baht)Price /package (30 tablets):

Gefitinib = 73,890 baht, Erlotinib = 90,808 baht.
Conclusion: In clinical benefits of Gefitinib were not inferior to Erlotinib in realized practice and more cost-effective than Erlotinib in the treatment of Thai patients with advanced NSCLC on payer's perspective.
Keywords: TKI, Cost-effectiveness, gefitinib, erlotinib

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P3.125 ROLE OF RE-EXAMINATION FOR EGFR MUTATION USING THE SAME SAMPLES IN PATIENTS SHOWING UNEXPECTED CLINICAL BEHAVIOR AFTER ADMINISTRATION OF EGFR-TKI

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Background: Epidermal growth factor receptor (EGFR) mutation has great influence on effect of EGFR tyrosine kinase inhibitor (EGFR-TKI) (ex. gefitinib and erlotinib) in lung cancer treatment. However, no best assay for EGFR mutation has been established at this time. We investigated the accordance rate of PNA-LNA PCR clamp method, PCR invader method, and Cycleave method, which are all high sensitive and approved methods of EGFR mutation examination in Japan.
Methods: PCR invader method was routinely used for clinical practice in our hospital. If there was discrepancy between clinical behavior after administration of EGFR-TKI and EGFR mutation status, other analyses were additionally performed using the same samples. Either cases which were not effective for EGFR-TKI although EGFR mutation was positive (A), or cases which were effective for EGFR-TKI although EGFR mutation was negative (B) was eligible for this analysis.
Results: Between May 2007 and December 2010, a total 69 cases were treated with EGFR-TKI after finishing initial EGFR mutation examinations. Thirty-six cases were treated with EGFR-TKI of which EGFR mutation was positive (5 cases with erlotinib, 31 cases with gefitinib), and 33 cases were treated with EGFR-TKI of which EGFR mutation was negative (17 cases with erlotinib, 16 cases with gefitinib). Out of 69 cases, 15 cases (22%) were eligible for this analysis. Categories were 8 cases in A and 7 cases in B, respectively. Overall accordance rate was 87% (13/15) among three methods. We found one case which was EGFR mutation positive by both PNA-LNA PCR clamp and Cycleave methods in spite of being negative by PCR invader method, and found one case which was EGFR mutation negative by Cycleave method in spite of being positive by PCR invader method (being not evaluated by PNA-LNA PCR clamp method due to small specimen). The former had partial response (PR) for erlotinib, and the latter had progressive disease (PD) for erlotinib. There were 4 cases which had PR for erlotinib although EGFR mutation was negative by above three methods. In contrast, no responder for gefitinib was observed in 16 cases without EGFR mutation.
Conclusion: Although our study restricted to the patients showing unexpected clinical behavior after administration of EGFR-TKI, the accordance rate among high sensitive methods was still high. However, because EGFR mutation testings do not always show the same results among three high sensitive methods, if the treatment result of EGFR-TKI is not consistent with EGFR mutation status, the re-examination of EGFR mutation in a different method using the same samples may be useful. And even if EGFR mutation is negative, erlotinib may be effective.
Keywords: Epidermal growth factor receptor, Non small cell lung cancer, EGFR mutation, EGFR-TKI

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P3.126 PHASE 1 STUDY OF ORAL VINORELBINE IN COMBINATION WITH ERLOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) USING A METRONOMIC SCHEDULE

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Background: In the salvage setting for NSCLC, response rates of around 10% are achieved with monotherapy erlotinib in unselected patients. Combining oral vinorelbine with erlotinib offers potential synergism and convenience of oral therapy with potential of increasing response rate. Metronomic vinorelbine thrice a week (TIW) provides additional potential for anti-angiogenic effects.
Methods: A phase I study utilizing a 3+3 design was conducted. Erlotinib was dosed 100 mg OD with escalating doses of vinorelbine starting at 30 mg TIW. Advanced (stage IIIB/IV) NSCLC who had at least 1 prior line of chemotherapy (> 1 line 61.5%) were included. Patients with BSA < 1.4 kg/m^2 were excluded. Correlative studies of pharmacokinetics of both drugs and levels of circulating endothelial cells (CEC) and circulating endothelial progenitors (CEP) were examined.
Results: Thirteen patients were accrued. Patient tumour types included adenocarcinoma (54%). squamous cell carcinoma (23%), lymphoepithelioma-like carcinoma (8%) and NOS (15%). All patients had ECOG status 0-1 and 70% (n=9) were non-smokers while the remaining 30% were ex- or current smokers. Dose limiting toxicity of grade 4 neutropenia was reached with the combination of vinorelbine 140 mg (50, 50, 40) a week and erlotinib 100 mg daily. Other Grade 3/4 toxicities included diarrhea (7.7%), fatigue (7.7%), infection (7.7%) and neutropenia (15.4%). Among the 13 patients accrued, 40% (4 of 10) achieved SD and 60% had PD. Three patients remained on treatment.
Conclusion: The recommended phase II dose for metronomic schedule vinorelbine is 40 mg thrice a week with erlotinib 100 mg OM. Additional pharmacokinetic data and CEC/CEP correlations will be updated at the meeting.
Keyword: metronomic

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P3.127 CLINICAL SIGNIFICANCE OF CASPASE-3 EXPRESSION IN PATHOLOGIC-STAGE I, NONSMALL-CELL LUNG CANCER

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Background: Caspase-3 is a cysteine protease that plays an important role in the process of apoptotic cell death. Whereas many studies on the clinical significance of apoptosis in the therapy of malignant tumors have been reported, little has been studied clinically on caspase-3. In the present study, the clinical significance of caspase-3 expression in resected nonsmall-cell lung cancer (NSCLC) and its correlation with incidence of apoptosis were examined.
Methods: A total of 118 consecutive patients who had undergone complete resection for pathologic Stage I NSCLC were retrospectively reviewed. Caspase-3 expression was examined immuno-histochemically using a polyclonal antibody that recognized uncleaved caspase-3.
Results: 1)Caspase-3 was expressed in both the nucleus and the cytoplasm of cancer cells. All the tumors with caspase-3 staining had a diffuse pattern. The distribution of staining was homogenous in both the nucleus and the cytoplasm. There was no significant correlation between the degree of caspase-3 expression and age, sex, performance status (PS), pathologic (p-) T-factor, histologic type, or degree of cancer cell differentiation. In addition, we could not demonstrate a direct or an inverse proportion between caspase-3 expression and AI, PI, and p53 status; 2) Postoperative survival according to the degree of caspase-3 expression is shown in. Five-yearsurvival rates for caspase-3 (+++) patients and caspase-3 (++) patients were 60.0% and 68.4%, respectively; those for caspase-3 (+) patients and caspase-3 (- to ±) patients were 82.6% and 80.8%, respectively. Because a definite difference in postoperative survival between caspase-3 (++) and (+++) patients and caspase-3 (- to ±) and (+) patients was suggested, postoperative survival of these two patient groups was compared. Five-year survival rates for "strong" (++ or+++) caspase-3 expression

pa-tients and "weak" (- to ± or +) caspase-3 expression patients were 66.6% and 82.1%, showing a significant poor prognosis for "strong" caspase-3 expression patients. 3) Multivariate analysis confirmed that enhanced caspase-3 expression was an independent and significant factor for predicting a poor prognosis. Sex and aberrant expression of p53 were also significant prognostic factors.
Conclusion: Our study demonstrates that the postoperative prognosis of patients with tumors showing enhanced expression of "uncleaved" caspase-3 was poor even when complete resection could be performed. These results suggest that enhanced expression of "uncleaved" caspase-3, inactivated caspase-3, is correlated with poor prognosis in resected NSCLC.
Keywords: caspase-3, Prognosis, Lung cancer, apoptosis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.128 CEA AND CYFRA 21-1 AS AN EARLY PREDICTOR TO RESPONSE TO FIRST LINE CHEMOTHERAPY IN ADVANCED NON SMALL CELL LUNG CANCER

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Background: In an era of ever evolving, promising new therapies for advanced NSCLC, early predictors of response to therapy, are needed. We evaluated early variations in CYFRA 21-1 and CEA serum levels of patients with advanced NSCLC receiving first line chemotherapy and correlated the results with objective tumor response
Methods: 29 consecutive, previously untreated, patients of advanced NSCLC, with measurable disease on CT scan were evaluated. All patients were treated with conventional systemic chemotherapy, although the choice of chemotherapy was left to the discretion of the treating physicians. Serum samples were obtained before start of 1st and 2nd cycles of chemotherapy. CYFRA 21-1 was measured with an electrochemiluminescense immunoassay on an automatic analyzer (Elecsys 2000; Roche Diagnostics). CEA Assays were performed us**in**g commercial kits (**CEA** test; CIS Bio**In**ternational, France). Normal reference values for **CEA** were upto 5 ng/mL. Response was evaluated using RECIST criteria.
Results: 10 patients had partial response, 9 patients had stable disease and 9 had progressive disease. None of the patients had complete response. 21/29 (72 %) patients had an elevated baseline value of CYFRA 21-1. 62 % patients (18/29) had a decrease in CYFRA 21-1 after 1 cycle of chemotherapy. The average reduction in the 2nd reading was irrespective of whether baseline value was normal or not. The average reduction was statistically significant (P = 0.002; 95% CI, from 0.8369 to 3.49464; paired sample t test). 8/ 10 (80%) patients with partial response had a reduction in their 2nd reading of. CYFRA 21-1 () which was significant. We observed that 6/9 (66%) patients whose disease remained stable also had a decrease in their subsequent reading (P=0.0106), though it was not significant statistically. Although 5/ 9 (55%) patients, who had an increase in their 2nd reading had progressive disease, but it was not statistically significant (P= 0.537). 14/ 19 (73%) who either had partial response or stable disease, had a reduction in their 2nd value of CYFRA 21-1 and was significant statistically (P 0.004). We also observed that except for 1 patient, all patients who had a decrease of 42% or more, were those who had either responded to chemotherapy or had stable disease (P 0.001), which was statistically significant. While correlating the values of CEA we found that 15 / 29 (51%) patients had an elevated baseline CEA. The increase was however not significant statistically (P = 0.261). 7/15 had a decrease from their baseline value which was irrespective of whether baseline value was normal or not. 2/10 (20%) patients with partial response had a reduction in their 2nd reading of CEA (P= 0.719) which was not significant statistically. 3/9 (33%) patients whose disease remains stable also had a decrease in their subsequent reading, though it was not significant statistically (P=0.5106). 4 / 9 (44%) patients, who had an increase in their 2nd reading had progressive disease, but it was not statistically significant (P= 0.427).
Conclusion: Monitoring of serum marker CYFRA 21-1, early during first-line chemotherapy may be a useful prognostic tool for evaluation of early tumor response in patients with advanced NSCLC. We failed to demonstrate any predictive value of CEA

for response to chemotherapy. It may be concluded that monitoring of CYFRA 21-1 and not of CEA may be used as a putative marker of response to chemotherapy in advanced NSCLC

Keywords: Non small cell lung cancer, Chemotherapy, Cyfra 21-1, CEA

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P3.129 A NOMOGRAM TO PREDICT BRAIN METASTASIS AS FIRST RELAPSE SITE IN CURATIVELY RESECTED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Metastasis to the brain is diagnosed in 40 to 50% of patients with locally advanced non-small cell lung cancer (NSCLC). However, the occurrence of brain metastasis from completely resected NSCLC cannot be accurately predicted in patients receiving curative resection. We hypothesized that a nomogram could be constructed by combining selected clinical and pathological variables to predict the likelihood of occurrence of brain metastasis as first relapse site in patients with NSCLC receiving curative resection.

Methods: From 2001 to 2008, 1677 consecutive patients treated with curative surgery for NSCLC were identified. The logistic regression analysis to predict the brain metastasis at 24-month was performed. The clinical and pathologic variables with P-value <0.15 were built into a nomogram estimating probability of brain metastasis as first relapse site at 24-month after curative resection. The model was validated for discrimination and calibration using bootstrap resampling.

Results: Two hundred six patients with follow-up duration of less than 12 months were excluded from analysis. Finally, a total of 1471 patients were analyzed. Median follow-up duration was 42.3 months (range, 12.0-114.9). Brain metastasis as first relapse site occurred in 76 patients (5.2%). The logistic regression analysis exhibited that smoking (P=0.11), adenocarcinoma (ADC) histology plus N1 (P=0.12), and ADC plus N2/3 (P=0.01) were associated with the brain metastasis as first relapse site at 24-month. The nomogram showed a moderate accuracy for prediction of 24-month brain metastasis, with an area under the curve (AUC) of 0.768 (bootstrap corrected, 0.730).

Conclusion: The nomogram integrates 3 clinicopathologic variables to provide an individual risk estimate of brain metastasis as first relapse site in a patient with NSCLC receiving curative resection. This nomogram could be used to develop radiologic screening or preventive treatment strategies for brain metastasis.

Keywords: nomogram, Brain Metastasis, Non-small cell lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.130 THE SIMILAR SURVIVAL BENEFITS OF STABLE DISEASE AND PARTIAL RESPONSE TO FIRST-LINE GEMCITABINE/CARBOPLATIN IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: The role of stable disease (SD) in survival benefits has not been clearly demonstrated in advanced non-small cell lung cancer (NSCLC) treated with first-line platinum-based chemotherapy. The aim of this study is to evaluate survival benefits of first-line gemcitabine /carboplatin (GC) in Chinese patients with advanced NSCLC achieving SD in routine clinical practice.

Methods: We retrospectively investigated 146 advanced NSCLC patients receiving first-line GC chemotherapy in the electronic medical records from January 2003 to July 2006. Survival was estimated according to the Kaplan-Meier method. Multivariate

Cox regression analysis was performed to identify prognostic factors.
Results: No patients acheived complete response (CR). 27 attained partial response (PR) and the objective response rate (ORR) was 18.5% (27/146). 61 had SD. Disease control rate (DCR), consisting of CR, PR and SD, was 60.3% (88/146). Median progression-free survival (mPFS) was 6.6 months (95%CI, 5.2-8.1) for patients with PR and 6.7 months (95%CI, 6.3-7.2) for patients with SD, P = 0.341. Wet stage B and PR or SD to GC were significantly associated with better PFS (P = 0.024, 0.000 and 0.000 respectively). Median overall survival (mOS) was 17.5 months (95% CI, 10.6-24.4) for patients with PR and 15.1 months (95% CI, 11.4-18.8) for patients with SD, P = 0.552. Wet stage B, PR or SD to GC, and subsequent treatment with epidermal growth factor receptor tyrosine kinase inhibitors were significantly associated with better OS (P = 0.002, 0.000, 0.000 and 0.004 respectively).
Conclusion: First-line GC chemotherapy has comparable PFS and OS benefits in Chinese patients with advanced NSCLC achieving PR or SD. PR or SD is a strong predictor of PFS and OS.

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P3.131 PHASE II TRIAL OF ERLOTINIB AS FIRST-LINE THERAPY IN NON-SMALL CELL LUNG CANCER OVER-EXPRESSING EGFR

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Background: Erlotinib has demonstrated efficacy in the second-line management of non-small cell lung cancer. This study was undertaken to investigate its use in chemotherapy-naïve patients with tumours that over-express EGFR.
Methods: Eligible patients had cytologically or histologically confirmed stage IIIb/IV non-small cell lung cancer over-expressing EGFR on immunohistochemistry (Dako EGFR staining kit). EGFR over-expression was present if more than 10 percent of tumour cells demonstrated weak to moderate membrane staining (score 2+) or, strong, complete membrane staining (score 3+). Patients were of WHO performance status (PS) 0-2. Erlotinib was administered at 150mg daily until disease progression, unacceptable toxicity or at patient request. The primary end point was objective tumour response rate.
Results: Between June 2008 and October 2010, twenty-six patients were accrued. Most patients were PS 1 (PS 0, 31%; PS 1, 69%; PS 2, 0). Partial response occurred in three patients (11.5%), stable disease in eight patients (30.8%), and progressive disease in thirteen patients (50%); two patients were not evaluable. The most common adverse events were rash (any grade, 92%; grade 3, 11.5%) and diarrhoea (any grade, 65.4%; grade 3, 11.5%). @ font-face { font-family: “Arial”; }@font-face { font-family: “Cambria”; }p.MsoNormal, li.MsoNormal, div.MsoNormal { margin: 0cm 0cm 0.0001pt; font-size: 12pt; font-family: “Times New Roman”; } div.Section1 { page: Section1; } The median time to progression was 2.5 months. Median overall survival was 6.7 months. Mutational analysis was performed in twenty patients (77%): two patients had EGFR mutations (one sensitising mutation and one resistance mutation), and six patients were positive for KRAS mutation.
Fifteen patients (57.8%) proceeded to second-line platinum-based chemotherapy (partial response n=3, stable disease n=5, progressive disease n=5 and NA n=2). Three patients (11.5%) underwent third line chemotherapy (partial response n=2, progressive disease n=1).
Conclusion: In patients selected on the basis of EGFR protein over-expression, erlotinib demonstrates modest activity in the first-line setting.
Keywords: first-line, EGFR, NSCLC, erlotinib

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P3.132 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF VANDETANIB MAINTENANCE THERAPY FOR ADVANCED OR METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC) FOLLOWING 1ST-LINE PLATINUM-DOUBLET CHEMOTHERAPY

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Background: Vandetanib (VAN) is a once-daily oral inhibitor of VEGFR, EGFR and RET signalling. Several studies have shown the efficacy and tolerability of vandetanib in patients (pts) with advanced NSCLC. This study assessed VAN maintenance therapy in NSCLC.

Methods: Pts who had not progressed after 4 cycles of platinum-based chemotherapy were randomized 1:1 to VAN 300 mg/day or placebo (P). The primary objective was to compare indirectly the progression-free survival (PFS) rate at 3 months (mo) at the interim analysis, which was conducted once 24 PFS-evaluable pts had been accrued to each arm and followed for 3 mo. According to the optimal two-stage design by Simon (1989), it was planned that additional enrolment would proceed only if there were at least 9 pts who remained progression-free at 3 mo. At the interim analysis, the numbers of progression-free pts at 3 mo were 9/24 in the VAN arm, with acceptable toxicities, and 7/24 in the P arm. Additional pts were therefore enrolled to the VAN arm and accrual to the P arm was stopped. The final analysis evaluated PFS, overall survival (OS), objective response rate (ORR), disease control rate (DCR) and duration of response (DOR), as well as the safety profile and tolerability of VAN.

Results: The intention-to-treat (ITT) analysis comprised 117 pts (75, VAN; 42, P), excluding 1 pt randomized to VAN but not treated. The median duration of follow-up was 12.1 mo with VAN and 17.0 mo with P. Baseline characteristics were balanced in both arms (overall: 64% male, 74% WHO PS 1, 64% smokers, 74% adenocarcinoma histology and 63% partial responders to chemotherapy). The final analysis showed that median PFS was 2.7 mo (95% CI: 1.9, 4.4) with VAN and 1.7 mo (95% CI: 0.9, 2.6) with P; median OS was 15.6 mo with VAN and 20.9 mo with P; ORR was 18.7% (95% CI: 9.9, 27.5) with VAN and 2.4% (95% CI: 0.0, 7.0) with P; DCR with VAN was 44.0% (95% CI: 32.8, 55.2) and 40.5% (95% CI: 25.6, 55.3) with P, and median DOR with VAN was 9.2 mo (95% CI: 5.0, -). For pts receiving VAN, the most common adverse events were rash, diarrhoea, pruritus and anorexia; there were no deaths due to treatment-related serious adverse events.

Conclusion: These results show that single-agent vandetanib maintenance treatment, after 4 cycles of platinum-based chemotherapy, was tolerable and prolonged PFS in pts with NSCLC compared with placebo. Based on these results, vandetanib maintenance therapy should be considered for further study. Correlative biomarker analysis will be presented.

Keywords: Phase II, maintenance, Non-Small-Cell Lung Cancer, vandetanib

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P3.133 CHEMOTHERAPY-INDUCED NEUTROPENIA AS A PROGNOSTIC FACTOR IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH MORE THAN 4 CYCLES OF FRONT-LINE PLATINIUM-BASED CHEMOTHERAPY.

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Background: Neutropenia is a common side effect of platinium-based chemotherapy. We analyzed the association between the grade of chemotherapy-induced neutropenia and the clinical outcome for patients with advanced non-small-cell lung cancer (NSCLC). A possible explanation for the association between chemotherapy-induced neutropenia and clinical outcome is that the absence of neutropenia may suggest a lack of efficacy of the administered chemotherapy regimen possibly due to pharmacogenetic reasons and varied metabolism of anticancer drugs.
Methods: Thirty nine patients with locally advanced/metastatic NSCLC, treated with front-line more than 4 cycles of platinium based chemotherapy were retrospectively analyzed. The mean number of cylces of front-line chemotherapy they were treated was 5.8. Patients were categorized into two groups according to the presented worst neutropenia grade: mild (grades I/II) and severe (grades III/IV).
Results: One year survival was significantly better in patients developing severe grade of neutropenia compared with those with mild neutropenia; the 1 year survival rate were 18.2%(2/11), 60.7%(17/28) for the groups with mild and severe neutropenia, respectively(p value=0.017). The median overall survival were 8.4, 20.4 months for the same groups, respectively. The disease controlled rate (including complete remission, partial response and stable disease) was better in patients with severe grade of neutropnenia; 45.5%(5/11) and 60.7%(17/28) for the groups with mild and severe neutropenia, but there was no statistical significance(p value=0.387).
Conclusion: Chemotherapy-induced neutropenia can be a predictor of better clinical outcome for patients with advanced NSCLC.
Keywords: neutropenia, NSCLC

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P3.134 PHASE II TRIAL OF PACLITAXEL POLIGLUMEX(CT-2103) IN PRE- AND POST-MENOPAUSAL WOMEN ON HORMONAL REPLACEMENT THERAPY (HRT) WITH NON SMALL CELL LUNG CANCER (NSCLC)

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Background: Relationship of estrogen use, smoking, and NSCLC has been reported in several studies. Capthesin B is expressed on most NSCLC and is the major metabolizing enzyme for CT-2103. It is under control of estrogen and in phase III front line studies, women with estradiol levels >30 had the largest survival benefit. The objective of this study was to evaluate CT-2103 as single agent therapy for women with baseline estradiol levels >30 or in combination with EstroGel in post-menopausal women with heavily pretreated advanced NSCLC. The primary endpoint was progression free survival with safety, response, and overall survival as secondary endpoints.
Methods: 29 stage IV NSCLC patients with PS 0, 1 or 2 who had previous treatment with at least one cytotoxic chemotherapy and an EGFR inhibitor, participated. CT-2103 was given as IV infusion once every 21 days (1 cycle). Tumor response (using RECIST criteria) was assessed after even numbered cycle. Toxicities assessed at each patient visits. Study discontinued at the time of progression or unacceptable toxicity.
Results: 29 patients with 3.4 average lines (ranging 2-7) of previous treatment (8 patients received 4 or more lines of therapy), received CT-2103 treatment. Plus estradiol patches for serum levels <30. Average number of CT-2103 cycles was 2.8 (1-6 cycles). Median time to progression was 44 days (36.5-51.5) with median overall survival 223 days (153-282). 11 (37.9%) of 29 patients had stable disease and 1 (3.4%) partial response. No major toxicity reported except grade I and II peripheral neuropathy in 6 (20.6%), no hair loss or allergic reaction reported.
Conclusion: Paclitaxel poliglumex was relatively well tolerated. Despite encouraging preliminary clinical results in women with high estradiol levels and intriguing preclinical observations, the PFS and overall survival results suggest that further testing of this treatment strategy is not warranted.
Keywords: Non-small cell lung cancer, new treatment, paclitaxel poliglumex

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P3.135 CHEMOTHERAPY EFFECTIVENESS AFTER FIRST-LINE GEFITINIB (G) TREATMENT OF ADVANCED BRONCHIOLOALVEOLAR CARCINOMA (BAC): EXPLORATORY ANALYSIS OF THE IFCT-0401 TRIAL

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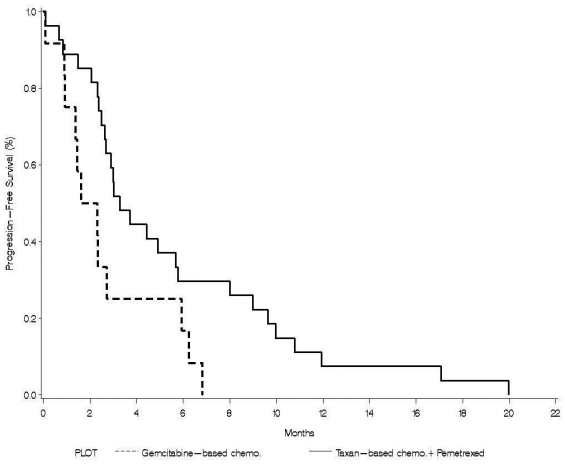
Background: At the present time, there is no treatment standard for the patients with advanced BAC. Chemotherapy is widely perceived to be ineffective in advanced BAC. No information was available concerning platin doublets. Two phase II prospective trials have tested two different schedules of paclitaxel monotherapy as front-line therapy with low OR of 11-14% and a relatively high toxicity. Interestingly, only mucinous cytological subtype (M) might be more responsive to paclitaxel. EGFR-TKI have demonstrated interesting activity in three phase II trials, particularly in non-mucinous cytological subtype (NM) as shown in the IFCT-0401 trial using G as first-line therapy. We aimed to study chemotherapy efficacy after gefitinib failure among patients enrolled in the IFCT-0401 trial.
Methods: 88 patients with advanced BAC were enrolled in the IFCT-0401 trial and received G 250 mg/d as front-line therapy. For patients still eligible for chemotherapy after G-failure, carboplatin plus paclitaxel regimen was recommended for PS 0-1 patients and gemcitabine monotherapy for PS 2 patients.
Results: 44 patients received a second-line treatment after G failure and 41 were treated with chemotherapy. 40 patients had a PS 0 or 1. 27 patients received a taxan-based chemotherapy (22, paclitaxel+carboplatin and 5, docetaxel+cisplatin), 12, a gemcitabine-based chemotherapy (9, with cisplatin and 3, monotherapy), 2, a pemetrexed monotherapy and 3, other regimens (2, bortezomib and 1, erlotinib). PFS in second-line setting was 2.8 months (95% CI, 2.3-4.2). OR was 23% (8 PR, 15 SD, 15 PD, 6 NE) and DCR at time of the best response was 65.7%. Taxan-based (n=27) and gemcitabine-based (n=12) chemotherapies achieved 29.2 versus 0% OR, respectively (p=0.15), and 3.0 versus 1.9 months of median PFS (p=0.056). The two patients treated with pemetrexed monotherapy have experimented prolonged response over 10 and 20 months, respectively. In univariate Cox model analysis, a significantly probability of improved PFS was associated with use of taxan-based chemotherapy and pemetrexed monotherapy (HR=0.44, 95% CI, 0.21-0.90, p=0.026)(see figure below). Difference in PFS, OR and DCR between taxan-based chemotherapy and pemetrexed monotherapy versus gemcitabine-based chemotherapy was preserved in third-line treatment.



Conclusion: Our results showed that: 1) only 50% of advanced BAC treated in first-line with G had received a second-line chemotherapy regimen; 2) a platin-doublet could be administered with some evidence of effectiveness to these patients with PS 0 or 1; 3) taxan-based and pemetrexed monotherapy seemed to be good candidates for future clinical trials and led us to choose this drugs to be tested in IFCT-0504 trial.
Keywords: bronchioloalveolar carcinoma, Chemotherapy

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P3.136 A RETROSPECTIVE ANALYSIS OF THE CLINICAL RESPONSES TO EGFR-TYROSINE KINASE INHIBITOR (EGFR-TKI) CONTINUOUS TREATMENT BEYOND SINGLE SITE DISEASE PROGRESSION IN METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS WHO BENEFITED FROM PRIOR EGFR-TKI THERAPY

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Background: Few treatment options are available for metastatic non-small cell lung cancer (NSCLC) patients who have responded to an EGFR-TKI treatment showing tumor progression. Whether to continue the same or another EGFR-TKI (erlotinib or gefinitib) after single site disease progression (SSP) is an important unanswered clinical question. Unfortunately, there is little evidence to guide decision-making. The modest toxicity and the possible, but unproven, benefit from the continued use of an EGFR-TKI suggest to continue administration of this drugs after local treatment of SSP until subsequent systemic progressive disease (SPD). The present study was conducted to evaluate the efficacy and toxicity of this therapeutic strategy.
Methods: We retrospectively analyzed 12 patients who had obtained a partial response (PR) or stable disease (SD) by treatment with an EGFR-TKI to describe their clinical outcome once receiving local treatment for SSP and continuing an EGFR-TKI until further SPD
Results: Between December 2001 and November 2010 we identified 12 pts at 4 Italian Institutions (Aviano, Catania, Milano and Perugia): median age: 62 yrs (range 44-78), male: 7 pts, PS0: 6 pts, smokers: 7pts. EGFR mutated:4, wild-type:2, unknown 6. Eight pts were treated with erlotinib and 4 with gefinitib (first-line 1 pt, second 7 pts and third 4 pts). One pt achieved CR (8%), 6 pts PR (50%) and 5 stable disease (42%). SSP occurred after a median time of 9.8 mos (range 1.2-28.6) in brain 8 pts (66%), lung 1, bone 2 and adrenal gland 1. Local control of SSP was obtained by radiotherapy in 88% of pts (CR 2 pts, PR 6, stable disease 2, progression 2). After SSP, all patients continued EGFR-TKIs for a median time of 7 mos (range 1.6-48.8). Up to now 8 pts had further progressive disease and stopped EGFR-TKIs while 4 are still on treatment experiencing disease control. Actuarial median freedom from progression (FFP) evaluated from EGFR-TKI starting until SSP was 8.9 mos; FFP from SSP to SPD was 8.2 mos. Overall median FFP was 24.6 mos (from EGFR-TKI starting until SPD) and median overall survival was 39.7 mos. The toxicities associated with the protracted EGFR-TKI treatment were generally acceptable and comparable to those observed for the initial EGFR-TKI therapy.
Conclusion: Our data suggest that the protracted use of an EGFR-TKI after SPD and local treatment, particularly beyond brain progression, can be an effective treatment option for EGFR-TKI responders since this seems to be associated with further systemic disease control and possibly longer survival. We believe that these results deserve further study since they could have important clinical implications.
Keywords: gefitinib, erlotinib, EGFR, NSCLC

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P3.137 EFFICACY AND SAFETY IN THE CROSS-OVER ARM OF OAM4558G; A PHASE II STUDY EVALUATING METMAB IN COMBINATION WITH ERLOTINIB IN ADVANCED NSCLC.

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Background: A global Phase II double-blinded, randomized trial comparing MetMAb+erlotinib (M+E) versus placebo+erlotinib (P+E) in 2nd/3rd line NSCLC was recently completed. M+E demonstrated both PFS and OS advantages in Met Dx+ NSCLC. Following disease progression, eligible patients on the P+E arm were allowed to crossover to receive open-label M+E
Methods: Efficacy (PFS and OS) and Safety were assessed in the crossover patients. Eligibility criteria for crossover included: ECOG PS 0-2, absence of untreated and/or active CNS metastasis, initiate M+E within 28 days from documented PD.
Results: Of the 128 randomized patients, 26 participated in the crossover, of which 12 were Met Dx+,12 were Met Dx-, and 2 were undetermined. Among the 12 Met Dx+ patients, 11 (92%) patients had ECOG 0/1 at baseline, 2 (17%) patients had squamous tumor, 2 (17%) patients never smoked, 4 had KRAS mutant tumors and none had EGFR mutant tumor. Among the 12 Met Dx- patients, all patients had ECOG 0/1 at baseline, 4 (33%) had squamous tumors, 1 (8%) never smoked, 3 (25%) had KRAS mutant tumors and 2 (17%) had EGFR mutant tumors. Most patients progressed at the first tumor assessment following cross-over to M+E. Among 12 Met Dx+ patients, 5 patients died and 3 progressed at or prior to the first tumor assessment; of the 4 patients who did not progress at the first tumor assessment, the median PFS was 5.2 months (95%CI: 2.7-NA months) after crossover. Among 12 Met Dx- patients, 4 patients died prior to and 5 progressed at the first tumor assessment; of the 3 who did not progress at first tumor assessment, 2 discontinued treatment (MD decision) and the 3rd continues on M+E (>7 months). After crossover to M+E, the Met Dx+ patients had median OS (mOS) post PD (defined as time from 1st PD to death from any cause) of 2.2 months (95%CI: 1.1-6.4 months); and the Met Dx- patients had an unreached mOS post PD. For patients in P+E arm who had progressive disease but did not crossover to M+E (n=19), the Met Dx+ patients (n=10) had mOS post PD of 3.5 months (95%CI: 0.6-5.7 months); and the Met Dx- patients (n=8) had mOS post PD of 6.7 months (95%CI: 1.1-NA months). The most frequent adverse events regardless of attribution include: nausea (n=7; 27%), dyspnoea (n=6; 23%), vomiting (n=6; 23%), diarrhoea (n=5; 19%), and rash (n=4; 15%). Overall incidence and spectrum of adverse events following crossover is comparable to the known safety profile of the combination.
Conclusion: Met amplification/activation has been described as a mechanism of resistance to EGFR inhibition, providing a rationale to add M to E following progression on E alone. While this data set is limited, it is intriguing that of the patients that crossed over to M+E, a small fraction (regardless of Met status at time of randomization) had a longer PFS on M+E than on P+E. Tissue was not available in this study to assess Met status at time of crossover, but would be a consideration for future studies.
Keywords: cMet, MetMAb, erlotinib, NSCLC

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P3.138 BEVACIZUMAB BEYOND PROGRESSION IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): PRELIMINARY RESULTS OF A PHASE II STUDY

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Background: The VEGF and epidermal growth factor receptor (EGFR) pathways represent 2 clinically validated and interrelated targets for NSCLC. Adding the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (B) to first line platinum-based chemotherapy improves outcome in NSCLC. However, the optimal duration of treatment with B is unknown. Preclinical data suggest rapid vascular re-growth in tumours after reversal of VEGF inhibition supporting studying the concept of continued use of VEGF inhibition in progressive patients. Preclinical studies have shown that VEGF and EGFR inhibitors (e.g. erlotinib) can have additive effects and clinical trials have also produced promising data. In second line therapy combining bevacizumab with anti-EGFR directed therapy increases benefit compared with anti-EGFR agents alone. This open label single centre phase II study investigates the efficacy of 2nd line erlotinib plus bevacizumab (BE) subsequent to a

1st line combination of carboplatin, paclitaxel and bevacizumab (CPB).
Methods: Previously untreated patients with advanced non-squamous NSCLC receive 1st line treatment with 3-weekly C (AUC 6 day 1 i.v.) P (200 mg/m2 i.v. day 1) B (15 mg/kg i.v. day 1) for a maximum of 4 cycles or less in case of early progression, 3-weekly bevacizumab continues until progression. At (early) progression B continues and E (150 mg/day orally) is added. The primary objective of the study is to assess the efficacy, defined as disease control rate (CR+PR+SD according to RECIST) at 12 weeks treatment BE.
Results: Informed consent was obtained from 25 patients (pts), 23 started therapy; at first data-analysis 12 pts progressed of whom 8 pts started 2nd line BE. Reasons for not entering 2nd line were rapidly declining PS in 2 pts and pt's wish in the other 2. Of the 8 pts with BE, 1 received 9 cycles of BE (27 weeks, best respons SD) and 1 received 4 cycles (12 weeks, SD). Of the remaining 6 pts, 2 progressed within the first 6 weeks, 3 pts discontinued treatment before first radiological evaluation (pt wish in all 3 due to declining performance status, most likely disease-related), and 1 pt died of pulmonary hemorrhage (PH) after 5 weeks BE. No unexpected (serious) adverse events were observed. Besides the one treatment related death (PH), 2 other SAE were reported: one treatment related (dehydration caused by diarrhea) and one disease related (pain syndrome necessitating hospital admission).
Conclusion: The study is ongoing. The minimum DCR below which 2nd line BE treatment after first line CPB is of no interest is set at 35%, hence if at most 8 of first 21 patients show controlled disease, the trial will be stopped concluding BE is not effective enough (2-phase Simon 'minimax' design; power 80%; type I error 5%;). Otherwise, a total of 39 pts will be entered in the BE; if 19 pts or more show DCR, the conclusion will be that the effectiveness of the treatment is larger than 35%. Currently DCR at 12 weeks is 2 out of 8 and treatment with 2nd line BE seems feasible.
Keywords: Advanced NSCLC, targeted therapies, bevacizumab beyond progression, erlotinib

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P3.139 THE ROLE OF NANOPARTICLE ALBUMIN-BOUND PACLITAXEL (NAB-P) IN THE NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS.

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Background: The well known P and docetaxel are hydrophobic substances, they need premedication with steroids and antihistamine, long infusion time and they present serious adverse events, sometimes caused by the solvent in use. Nab-P is a novel water-soluble formulation of P prepared by high-pressure homogenization of P in the presence of serum albumin into a nanoparticle colloidal suspension. Nab-P utilizes the albumin receptor (gp60)/caveolin-1 (CAV1) pathway achieving high intratumoral paclitaxel accumulation. Aim of this article is to present the latest data on the use of nab-P in the treatment of NSCLC.
Methods: Our source was MEDLINE till the end of 2010 with key words nab-P and NSCLC.
Results: We found three phase I trials, three phase II trials and one dose-finding non-randomized trial for a phase III trial. We have also found the abstract of the last nominated phase III randomized trial presented in the American society of clinical oncologists (ASCO) annual meeting of 2010. Nab-P presents some technical advantages over P including shorter infusion time of 30 minutes and no need for steroid and antihistamine premedication. Nab-P has significant single agent activity. When combined with carboplatin (C) or C and bevacizumab, nab-P has promising activity in the first line treatment of NSCLC. A recent phase III trial with 1038 patients has shown that nab-P in combination with C significantly improves overall response rate (ORR) versus P-C. Histologic subset analysis has shown significantly improved ORR for nab-PC versus PC in squamous cell carcinoma patients. Regarding the toxicity profile of nab-P presented significantly less high-grade adverse events and reduced risk of hypersensitivity reactions compared with P.
Conclusion: Nab-P has a safe and efficient profile.

In patients with hypersensitivity reactions after receiving the older taxanes can be an alternative solution. Squamous cell carcinoma histotype may have an advantage if treated with nab-P which may in part be attributed to the aberrant CAV1 overexpression in these patients and the high intratumoral accumulation of nab-P via the gp60-CAV1 pathway.

Keywords: nab-p, treatment, NSCLC, squamous cell carcinoma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.140 PROSPECTIVE OBSERVATIONAL COMPARISON OF SAFETY IN PATIENTS RECEIVING SECOND OR THIRD LINE TREATMENT FOR NON-SMALL CELL LUNG CANCER (NSCLC) IN US COMMUNITY PRACTICES

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Background: This prospective observational study was designed to evaluate health-related quality of life, adverse events, and healthcare utilization among patients receiving either pemetrexed (PEM) or erlotinib (ERL) as a single agent for second line treatment of NSCLC in community clinics in the United States.

Methods: Patients with ECOG=0-2 and a confirmed diagnosis of advanced or metastatic NSCLC beginning single agent second or third line ERL therapy, or second line PEM therapy were enrolled at 15 community sites. Patients were observed for 12 weeks or until discontinuing treatment. In addition to provider ratings of adverse events (AEs), patient reported outcomes were also collected.

Results: 62 patients (ERL=23; PEM=39) were enrolled. ERL patients were older than PEM patients (70.6 vs. 65.9; p = .04), and more likely to be White (91% vs. 67%; p = .03). There were no group differences in disease characteristics or treatment history. PEM patients had significantly greater use of supportive medications, including antiemetics (44% vs. 13%; p = .023) and growth factors (36% vs. 9%; p = .03). Overall, the most common AEs were rash (29%), fatigue (26%), decreased appetite (23%), diarrhea (21%), anemia (19%), and nausea (18%). PEM patients had more Hematologic related nonserious AEs (41% vs. 9%; p = .009), and were significantly more likely to have serious AEs (33% vs. 9%; p = .03; see Table). ERL patients had significantly more Skin related nonserious AEs (65% vs. 18%; p = .0003). The most common self-reported symptoms rated as severe were fatigue (41%), pain (33%), sexual problems (27%) and shortness of breath (25%). Diarrhea was more likely to be self rated as severe by ERL patients (23% vs. 3%; p = .03). Self rated severe rash was nominally higher among the ERL group (9% vs. 0%; p = .15).

Serious Adverse Events	Erlotinib (N=23)	Pemetrexed (N=39)
Patients with ≥ 1 SAE	2	13
Neutropenia	0	1
Pancytopenia	0	1
Thrombocytopenia	0	1
Gastrointestinal Disorders*	1	2
Infections And Infestations*	0	3
Blood Creatinine Abnormal	1	0
Dehydration	1	0
Hyperkalaemia	1	0
Muscular Weakness	0	1
Renal Failure Acute	0	1
Respiratory, Thoracic And Mediastinal Disorders*	0	7
Oesophageal Stent Removal	0	1
Arterial Thrombosis	0	1
* System organ class of SAEs		

Conclusion: These data from the US community setting confirm previous clinical trial data that patients treated with second or third line ERL have fewer side effects when compared to cytotoxic chemotherapy.

Keywords: NSCLC, safety, erlotinib, Pemetrexed

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P3.141 VANDETANIB PLUS CHEMOTHERAPY FOR INDUCTION THERAPY FOLLOWED BY VANDETANIB OR PLACEBO AS MAINTENANCE FOR ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC): EFFICACY AND TOXICITIES UPDATE. A PHASE II PRECOG, LLC STUDY (PRE0501)

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Background: We conducted a randomized phase 2 study to test if vandetanib, a VEGFR and EGFR tyrosine kinase inhibitor, could improve PFS, compared to historical controls, in patients with NSCLC when given as induction therapy with docetaxel and carboplatin, followed by maintenance vandetanib or placebo. We examined safety and side effects, and in particular, those related to actual and presumed vascular events and diverticulitis.
Methods: Patients with stage 3B or 4 NSCLC were randomized to induction docetaxel (75 mg/m2) and carboplatin (AUC 6) on day 1 of a 21-day cycle, with daily vandetanib (100 mg/day po) for 4 cycles, followed by daily vandetanib (300 mg/day) or placebo until progression. Eligibility required good performance status (ECOG 0-1), measurable disease, and no prior cytotoxic or targeted agents for advanced disease. Ineligibility included uncontrolled hypertension, arrhythmia, or history of QT prolongation. Patients were assessed for adverse events (AEs) during every cycle and for 30 days post-treatment. AEs were also reported during follow-up.
Results: 162 patients were randomized between May 2008 and November 2009, and 158 began treatment. Median age was 63 (36-82). 91% had stage IV or recurrent disease and 52% were male. Efficacy results previously reported; showed prolonged PFS for vandetanib maintenance in a multivariate model adjusting for stage (p=0.02). A median of 4 cycles (1 - 25) of treatment was delivered to patients randomized to vandetanib maintenance, while a median of 3 cycles (1 - 19) was delivered to patients randomized to placebo maintenance. Toxicity was assessed on day 1 of each cycle, at least once for 157 treated patients, of whom 19 (9 vandetanib maintenance and 10 placebo maintenance) experienced no grade ≥ 3 toxicity. There was no difference between arms in the number of cycles administered (exact p=0.62) or the worst degree toxicities (exact p=0.92). Toxicities (≥ grade 3) occurring at a rate of ≥5% included neutropenia (48%), leukopenia (18%), diarrhea (12%), fatigue (11%), febrile neutropenia (11%), dyspnea (11%), thrombosis / thrombus /embolism (10%), dehydration (9%), rash/desquamation (8%), back pain (8%), hyponatremia (7%), hypokalemia (6%), anemia (6%), and lung infection with unknown absolute neutrophil count (5%). Diverticulitis was noted on several serious adverse event reports, so we explored potentially related symptoms, including diarrhea, mucositis, enteritis, GI hemorrhage, abdominal pain, colitis, fistula, and GI perforation. 98 patients had ≥ one of these symptoms, 31 grade 3 and 1 grade 4 (20% gr 3-4). One grade 3 perforation of diverticulitis was reported. Three events (2%) included the word "diverticulitis" in the narrative of a serious adverse event (SAE). The lack of a specific NCI CTCAE term for diverticulitis may lead to inconsistencies in reporting and is representative of difficulties that may exist in assessing this and other targeted therapy toxicities.
Conclusion: s: In this study, maintenance oral antiangiogenic therapy with vandetanib improved PFS and showed toxicities similar to other angiogenesis inhibitors.
Keywords: Tyrosine kinase inhibitor toxicities, Advanced Non-Small Cell Lung Cancer, maintenance therapy

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P3.142 RAPID DISEASE PROGRESSION IN NON-SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY STAGED BY PET/CT

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Background: PET/CT scanning is becoming increasingly prevalent for treatment planning in patients with non-small cell lung cancer (NSCLC). However, the majority of PET/CT treatment planning is performed with fusion of previously obtained PET/CT scans and the interval between the acquisition of these scans and simulation can vary from weeks to months. This investigation was performed to determine whether appropriately staged patients undergoing PET/CT simulations on a hybrid unit had either staging or treatment intent changes despite having PET/CT scans performed within the prior four months.
Methods: 115 consecutive patients were simulated on a dedicated PET/CT scanner between 4/29/09–2/15/11 with the intent of definitive treatment for non-metastatic, non-recurrent stage II-III NSCLC. All patients had accompanying diagnostic nuclear medicine interpretations. Of these, 42 patients had previous PET/CTs in the four months preceding simulation and all were appropriately staged without evidence of distant metastases. Patients were analyzed for change in stage and/or treatment intent and disease progression was defined as a change in TNM stage grouping. SUV velocity was defined as [(SUVscan2-SUVscan1)/ interscan interval]. Probability of upstaging as a function of interscan interval was performed using a non-parametric, right-censored distribution analysis plotted in the reverse Kaplan-Meier fashion. AJCC 2002 staging was used for all patients.
Results: A total of 42 patients were eligible for inclusion, of which 20 were males and 22 were females. The median age was 69. Overall, 20 of 42 patients (48%) were upstaged following treatment planning PET/CT. Twelve (29%) had evidence of new metastatic disease with the remaining 8 (19%) diagnosed with a change in T or N staging requiring alteration of treatment fields (i.e., new N2 or N3 disease). Ten patients (24%) were not treated with radiation and received systemic therapy alone. The median interval between scans for all patients was 45 days. At a scan interval of 30 days, the rate of upstaging was 10%. Further numerical analysis was performed with the Penn-only cohort of patients (n=11) scanned under identical conditions. Non-upstaged patients had a mean SUV velocity of 0.071 units/day compared to a SUV velocity of 0.14 in patients upstaged by their second PET/CT scan (p=0.011).
Conclusion: Radiation treatment planning with hybrid PET/CT scans repeated within 120 days of an initial staging PET/CT resulted in the identification of critical new findings. For a subset of patients who underwent both scans under identical conditions, upstaged patients had a significantly higher SUV velocity than patients who were not upstaged, which was statistically significant. Overall, 24% of patients had interval progression changing treatment intent from curative to palliative. Nearly one half progressed in N or M stage. Without the repeat PET/CT, a substantial proportion of patients may have received inappropriate treatment for metastatic disease. This study supports the notion that progression of disease may occur between the staging PET/CT and initiation of therapy with increasing interval from the scan. Therefore, clinicians should exercise caution when time to initiation of therapy is greater than 30 days from the staging PET/CT.
Keywords: PET/CT, treatment planning, Lung cancer, RADIATION

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P3.143 CHEMOTHERAPY VERSUS ERLOTINIB IN THE SECOND LINE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Modern treatment modalities in pneumooncology include „targeted therapy“of tyrosine kinase inhibitors, designed to block epidermal growth receptor (EGFR) initiation cascade. Erlotinib (Tarceva®) is EGFR tyrosine kinase inhibitor commonly used in clinical setting for the treatment of advanced non-small cell lung cancer (NSCLC). Presented study is directed on erlotinib and chemotherapy efficacy comparison in the second line treatment of advanced NSCLC.

Methods: We have analysed data from Tarceva register of advanced NSCLC patients, treated at the Department of Tuberculosis and Respiratory Diseases, Teaching Hospital in Pilsen. 290 patients were analysed. Population treated by chemotherapy in the second line and by erlotinib in the third line concerns 150 patients, 40 females and 110 males, 79 squamous cell carcinoma patients, 59 adenocarcinoma patients, 10 undifferentiated NSCLC patients, and 2 patients with nonspecified type of NSCLC, 138 patients with positive smoking history and 12 non-smokers. Population treated by erlotinib included 140 patients, 43 females and 97 males, 67 squamous cell carcinoma patients , 61 adenocarcinoma patients, 8 undifferentiated NSCLC patients and 4 nonspecified type of NSCLC patients, 107 patients with positive smoking history and 33 non-smokers.
Results: 2 patients treated by chemotherapy reached CR, 23 PR, 51 SD, 63 PD and response was not assessed for 11 patients, while from erlotinib treated patients, 5 reached CR, 10 PR, 55 SD, 58 PD and 12 patients were not asessed for treatment response. There was no statistically significant difference between the compared groups (p = 0.300). From 9 patients wih positive EGFR mutation treated by erlotinib, 4 patients had CR, 2 PR and 3 had SD. Chemotherapy treated patients reached median TTP of 2.1 months, median TTP for patients treated by erlotinib, without documented EGFR mutation (including patients not assessed for EGFR), was 1.9 months. The difference between compared arms was not statistically significant (p = 0.879). Patients with activating EGFR mutation treated by erlotinib had median TTP 8.4 months and the difference between the 2 previous groups was statistically significant (p = 0.027). Results of OS are currently under analysis and are not at disposal yet.
Conclusion: The results of our analysis demonstrate benefit of erlotinib treatment in the second line NSCLC treatment also for patients without documented activating EGFR mutation and the benefit is comparable with conventional chemotherapy treatment, which is associated with significantly higher risk of serious adverse reactions. The TTP comparison, as well as the analysis of best achieved response rate demonstrated significant benefit of erlotinib treatment for patients with positive EGFR mutation.
Keywords: EGFR-TKI, targeted therapy of NSCLC

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P3.144 ERLOTINIB POST-MARKET SURVEILLANCE STUDY IN A FRENCH ACADEMIC HOSPITAL

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Background: Lung cancer is the leading cause of death related to cancer in developed countries. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, has been authorized in treatment for non-small cell lung cancer (NSCLC) patients who have already had another chemotherapy. In France, 35% and 50% of NSCLC patients receive erlotinib in second or third line of treatment, respectively. In total, more than 10 000 new treatments with erlotinib are started each year in France.
Methods: We analysed retrospectively the first consecutive one hundred NSCLC patients treated with erlotinib in your academic hospital, located in the west of France.
Results: Between May 2005 and October 2007, erlotinib was prescribed to 80 men and 20 women with a NSCLC median diagnosis age of 61.1 and 60.3 years, respectively. During this period, none genetic analysis was available. Histology was adenocarcinoma/squamous carcinoma/large cell carcinoma in 52/33/15 cases. Erlotinib was started in 1st/2nd/3rd/4th/5th/6th line in 1/20/59/4/0/6 cases, respectively. Twenty patients received erlotinib with French 'Temporary Use Authorization'. Only 6 patients had no metastatic NSCLC at the erlotinib start. Median erlotinib therapy duration was 52 days. Six patients received erlotinib therapy longer than one year. The best therapeutic response according to RECIST 1.0 criteria was: partial response: 6%; stable disease: 12%; progressive disease: 53% and not evaluable: 29%. No complete response was observed. The most frequent side effects were: rash skin (40%), diarrhoea (23%), dry skin (11%) and nausea (7%).
Conclusion: This mono-centric post-market surveillance study reveals that erlotinib is usually used in 2nd and 3rd line in NSCLC patients in your hospital. Our results are compatible with other French post-market surveillance studies.
Keywords: Non-small cell lung cancer, post-market surveillance study, erlotinib

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.145 CARBOPLATIN-DOCETAXEL-BEVACIZUMAB (BVZ) AS FRONT-LINE TREATMENT IN PATIENTS (PTS) WITH STAGE IV NOSQUAMOUS NON SMALL CELL LUNG CANCER (NSCLC). A PHASE II STUDY.

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Oncologia, Fundacion Jimenez Diaz. Universidad Autonoma De Madrid/Spain

Background: BVZ added to carboplatin-paclitaxel has demonstrated to prolong overall survival in nonsquamous NSCLC. However, the combination of BVZ with carboplatin-docetaxel has not been widely explored. We have designed a phase II trial to study the efficacy and tolerability of this combination in this setting.
Methods: Pts were treated with up to 6 cycles of carboplatin (AUC 5), docetaxel (75 mg/m2), and BVZ (7.5 mg/kg) on day 1 every 21 days. Pts with an objective response or stable disease continued maintenance BVZ (7.5 mg/kg) every 21 days until disease progression. The primary endpoint was median progression-free survival. Secondary endpoints were safety, response rates, and overall survival.
Results: 26 pts were enrolled, 16 male and 10 female. Median age was 61 years (range 39-70); ECOG 0/1/2: 4%/77%/19%; 23 pts had adenocarcinoma and 3 pts undifferentiated large cell carcinoma. The median number of chemotherapy and maintenance BVZ cycles/patient was 6 (3-6) and 9 (3-19), respectively. All the pts were evaluable for efficacy and toxicity. In an intent to treat analysis the response rate was 57.7%, 30.8% of pts showed stable disease and 11.5% progression. Median progression free survival was 10 months (95% CI: 8 – 12 m) and median survival 19 months (95% C.I: 10 – 28 m). Grades 3-4 adverse events included neutropenia (15.3%), febrile neutropenia (7.69%), anemia (3.8%), mucositis (3.8%), diarrhea (3.8%), nausea/vomiting (3.8%).
Conclusion: Carboplatin, docetaxel, and BVZ demosntrated to be feasible and very effective as front-line treatment of stage IV nonsquamous NSCLC.
Keywords: Non small cell lung cancer, Carboplatin, Docetaxel, bevacizumab

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P3.146 A PHASE II STUDY OF ERLOTINIB IN JAPANESE EGFR MUTATION POSITIVE PATIENTS WITH PRETREATED NON-SMALL CELL LUNG CANCER (NSCLC):LUNG ONCOLOGY GROUP IN KYUSHU, JAPAN (LOGIK0803)

Kazuhiko Yamada[1], Satoru Kawakami[2], Kouichi Saruwatari[3], Ryotaro Morinaga[4], Miiru Izumi[5], Naoko Aragane[6], Shuya Nagata[7], Junji Kishimoto[8], Koichi Takayama[5], Yukito Ichinose[9]
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Background: It has been reported that erlotinib is useful for treatment of non-small cell lung cancer (NSCLC) in EGFR mutation positive (EGFR-mt) patients (SLCG NEJM 2009 OPTIMAL ESMO 2010). However, there is no study in the Japanese population. We conducted a multicenter Phase II study to evaluate the efficacy and safety of erlotinib in EGFR-mt Japanese patients with NSCLC.
Methods: For EGFR-TKI-naive EGFR-mt patients, erlotinib was administered at a daily dose of 150 mg. The primary endpoint was the overall response rate (ORR). The secondary endpoints included the disease control rate (DCR), progression-free survival (PFS) and safety.
Results: At 15 participating institutions, 26 patients were enrolled between April 2009 and January 2011. Demographic and baseline characteristics of patients were: median age 67 years (51 to 79 years); males/females 11/15; adenocarcinoma/others 24/2; smoking/nonsmoking 20/6; ECOG PS 0/1/2 15/9/2;

exon 19/21 19/7; and second/third treatment line 25/1. Thirteen patients were evaluable as of January 2011. The median duration of treatment was 301 days (range: 50 to 446). PR and SD were observed in 9 (70%) and 2 patients (15%), respectively. Of 11 patients with EGFR mutation in exon 19, PR, SD and PD were observed in 7, 2 and 2 patients, respectively. PR was observed in 2 patients with EGFR mutation in exon 21. Common adverse reactions included rash (92.3%), pruritus (76.9%) and hepatic function disorder (46.2%). Most of adverse reactions were grade 2, and tolerable in all patients. Neither interstitial lung disease nor treatment related death was observed.
Conclusion: This is the first prospective study of erlotinib performed in EGFR-mt Japanese NSCLC patients. The results were comparable to those obtained from studies of gefitinib (NEJ002 NEJM 2009 and WJTOG3405 2010). Currently, patients are under follow-up. Analysis of final results will be completed in June 2011. The presentation at this meeting will be done for results including PFS data.
Keywords: erlotinib, EGFR mutation, Non-small cell lung cancer

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P3.147 AZD0530, AN INHIBITOR OF SRC KINASES, IN PLATINUM-PRETREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A TRIAL OF THE PMH PHASE II CONSORTIUM.

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Background: Src kinases, overexpressed in many malignancies including NSCLC, may play an important role in tumour cell migration, invasion and metastases, and thus are potential therapeutic targets. AZD0530 (saracatanib) is an orally available small molecule inhibitor of Src kinases. Given the purported role of Src in the malignant phenotype, disease stabilization may more likely be observed than objective tumour response.
Methods: Eligibility: advanced recurrent NSCLC with at least stable disease after only one prior platinum-based regimen for advanced disease (adjuvant chemotherapy also permitted); age > 18; ECOG PS 0-2; no prior EGFR inhibitors; adequate organ function and no significant proteinuria; written informed consent. AZD0530 is administered at 175 mg po daily in 28-day cycles; response assessed by RECIST q2 cycles, toxicity by CTCAE v 3.0. Primary end point is the proportion of patients (pts) progression-free (PF) at the end of cycle 4. Two-stage design with H0 ≤ 15 % and H1 ≥ 35 %: if ≥ 3 of 17 PF at cycle 4, then go to stage II; accept as active if ≥ 8 of 32 PF. Levels of c-Src protein expression and activity on archival tissue will be correlated to outcomes.
Results: As of 01/11, 32 pts accrued: median age 65 (range 33-77), female = 24, PS 0/1 = 31. All 32 pts are evaluable for toxicity. The most common adverse events considered at least possibly related to study therapy were: fatigue (n=10; 2 gr3); nausea (n=11, 0 gr3); anorexia (n = 11, 0 gr3); diarrhea (n=9, 2 gr3); proteinuria (n=7, 1 gr3); anemia (n=9, 1 gr4); AST / ALT increase (n=7 each; 1 gr3 ALT). Three patients came off study prior to response assessment due to potentially-related toxicity: one each with gr4 gastrointestinal hemorrhage, gr3 pneumonitis and gr3 diarrhea; there were no gr5 toxicities. To date, 23 pts are evaluable for efficacy (2 too early, 3 off prior to cycle 4 due to pt request without progression, 3 off for toxicity, 1 pt ineligible as determined on pathology review to not have NSCLC). 5 / 23 pts were PF after 4 cycles; in two of these pts, confirmed partial responses were observed.
Conclusion: Stage II will continue until 32 response-evaluable pts accrued. Treatment with AZD0530 is generally well-tolerated. AZD0530 has shown preliminary interesting activity in pts with recurrent platinum-pretreated NSCLC, with 2 PR and several pts with prolonged stabilization of disease. Correlative studies on archival tissue will be available for presentation.
Keywords: src kinase inhibitor, non-small cell, Phase II

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P3.148 A RANDOMIZED PHASE 2 STUDY COMPARING MAINTENANCE PEMETREXED (PEM) PLUS BEST SUPPORTIVE CARE (BSC) VERSUS BSC ALONE FOLLOWING INDUCTION TREATMENT WITH PEM-CISPLATIN (CIS) IN ADVANCED NONSQUAMOUS (NONSQ) NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: In a previous phase III study among patients (pts) who had received 4 cycles of platinum-based chemotherapy, maintenance therapy with Pem resulted in improved progression-free survival (PFS) and overall survival (OS) when compared with placebo (Ciuleanu, Lancet, 2009). Prespecified histology subgroup analyses of the trial demonstrated that the benefit of Pem was limited to pts with Nonsq NSCLC (OS=15.5 m for Pem and 10.3 m for placebo in Nonsq group, P<0.001). We report the final results of a randomized phase II trial comparing maintenance Pem plus BSC versus BSC alone following 4 cycles of Pem-Cis induction therapy in advanced Nonsq NSCLC.
Methods: Pts with Stage IIIB/IV NSCLC and good performance status (ECOG PS 0 or 1) were included. In response to phase III trial data, in July 2008, a protocol amendment restricted enrollment and the primary analysis population to pts with predominantly Non-sq histology only. Induction treatment consisted of 4 cycles of Pem (500 mg/m^2) and Cis (75 mg/m2) repeated once every 3 weeks. Pts without disease progression were randomized to receive maintenance Pem (500 mg/m^2, repeated once every 3 weeks) plus BSC or BSC alone until disease progression. All pts received vitamin B_{12}, folic acid, and dexamethasone when receiving Pem. Primary endpoint was PFS from time of randomization and was analyzed using a Cox model stratified for response to induction at a one-sided alpha of 0.2.
Results: Between 1/2008 and 8/2009, 108 pts with Non-sq NSCLC were entered; 55 were randomized to maintenance treatment. The primary endpoint, PFS in the maintenance phase, was significant at the one-sided 0.2 alpha level (HR= 0.76; 95% CI: 0.42 - 1.37; p<0.2).
Conclusion: This phase II study met its primary endpoint of improved PFS. Induction Pem-Cis and maintenance Pem were well tolerated.
Keywords: NSCLC, Pemetrexed

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P3.149 PHASE II STUDY OF BEVACIZUMAB AND ERLOTINIB IN TREATMENT-NAïVE ELDERLY PATIENTS (> 65 YEARS OF AGE) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: The median age of newly diagnosed NSCLC patients (pts) in the US is 71 and more than 60% of newly diagnosed pts are 65 years of age or older. The 'fit elderly' (PS 0-1) derive the same level of benefit from systemic therapy as others, but with a lower tolerance for toxicities. Innovative treatment strategies with less toxicity are, therefore, needed. Our study explored the efficacy and tolerability of an 'all-biologic' therapy in treatment-naïve elderly pts

with advanced NSCLC.
Methods: Fit elderly pts (>65 years) with treatment-naïve stage IV or IIIB (malignant pleural effusion (MPE)) were treated with full dose erlotinib (150 mg/d) and bevacizumab (15 mg/kg Q 3 wks) in 21 day cycles. Progression Free Survival (PFS) was the primary endpoint. EGFR status was not required for enrollment. Imaging was performed every 2 cycles. Attributable grade 3 and 4 adverse events (AEs) were documented.
Results: Enrollment was completed between Aug. 2007 and Jan. 2011. Mature data are available for 26 of 33 patients accrued. Median age is 74 (range: 70-84). Sixteen pts (62%) have ECOG PS of 1. Seven pts have stage IIIB disease by the AJCC v. 6 criteria. Kaplan-Meier estimate of median time from starting therapy to going off protocol is 4.8 months (95% confidence interval = 1.7-14.9). Of the 20 pts now off protocol, the median number of cycles is 4 (range: 1-40). Six pts are currently on protocol, (range 4 to 33 cycles). Drug-related grade 3(G3) and 4(G4) AEs include hypertension (G3: 5 pts), fatigue (G3: 1 pt), rash (G3: 3 pts), diarrhea (2 G3 and 1 G4), anorexia (G3: 1 pt), infection with neutropenia (G3: 1 pt), bowel perforation (G3: 1 pt), abnormal protein/creatinine ratio (G3: 1 pt). Eight patients have had partial responses, thirteen stable and five progressive diseases. The estimated median PFS for all patients is 6.6 months (95% CI =3.6-14.9 months). Fourteen of 26 patients have died; estimated one year OS is 56.6% (95%CI=24.7-65.4%), and estimated median OS is 14.1mo (95%CI 6.2mo-undefined). Smoking and EGFR status data have been collected.
Conclusion: Our data suggest that a non-cytotoxic combination of erlotinib and bevacizumab is effective and well tolerated for the first-line management of elderly patients with advanced NSCLC. Correlation of outcome with EGFR and smoking status is pending.
Keywords: Lung cancer, erlotinib, bevacizumab, Elederly

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P3.150 SURVIVAL AFTER FAILURE OF FIRST LINE BEVACIZUMAB COMBINATION THERAPY IN NON SMALL CELL LUNG CANCER PATIENTS.

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Background: Preclinical data suggests rapid regrowth of tumor vasculature following cessation of bevacizumab (bev) therapy which may lead to accelerated tumor growth. This may result in a shorter overall survival following discontinuation of 1st line bev containing regimen.
Methods: We investigated the effect of bev therapy in the first line setting on post bev survival (PBS) in patients (pts) treated for metastatic NSCLC at our institution, we calculated PBS of all pts who received bev in the first line setting for the diagnosis of NSCLC from January 2006 until February of 2011 and compared it to the published OS of the two arms of the TAX-317 study. TAX-317 was chosen because it predated the Bev era and gave us a good estimate of OS following failure of 1st line therapy with and without second line therapy. OS as calculated in TAX-317 is comparable to the PBS endpoint of our study. PBS was calculated from the time bev was discontinued until death.
Results: Bev was prescribed for 106 pts. 50 pts met our inclusion criteria of receiving more than one dose of bev in the first line setting only. The median PBS for pts receiving 2nd line therapy beyond first line bev containing therapy (36 pts, group 1) was 12.9 months (CI 7.4-18.8). The lowest confidence interval (CI) limit of 7.4 is within the CI limits of the median OS for pts treated with 2nd line Docetaxel in TAX-317. The median PBS for pts not receiving therapy beyond 1st line bev therapy (14 pts, group 2) was 4.9 months (CI 1.1-13.4).

	Median	95% CI
Group 1	12.9	7.4-18.9
Tax-317 Docetaxel arm	7	5.5-9.0
Group 2	4.9	1.1-13.4
Tax-317 BSC arm	4.6	3.7-6.0

Conclusion: The results of our retrospective analysis show no apparent detriment to survival post cessation of bevacizumab.
Keywords: NSCLC, bevacizumab

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P3.151 PHASE 1B RESULTS OF C-MET INHIBITOR TIVANTINIB (ARQ 197) IN COMBINATION WITH GEMCITABINE (GEM) IN A COHORT OF PATIENTS (PTS) WITH ADVANCED THORACIC TUMORS.

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Background: ARQ 197 is an oral, selective, non-ATP competitive inhibitor of c-MET. In vitro data suggest its synergy with Gem in several tumor cell lines. This Phase 1b study evaluates safety, pharmacokinetics (PK), biomarkers, and preliminary efficacy of the combination of tivantinib with Gem in pts with advanced solid tumors. Here we present results in the cohort of pts with thoracic tumors.
Methods: Multi-center, Phase 1b 3+3 dose escalation trial. Oral tivantinib was administered at doses of 120-360 mg bid across different schedules (continuous vs. continuous with 1 week (wk) break every 2 or 3 wks) in combination with fixed Gem dosing and frequency (1000 mg/m2/weekly 3 out of 4 wks). Tumor assessments occurred every 8 weeks.
Results: As of January 28, 2011, a total of 7 pts with thoracic tumors were enrolled, including 6 with Non Small Cell Lung Cancer (4 adenocarcinoma, 2 squamous) and 1 with squamous head/neck carcinoma (ECOG 1; mean age 61 yrs, range 40-77 yrs; with median number of prior systemic therapies 3 [1-4]). All pts were Gem-naÃ¯ve. Adverse events (AEs) considered at least possibly treatment-related were reported in 6 pts. The most commonly observed (>30%) AEs in this patient population include neutropenia (6pts; 4 were G3-4), nausea (5 pts, no G3-4), fatigue (4 pts; 2 were G3-4), thrombocytopenia (3 pts; 1 was G3). Two pts experienced treatment-related serious AEs (pneumonitis, stomach angiodysplasia). Five pts remained on study for >12 wks (median 13; range 6-64), 4 are ongoing. Six pts are evaluable for post-baseline tumor assessment (assessments occur every 8 weeks). Four pts (3/3 lung adenocarcinoma, 1 head/neck) attained partial response while on study with mean tumor shrinkage 44% (31-71%), and median duration 12 weeks (8+ to 56). Details on efficacy and scheduling will be presented.
Conclusion: Orally administered tivantinib at the MTD of 360 mg bid in combination with Gem is generally well tolerated and shows encouraging signs of antitumor activity in lung and head/neck cancer.
Keywords: c-Met, targeted therapy, phase 1

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P3.152 IMPACT OF PROLONGED CHEMOTHERAPY EXPOSURE ON METASTATIC NON-SMALL CELL LUNG CANCER SURVIVAL: BENEFITS OF SECOND-LINE AND EXTENDED FIRST-LINE.

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Background: The optimal duration of chemotherapy (CT) remains an open question in metastatic non-small cell lung cancer (NSCLC), and a metanalysis suggested a minor survival benefit from extended CT. Moreover, maintenance and early second-line CT are now acceptable options in this setting, while second-line treatment demonstrated proven impact in phase III trials. Our group therefore evaluated the concept of prolonged CT exposure in a real-world scenario.
Methods: Medical charts from patients with metastatic NSCLC treated in a private oncologic center in Brazil between 1999 to 2010 were retrospectively reviewed. The aim was to assess the impact of extended chemotherapy - defined as more than 4 cycles in the first-line - and of multiple lines of treatment. Altogether, the prolonged CT exposure was evaluated as a prognostic factor, comprising extended first-line and subsequent lines of therapy. Statistical analyses were performed using the SPSS 17.0 software.
Results: Two-hundred thirty-nine patients were included. Median age was 63.1 years (range 27.7-

85.9). Most patients presented with advanced disease (80% frequency for stage IV / wet IIIB), 18% were never-smokers, and adenocarcinoma was the most frequent histology (50%). Twenty-nine percent of patients received more than 4 cycles of first-line CT, and 7% received more than 6 cycles. Second-line CT was used in 46%, while third-line was in 15%. After 11 months median follow-up, the median overall survival was 11.6 months (95% CI, 9.1-14.2). Patients treated with more than 4 cycles in the first-line presented longer overall survival (median 21.4 [95% CI, 17.1-25.8] vs 7.7 months [95% CI, 5.8-9.6]; P=.0001), which was corroborated in patients receiving more than 6 cycles (median 26.7 [95% CI, 5.8-9.6] vs 9.7 months; P=.003). Second-line CT was strongly correlated with higher survival (median 16.4 [95% CI, 13.7-19.2] vs 6.3 months [95% CI, 4.7-8.0]; P=.0001), as well as third-line (median 22.7 [95% CI, 15.8-29.6] vs 9.0 months [95% CI, 7.6-10.5]; P=.002). Notably, patients receiving both extended first-line and subsequent second-line CT achieved the greatest benefit from these strategies (median survival 21.5 [95% CI, 17.2-25.7] vs 8.4 months [95% CI, 7.2-9.5]; P=.0001). In the multivariate analysis, receiving more than 4 cycles in the first-line (HR 0.52; 95% CI, 0.29-0.94; P=.02) and the use of second-line CT (HR 0.37; 95% CI, 0.22-0.63; P=.0001) were considered independent prognostic factors. Current or former smoking status (HR 2.6; 95% CI, 1.10-6.00; P=.01) and weight loss (HR 2.2; 95% CI, 1.30-3.72; P=.003) were other independent factors.

Conclusion: Patients submitted to prolonged CT exposure demonstrated a significant and independent survival benefit in comparison to patients with lower CT exposure length. These data support the concept of prolonged treatment in metastatic NSCLC, both in the first- and second-line.

Keywords: Lung neoplasms, Chemotherapy, maintenance, Second-line

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P3.153 PROGNOSTIC FACTORS OF LEPTOMENINGEAL CARCINOMATOSIS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: As the patients with metastatic NSCLC survived longer, the incidence of leptomeningeal carcinomatosis(LC) has increased. However, the clinical features and prognostic factors of LC in NSCLC patients have not been well identified. The aim of this study was to identify the clinical features and prognostic factors of NSCLC patients with LC.

Methods: 149 NSCLC patients who had a diagnosis of cytologically proven LC between 2000 and 2008 at Samsung Medical center were retrospectively reviewed.

Results: The median age was 58 years (range, 34-80). Most of the patients (135, 95%) had adenocarcinoma histology. During median follow-up duration of 34 months, median overall survival from diagnosis of LC was 14 weeks (95% C.I ; 12-16). Univariate analysis revealed that good performance status (ECOG PS <2), high glucose, low protein and low WBC of initial spinal fluid, intrathecal (IT) chemotherapy and systemic chemotherapy were positive predictor for overall survival. At multivariate analysis, good PS (p=0.007), low protein (p=0.002), low WBC (p=0.014), IT chemotherapy (p<0.001) and systemic chemotherapy (p<0.001) remained as significant good prognostic factors for survival.

Conclusion: Even though the prognosis of LC from NSCLC is poor, small subsets of these patients survive longer. So, patients with good PS, low protein and WBC of initial spinal fluid need to be treated actively with IT and systemic chemotherapy.

Keywords: prognostic factors, Non-small cell lung cancer, leptomeningeal carcinomatosis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.154 WT1 AND MUC1-PULSED DENDRITIC CELL VACCINATION THERAPY FOR NON-SMALL-CELL LUNG CANCER

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Background: Dendritic cell (DC)-based immunotherapy has been recognized as limited clinical success of cancer vaccination with few adverse reactions. To overcome the problem of cancer vaccination treatment, both WT1 and MUC1 peptides, the most potent cancer associated antigens, applied on DC-based immunotherapy could be potentially strong therapeutic strategy against cancers.
Methods: Clinical investigation of WT1 and MUC1-pulsed DC vaccination therapy was conducted for primary endpoint as safety with the efficacy being a secondary endpoint in cancer patients approved. Patients who underwent intractable for a standard operation, radiotherapy, chemotherapy against non-small cell cancer (NSCLC) met the inclusion criteria: advanced cancer with clinical stage III or IV disease at the diagnosis; recurrence of cancer after standard treatment; progressive disease resistant to chemotherapy. Both WT1 for HLA-A*2402 or A*0201 typing and MUC1 peptides-pulsed DC vaccinations were manufactured from autologous aphaeresis monocytes ex vivo at Shinshu University Hospital following the SOP established by tella, Inc. (Tokyo, Japan). 1-2x10^7 of mature DC harboring WT1 and MUC1 peptides were performed intradermal (i.d.) injection at axillar and inguinal areas together with tolerable 1 to 5KE/dose of OK-432 every 2 weeks for at least 5 to 7 times (one course) during individual chemotherapy regimen.
Results: 9 patients, median age of 60 years old (range 34 to 67), 6 male and 3 female were enrolled. 7 patients had adenocarcinoma, 1 had squamous cell carcinoma, and 1 had non-classified NSCLC. Stage IIIA/IIIB/IV was 1/1/7, respectively. Performance status 0/1/2/3 was 1/5/2/1, respectively. DC vaccinations were administered 1 to 31 times (average was 9 times). 6 patients were evaluated according to the RECIST after completing at least one course of DC vaccination. 1 patient achieved partial response and 1 was stable disease, resulted in 17 % of response rate and 33% of disease control rate, respectively. Median survival time from start of DC vaccination therapy was 174 days. 43% of the patients showed temporal fever due to DC and/or OK-432 at grade 1 to 2 toxicity. All of the patients revealed erythema with or without induration at the sites of i.d. DC.
Conclusion: Case series of WT1 and MUC1-pulsed DC vaccination therapy suggested a feasible, well-tolerable, and might provide an alternative treatment option for advanced NSCLC patients.
Keywords: NSCLC, DC, WT1

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P3.155 THE OUTCOME OF THE ADVANCED NON-SMALL CELL LUNG CANCER TREATMENT USING STANDARD DOUBLETS OUTSIDE OF CLINICAL TRIALS.

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Background: Among patients with locally advanced or disseminated non-small lung cancer not eligible for radical radiochemotherapy, chemotherapy is a standard treatment modality. Only patients with good performance status without additional severe comorbidities can be treated within clinical trials. Patients not eligible for clinical trials are treated accordingly to standards and financial means of particular country. Palliative chemiotherapeutic regimens can be divided into first-line, second-line and third-line settings. Palliative chemotherapy has been used long enough that its effectiveness can be a valuable database for comparison with nowadays more widely used targeted chemotherapies.
Methods: It is a retrospective analysis of group of patients treated outside clinical trials between September 2006 and September 2010 in Clinical Oncology Unit in Oncology Centre, accordingly to contemporary chemotherapy standards. Criteria by which data were evaluated were: sex, histological type of tumor, chemotherapy regimen, number of chemotherapy lines and overall survival time.

Results: A total of 390 patients were treated with palliative chemotherapy - among them were 103 women and 287 men. Of those 109 (27,9%) had been evaluated as a locally advanced disease and were not candidates for radical R-CHTH treatment. 281 patients (72%) had disseminated disease at a time of diagnosis. Histological subtypes of NSLC were: squamous cell lung carcinoma and adenocarcinoma in 118 (30,2%) and 98 patients (25,1%) respectively. The rest of 174 patients had been diagnosed by usage of fine-needle biopsy as a non-small lung cancer without additional pathological subtype specification. All patients had good performance status (PS 0 - 2), all of them had some cardiovascular issues, only few were not tobacco users. All patients received at least one line of chemotherapy, mainly platinum-based regimens. Used chemotherapy schedules were: cisplatin/vinorelbine (129 patients - 33,1%), carboplatin/vinorelbine (126 - 32,3%), carboplatin/gemcytabine (48 - 12,3%), cisplatin/gemcytabine (44 - 11,2%), paclitaxel/cisplatin (30 - 7,7%), docetaxel/cisplatin (9 - 2,3%), pemetrexed (4 - 1%). 57 patients (15%) received only 1 or 2 courses of chemotherapy because of disease progression or rapid deterioration in general condition. 105 patients (27,9%) received second-line therapy - among used schedules were docetaxel in monotherapy (46 patients - 11,8%), pemetrexed (7 - 1,8%), erlotinib (6 - 1,5%) and 46 patients (11,8%) again received platinum-based agent. In third-line chemotherapy, administered to 23 patients (5,9%), pemetrexed or erlotinib were used. Median survival time was 11,98 months. One third (34,27%) of patients did not survive more than 5 months from the beginning of treatment. It is a group of patients who did not receive more than 2 courses of chemotherapy because of disease progression. Long-time survival rate (more than 24 months) was noted in 47 patients (12%).
Conclusion: Demonstrated results seem to support usefulness of usage of palliative chemotherapy among patients with advanced non-small lung cancer. Our results are consistent with the observations reported in other publications.
Keywords: non-small lung cancer, advenced non-small lung cancer, Chemotherapy, Overall survival

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.156 PRELIMINARY RESULTS OF INDUCTION CISPLATIN/DOCETAXEL FOLLOWED BY SHORT COURSE THORACIC RADIOTHERAPY AND CISPLATIN/DOCETAXEL OF CONSOLIDATION IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A PROSPECTIVE PHASE II TRIAL.

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Background: Standard fractionated radiotherapy combined with concomitant radiosensitive chemotherapy represents standard treatment for locally advanced (LA) Non-Small Cell Lung Cancer (NSCLC). 3-Dimensional-Hypofractionated Accelerated Radiotherapy (3D-HAR) delivered by helical tomotherapy may improve local control disease and reduce the duration and incidence of side effects due to radiotherapic treatment. In our ongoing phase II prospective trial full dose chemotherapy is combined with 3D-HAR for treatment of LA-NSCLC to verify their activity and tolerance.
Methods: Patients with biopsy proven involvement of 3 or more ipsi- or controlateral mediastinal lymph nodes (N) or with radiological evidence of mediastinal infiltration were treated with induction chemotherapy with Cisplatin (75 mg/m^2; day 1 every 21 days) combined to Docetaxel (75 mg/m^2; day 1 every 21 days) for 2 courses followed by 3D-HAR (30 Gy in 5 fractions at the reference isodose) and afterword 2 courses of consolidation chemotherapy with Cisplatin (75 mg/m^2; day 1 every 21 days) combined to Docetaxel (60 mg/m^2; day 1 every 21 days). All patients performed a total-body CT scan and a PET/CT-scan of staging and restaging. Hence a bronchoscopy was performed at staging, at the end of radiotherapy and at treatment completion.
Results: From December 2008 to December 2010, 16 patients were analyzed of whom 3 (19%) females and 13 (81%) males with a median age of 60 years (range: 44 – 70) and with adenocarcinoma in 10

(63%) patients and squamous cell carcinoma in 6 (37%) patients. Pathological mediastinal lymph nodes involvement (pN) were documented in 10 (63%) patients, whereas radiological mediastinal infiltration of disease was detected in 10 (63%) patients. Overall there were 3 (19%) stage IIIA disease and 13 (81%) stage IIIB disease; side disease was left in 6 (37%) patients and right in 10 (63%) patients. Overall 57 courses of chemotherapy were infused (range: 1 – 4). One patient stopped treatment after first course of induction chemotherapy for the onset of grade 4 apiretic neutropenia and hypovolemic shock due to grade 3 vomiting; one patient interrupted treatment after first course of consolidation chemotherapy for the onset deep venous thrombosis with worsening of clinical performance status. Overall only one patient did not performed 3D-HAR for treatment interruption after first course of induction chemotherapy. Hematologic grade 3/4 toxicity was mainly neutropenia occurred in 13 (81%) patients and corrected with the use of granulocyte colony stimulating factors. Non-hematologic grade 3/4 toxicities were represented by: diarrhea in 1 (6%) patient, asthenia in 1 (6%) patient and nausea/vomiting in 3 (19%) patients of whom one with hypovolemic shock successfully corrected with intravenous hydration. No grade 3/4 toxicities related to radiotherapy was recorded.
Conclusion: Our preliminary results of prospective phase II trial using 3D-HAR combined with induction and consolidation full dose chemotherapy with Cisplatin and Docetaxel seems to be well tolerated without severe side effects in thorax; the grade 3/4 side effects recorded were related to systemic toxicity and they have been successfully treated. We are waiting adequate follow-up for the efficacy analysis. Supported by GIPO.
Keywords: short course thoracic radiotherapy, induction Cisplatin/Docetaxel

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P3.157 COST-EFFECTIVENESS OF FIRST LINE TYROSINE KINASE INHIBITOR TREATMENT IN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATED ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS : A MARKOV MODEL

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Background: EGFR testing and first line tyrosine kinase inhibitor (TKI) for patients with activating mutations is an option for the treatment of advanced non-small cell lung cancer. There is few data's on the cost-effectiveness of this strategy. The objective of this study was to determine the incremental cost-effectiveness ratio of first-line treatment with TKI compared to recommended chemotherapy (cisplatin pemetrexed doublet) in patients with EGFR mutation.
Methods: A Markov model was developed. The model used clinical outcome and cost data from randomized clinical trials or prospective French cohort and utility scores derived from published data's. Costs were limited to direct costs for medications, physician visits, hospitalizations and treatment of adverse events. Analysis was limited to the period between initiation of treatment until first progression. All costs and cost-effectiveness ratios were expressed in 2010 Euro. Sensitivity analyses were performed.
Results: First line treatment with TKI was more effective than recommended chemotherapy (respectively 0.716 and 0.422 QALY), but also more expensive (respectively 29 702 and 18 796 per patient). The incremental cost-effectiveness ratio was then estimated at 37 095 €/QALY. Sensitivity analyses showed the robustness of the results.
Conclusion: Based on these data, first line treatment based on TKI appeared as cost effective in EFGR mutated advanced NSCLC patients.
Keywords: EGFR mutation, Cost-effectiveness, TKI, FIRST LINE

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P3.158 FIRST-LINE ERLOTINIB IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) CARRYING AN ACTIVATING EGFR MUTATION: A MULTICENTRE ACADEMIC PHASE II STUDY IN BELGIUM

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Background: Compared to chemotherapy, 1st line treatment with EGFR-TK inhibitors results in superior progression-free survival (PFS) in patients with advanced NSCLC with activating EGFR TK domain mutations. We conducted a prospective study with 1st line erlotinib in Belgian pts with EGFR TK domain mutations.

Methods: Multicentre phase II study. EGFR mutation status was determined in a central lab on macro-dissected biopsies obtained from pts with advanced adenocarcinoma with a non- or past smoking history. Pts were given erlotinib, 150 mg daily till disease progression or prohibitive toxicity. The primary end point of the study was a 70% PFS at 3 months.

Results: An EGFR mutation was found in 64 (28%) of 247 pts screened. Eighteen pts did not enter the study because of deterioration, withholding of consent after mutation analysis, or failing other clinical selection criteria. Forty six pts (8 male, 38 female) with median age of 72 years (35-83), median performance status of 1 (1-3) stage distribution Ib (1), IIIb (4) and IV (41) patients were included. EGFR mutations found: exon 18 (1), exon 19 (27), exon 20 (3) and exon 21 (15). Smoking history: 38 never smokers, 7 past smokers, 1 smoker. Median follow-up is 83 weeks. PFS was 83 % at 3 months and 74% at 6 months. Best response was: PR 26; SD 10, PD 10. The median time to progression and overall survival are not reached: 44+ and 56+ weeks respectively. One patient ended treatment prematurely because of skin toxicity while in PR for 83+ wks.

Conclusion: In this first formal prospective phase II genotype based study with erlotinib in first-line treatment of Caucasian pts with EGFR mutant advanced NSCLC, efficacy appears similar to the results obtained with gefitinib and erlotinib in randomized studies involving Asian patients and other first-line data with erlotinib. The study achieved its primary end point (PFS ≥ 70% at 3 months). The wider genotyping of the screened population and genotypic-clinical correlations will be presented.

Keywords: erlotinib, non-small lung cancer, EGFR mutation, Phase II

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P3.159 LONG-TERM SURVIVAL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND SYNCHRONOUS BRAIN METASTASIS TREATED WITH WHOLE-BRAIN RADIOTHERAPY AND THORACIC CHEMORADIATION

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Background: Brain metastases occur in 30% to 50% of patients with non-small cell lung cancer (NSCLC)

and confer a worse prognosis and quality of life. These patients are usually treated with whole brain radiotherapy (WBRT) followed by systemic therapy. Few studies have evaluated the role of chemoradiotherapy to the primary tumor after WBRT as definitive treatment in the management of patients with NCSLC with isolated synchronous brain metastasis.

Methods: We reviewed the outcome of 30 patients with primary NSCLC and synchronous brain metastasis at diagnosis without evidence of other sites of metastatic disease. Patients were treated with WBRT and induction chemotherapy with paclitaxel and cisplatin for two cycles. In the absence of progression, concurrent chemoradiotherapy for the primary tumor with weekly paclitaxel and carboplatin was indicated, with a total effective dose (BED) of 60 Gy. If disease progression was ruled out, four chemotherapy cycles followed

Results: Median progression-free survival (PFS) and overall survival (OS) were 8.43 ±1.5 and 31.8 ±15.8 months, respectively. PFS was 39.5% at 1 year and 24.7% at 2 years. The 1- and 2-year OS rates were 71.1% and 60.2%, respectively. Three-year OS was significantly superior for patients with N0-N1 stage disease vs. N2-N3 (60% vs. 24%, respectively, RR 0.03, p=0.038).

Conclusion: Patients with NSCLC and synchronous brain metastasis might benefit from treatment with WBRT and concurrent chemoradiotherapy to the primary lesion. The subgroup of patients with N0-N1 stage seems to achieve the greatest benefit. The result of this study warrants a prospective trial in stage IV disease with only brain metastasis to confirm the benefit of this treatment.

Keywords: NSCLC, Non-small cell lung cancer, synchronous brain metastases, definitive chemoradiotherapy

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P3.160 THE ROLE OF REGULATOR AND EFFECTOR T LYMPHOCYTES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND LUNG CANCER

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Background: The anticancer immunresponse may determine the outcome of lung caner. Few data are available on how effector T, NK cells and various regulatory subsets like Treg-s (foxp3+), or NK T-s respond to lung cancer (LC) or cancer treatment.

Methods: Blood was drawn from 28 pts (age 44 to 82, males12, females 16) suffering from non-small cell lung cancer (NSCLC, n=22) or small cell lung cancer (SCLC, n=6). Since 60% of LC pts also suffered from chronic obstructive pulmonary disease (COPD), one control group was formed from COPD pts (n=28) and another one from healthy individuals (n=28). Peripheral blood mononuclear cells were separated and analyzed by FACS using labeled monoclonal antibodies

Results: Activated effector T cells were determined by CD4CD45RO and CD8CD45RO positivity, the naive T cells were specified by CD4CD45RA and CD8CD45RA positivity, and the regulatory T lymphocytes by CD8FoxP3 positivity. The NKT cells were defined by Va24Vb11 (iNKT) and CD161CD3 (NKT) markers. In lung cancer pts, the ratio of activated CD4+ effector T cells was increased and the ratio of naiv CD4+ lymphocytes was decreased, as compared to COPD or healthy groups (p<0,05). In the CD8+ subgroup, the decrease of the number of naiv T cells was observed. The ratio of regulatory T lymphocytes (CD8+FoxP3+) was significantly elevated in lung cancer pts when compared with COPD and healthy groups (p<0,001). The numbers of iNKT and NKT cells decreased in COPD and this reached the level of lung cancer pts, and healthy control. The level of lymphocytes subpopulations did not changed after chemotheraphy

Conclusion: There was an important change of T lymphocytes subsets in lung cancer, as effectors, CD4 cells activated, naiv, CD8 cells diminished and regulatory, suppressive T cells increased. The NKT cells also activated in COPD, but their effectivity changed in lung cancer.

Keyword: lung cancer, regulatory T cells, naive T cells

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P3.161 SEQUENTIAL CHEMOTHERAPY WITH CISPLATIN PLUS VINORELBINE FOLLOWED BY WEEKLY DOCETAXEL IN LOCALLY ADVANCED OR METASTATIC NON SMALL-CELL LUNG CANCER: PRELIMINARY RESULTS

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Background: The use of platinum-based therapy prolonged survival in patients with NSCLC. A platinum-based doublet with a third-generation agent (vinorelbine, gemcitabine, paclitaxel, docetaxel) represents the standard first-line treatment for advanced NSCLC with good performance status. Traditional chemotherapy provides response rates of 20-40% and a median survival of 8-10 months. In an attempt to improve outcome, alternative schedules have been proposed, namely sequential, alternating, and maintenance/consolidation therapy. Sequential chemotherapy with a platinum-based doublet followed by a single agent is feasible in patients with a good PS. In our previous study, the planned sequential administration of GEM and VNR in elderly patients with locally advanced or metastatic NSCLC, suggests that the TTP may be increased with the use of the 2 single agents.
Methods: On the grounds of these data we designed a phase II study on sequential strategy using weekly docetaxel (D) (35 mg/sm day 1 and 8 every 3 weeks) given after 3 courses of cisplatin (75 mg/sm/iv day 1) and vinorelbine (25 mg/sm/iv day 1 and 60 mg/sm/ os day 8) (PV) every 3 weeks as first-line treatment in patients with locally advanced, unresectable, or metastatic NSCLC. The treatment was continued until disease progression. All patients were restaged after every three courses by CT-scan.
Results: Thirty-six patients were enrolled from November 2008 to December 2010: 24 males and 12 females, median age 62 years (range: 37-69), median PS 90% (range: 60-100), 7 stage IIIB and 29 stage IV (11 pts with brain mets.), histology: 12 squamous and 24 non-squamous. At the moment all the patients are evaluable for toxicity and 33 for response. The overall best objective response was 17 (51.5%) partial response, 11 (33.3%) stable disease and 5 (15.15%) progressive disease. Toxicity was mild, the main side-effect during PV was myelotoxicity, GIII-IV neutropenia occurring in 11%. Median TTP was 21 weeks (range: 1-91 weeks).
Conclusion: Sequential administration of cisplatin plus vinorelbine followed by weekly docetaxel in first-line treatment of advanced NSCLC was feasible, with high antitumor response and favorable toxicity profile. The study is ongoing.
Keywords: Advanced NSCLC, sequential chemotherapy

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P3.162 CLINICAL OUTCOMES FOR SPECIAL POPULATIONS OF PATIENTS WITH NON-SQUAMOUS NON-SMALL CELL LUNG CACER TREATED WITH FIRST LINE BEVACIZUMAB-BASED THERAPY IN AN OBSERVATIONAL STUDY (AVVA)

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Background: More than 50% of cases of advanced NSCLC are diagnosed in patients (p) older than 65 years. Furthermore, the majority of p with NSCLC present at the time of the diagnosis one or more comorbidities. Both subgroups are often under-represented in clinical trials based on perceptions that they do not wish for and/or cannot tolerate active systemic therapy.
Methods: AVVA is a multicenter, observational study in p with advanced non-squamous NSCLC (stage IIIB non candidates for radiotherapy or IV) treated with first-line bevacizumab-based regimen. A sub-analysis according to age 65 years or older and at least 1 comorbid condition was performed.

Preliminary results are presented.
Results: A total of 148 p were evaluated. Median age 57.5 (50-64) years; male 64%; tumor histology: 77% adenocarcinoma, 14% large-cell carcinoma; disease stage IV/IIIB 93%/7%; ECOG 0/1/2 37%/56%/7%. 24% of patients were 65 years or older and 64% of p presented at least 1 comorbid condition at baseline, being the most frequent HTN (19%), Dyslipidemia (16%), DM (12%), CVD (7%) and COPD (6%). Commonly used first-line chemotherapy (CT) regimens in combination with bevacizumab were carboplatin doublets in 71% of p and cisplatin doublets in 26%. In the whole population (n=148) median number cycles received was 6 and 8 for CT and bevacizumab respectively. Median PFS was 7.6 months (95%CI: 7.2-8.0) and DCR 85%. In patients 65 years or older (n=35) median no. of cycles was 6 for both CT and bevacizumab, PFS 6.6 months (95%CI:5.0-8.2) and DCR 85.6%. In patients with at least one morbid condition (n=95), median number of cycles received was 6 and 8 for CT and bevacizumab respectively, median PFS was 7.4 (6.3-8.2) and DCR 84.1%. The main grade (g) 3 or greater toxicity was DVT in 2.7% of p. The incidence of g3 or greater AEs of special interest were: hemoptysis 1%, proteinuria 1%, HTN 0%, thromboembolism 1%. DVT (2%) was the only g3 or greater AE reported in elderly p. In p with at least one comorbidity, DVT (3%), neutropenia (1%) and infection (1%) were the only g3 or greater AEs reported.
Conclusion: First-line bevacizumab-based therapy was effective and safe in older p and p with at least one comorbid condition. No new safety signals have been indentified and efficacy results match with previously reported data.
Keywords: NSCLC, first-line, bevacizumab, special populations

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P3.163 DAY CASE CISPLATIN DELIVERY FOR ADVANCED NSCLC PATIENTS: FASTER, CHEAPER, MORE DESIRABLE

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Background: The BTOG2 trial is a large phase III randomised clinical trial which investigated the optimal dose of cisplatin (50 versus 80 mg/m^2 3-weekly), in combination with gemcitabine, and whether carboplatin (AUC6-Wright) could safely and effectively be substituted for the optimal cisplatin dose in the treatment of advanced NSCLC. The protocol recommended that cisplatin would be given as an out-patient regimen, designed to ensure diuresis whilst maintaining electrolytic balance. A previously reported audit by these authors found that almost half (48%) of hospitals surveyed were admitting NSCLC patients, often overnight for cisplatin /gemcitabine chemotherapy delivery.
Methods: Between April 2005 and November 2009, 909 patients were randomised to receive cisplatin, in the UK and Eire, from 78 centres. Adverse event (AE) data was also collated as a secondary endpoint. The trial mandated submission of proposed chemotherapy delivery schedules and changes were required if necessary to reduce total duration of delivery, mandatory use of mannitol, short 1 hr delivery of cisplatin and decreasing of total fliud volume delivered to < 4 L. Data mining was used to investigate those AEs relating to renal function. In addition, data was examined for the worst reported serum creatinine values for each cycle.
Results: 2853 treatment cycles were available for analysis. The average duration of treatment duration decreased from nearly 9 to 6 hours and total volume of fluid delivered decreased from as much as 7 to less than 4 litres. These changes meant the rate of outpatient delivery of cisplatin increased from 48 to 97%. Toxicities feasibly related to the manner in which cisplatin was administered were comparable to the current available literature with < <1% experiencing grade >2. This concurred with the variation in serum creatinine throughout the treatment phase which showed <2% of patients with levels >160umol/L. When monitored as a time series on a patient by patient basis a slightly greater number (~4%) showed a increases from their own baseline serum creatinine levels of above 1.5 times, at some point throughout their treatment. Dehydration and electrolyte disturbances such as hypomagnesaemia, hypokalaemia and hypophosphataemia were each experienced by <2% of patients.
Conclusion: As a result of participating in BTOG2 97% of surveyed hospitals were able to deliver cisplatin in a day case setting. The perverse incentives of the current NHS Tariffs in the UK quote a higher price of almost 60% for patients

being admitted for cisplatin treatment as opposed to receiving it as an outpatient. With the prima facie case that patients prefer outpatient treatment over being admitted, it is important to achieve the maximum benefit from the existing drugs in a clinically deliverable way. The results indicate that administering cisplatin via a short hydration schedule of < 6 hours, even at 80 mg/m^2, is safe. If all currently delivered in-patient cisplatin is switched to outpatient treatment not only will patients benefit but costs will fall. It is unlikely that the many hospitals who changed their practice would have done so without the support of a running RCT. This is yet another unrecognised benefit of RCTs.

Keywords: BTOG2, Cisplatin, Hydration

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P3.164 EVALUATION OF THE FORMULA DEVELOPED BY THE JAPAN SOCIETY OF NEPHROLOGY FOR ESTIMATING RENAL FUNCTION OF PATIENTS WITH LUNG CANCER TREATED WITH CARBOPLATIN CONTAINING CHEMOTHERAPY.

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Background: The Calvert formula is routinely applied for the dosing of carboplatin based on glomerular filtration rate (GFR) as accurately measured using the 51-Cr-EDTA clearance. In general practice, an estimated value of creatinine clearance calculated by the Cockcroft-Gault formula is widely used as a substitution of the GFR. It is reported that there is ethnic difference in renal function and that decrease of GFR by aging is less in Japanese than Caucasian. In 2008, the project of Japan Society of Nephrology developed the following formula for calculation of GFR fitting to Japanese patients: GFR (ml/min/1.73m^2)= 194×Serum creatinine $^{-1.094}$×Age$^{-0.287}$ (×0.739, if female)
Methods: The aim of this study is to evaluate the efficacy of new estimating method of renal function for Japanese patients with lung cancer. Consecutive patients treated with carboplatin containing chemotherapy were examined. Dose of carboplatin were determined by the Calvert formula with target AUC of 5 and GFR calculated by the equation described above. Relationship between adverse effects and clinical features were analyzed.
Results: A total of 34 patients (male 22/female 12) were included. The number of patients received each chemotherapy were 15 for carboplatin/gemcitabine 6 for carboplatin/paclitaxel, 1 for carboplatin/docetaxel and 7 for carboplatin/pemetrexed. The mean count of neutrophil cyte and platelet at nadir was 1377±1160/μl and 12.3±6.8×10^4/μl respectively. One patient experienced severe thrombocytopenia requiring a blood transfusion, however the hematological toxicity of the others were mild. There were no correlation between hematological toxicity and clinical values including renal function, age, sex and body surface area.
Conclusion: The newly developed formula is effective to compensate inter-patient variability including age, sex and renal function in Japanese patients treated by carboplatin. Ethnic difference including renal function should be taken into consideration for personalized dosing.

Keywords: renal function, Carboplatin, personalize dosing, Calvert formula

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P3.165 DELIVERED DOSE INTENSITY OF GEMCITABINE 1250MG/M2 WITH CISPLATIN AT 80MG/M2 (GC80) AND 50MG/M2 (GC50) AND CARBOPLATIN AUC 6 (GCB6) IN A PHASE III TRIAL OF ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): CORRELATIONS WITH CLINICAL OUTCOMES

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Background: All drugs, including chemotherapy agents have dose-related effectiveness. For chemotherapy this is referred to as dose-intensity and is usually expressed as dose per unit of time. Drugs such as platins adduct DNA by zero order kinetics, thus the amount of DNA adduction is proportionate to dose. The key clinical question is whether this translates into superior meaningful clinical outcomes such as response rate and survival. Answering these key questions was the rationale behind choosing to compare two dose of cisplatin and a highest dose possible of carboplatin in the BTOG2 trial. In this large phase III trial supported by the British Thoracic Oncology Group patients with advanced non-small cell lung cancer were randomised to receive gemcitabine (1250 mg/m^2 on day 1 and 8) with either cisplatin at 80mg/^{2} or cisplatin at 50mg/m^2 or carboplatin AUC6. The protocol specified planned doses and durations of chemotherapy but in reality treatment delays and dose reductions due to toxicity mean that patients do not actually receive planned treatments. The BTOG2 trial provides an opportunity to investigate the delivered dose intensity (DDI) of these treatments in a large group of patients.
Methods: Carboplatin dose was calculated using the Calvert equation, incorporating estimated GFR based on the Wright equation including creatinine kinase. Dose intensity, response and toxicity were important secondary outcome measures in the trial contributing to the interpretation of the results of the primary outcome measure, overall survival time. Delivered dose intensity (DDI) for each patient was calculated as the mean of the per-cycle DDI which is the ratio of the delivered versus planned dose per day, calculated for platinum and gemcitabine separately.
Results: Starting doses for cycle 1 were generally as per protocol with 95% of GC80 starting on doses >75mg/m^2, 97% on GC50 >45mg/m^2 and 93% of GCb6 >AUC5. Doses of carboplatin are higher using estimated GFR from the novel Wright formula compared to standard Cockcroft-Gault approach. Dose reductions on cycles 2-4 were more apparent for GC80 compared to GC50 (56% vs 42% of patients experienced at least one dose reduction). The dose delivered still remained high with reductions to median dose of 77mg/m^2 by cycle 4. Dose reduction rate was highest on GCb6 with 71% of patients experiencing at least one reduction, with median dose of AUC 4.5 at cycle 4. Gemcitabine dose reductions paralleled those seen with platins, occurring more frequently with GCb6. Overall DDI for platinum was high for all treatments but lowest for GCb6 (96% vs 99% vs 87%) and reduced across all cycles for GC80 and GCb6. Response rates were GC50 23%, GC80 33% and GCb6 28%. There was no evidence that dose reductions, treatment delays or DDI was associated with response thus the delivered dose of GC80 was sufficient to generate this 10% difference.
Conclusion: Doses of cisplatin at 80mg/m^2 and carboplatin at AUC6 based on the Wright formula in combination with gemcitabine are deliverable but individuals have higher chance of treatment delays and dose reductions. However the reduced DDI does not appear to have an effect on clinical outcomes.
Keywords: BTOG2, Dose Intensity, NSCLC

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.166 LONG TERM ERLOTINIB RESPONDERS –CHARACTERISTICS OF NSCLC PATIENTS WITH A PROGRESSION FREE SURVIVAL OF MORE THAN 1 YEAR.

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Background: Erlotinib used in second or following lines for advanced NSCLC yields modest increase in progression free survival (PFS) compared to placebo (Schiller 2005).However, some patients experience

long PFS, some of these due to presence of EGFR mutations. We studied clinical parameters in a cohort of NSCLC patients with a PFS ≥1 year who were not examined for EGR expression or EGFR mutations.
Methods: Advanced disease NSCLC patients who received erlotinib treatment were identified and those with a PFS ≥1 year were included. Testing for EGFR mutations or EGF expression were not part of clinical practice during study period. Patients characteristics and treatment outcome was registered from patients records.
Results: A total of 46 patients from 5 hospitals fulfilled the inclusion criteria. None had known activating mutations in the EGF receptor. The majority of patients (70%) had received prior platinum based doublet chemotherapy. All were caucasians, with the following characteristics: Males (37%), age>75 years (46%), Squamous cell carcinoma (7% of patients), active smoker (11%), ECOG Performance Status 3 (9%), previous radiotherapy (28%), erlotinib as 2nd-4th line (70%). Rash appeared in 89% (grade 1, 2, and 3 in 30%, 48%, and 11%, respectively) and diarrhea in 59% (grades 1, 2, and 3 in 33%, 20%, and 4%, respectively). There were no difference in occurrence of rash between patients ≤75 years and >75years being 88% and 90 %, respectively, while frequencies of diarrhea were 72% and 43%, respectively (not significant (ns)). There were 13% partial and 2% complete responses overall, while response rates among patients ≤75 years and >75years were 12% and 19%, respectively (ns). Mean response duration was 85+ weeks. 22% are still on erlotinib treatment while 61% had progressed after mean of 91 weeks. Other reasons for discontinuation were side effects (7% overall, 4% in age ≤75 years, and 10% in age >75 years (ns)) and various other reasons (9%).
Conclusion: Long term PFS in excess of 1 year is possible with erlotinib both for patients having squamous cell carcinoma, performance status 3, advanced age >75 years, and for active smokers. Also heavily pretreated patients receiving erlotinib as 3rd or 4th line treatment are observed to achieve PFS ≥1 year. In this long-treated patient population age had no major impact on toxicity though with a non-significant trend towards less diarrheafewer diarrheas in elderly patients. Erlotinib may be a valid treatment choice for a wide range of clinical scenarios offering a possibility for long-term PFS in some patients.
Keywords: Targeted treatment, erlotinib, long-time responders, Advanced NSCLC

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P3.167 ADVERSE EVENTS AND PATTERNS OF TUMOR PROGRESSION IN MET DIAGNOSTIC SUBGROUPS IN OAM4558G; A PHASE II STUDY EVALUATING METMAB OR PLACEBO IN COMBINATION WITH ERLOTINIB IN ADVANCED NSCLC

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Background: MetMAb (M) is a monovalent monoclonal antibody that blocks HGF-induced Met signalling. A Phase II double-blinded, randomized trial of MetMAb+erlotinib (M+E) or placebo+erlotinib (P+E) in 2nd- and /3rd- line NSCLC has been recently completed. The M+E arm demonstrated both PFS and OS advantages in the c-Met IHC expression-positive 2+ /3+ (Met Dx+) patients only.
Methods: Adverse events (AEs) were assessed for relationship to MetMAb in the patients in different diagnostic groups. Tumor growth rate and onset of new lesions were also examined in order to understand their potential contribution to the clinical outcomes.
Results: In the M+E arm, median cycles of M were higher in Met Dx+ vs. Met Dx- pts (4 vs. 2) as were median E doses (61 vs. 42 respectively). The overall pattern of AEs was similar in the two treatment arms, with the exception of peripheral edema, which was higher in M+E treated patients regardless of c-Met

expression levels. Time to onset of any Grade ³3 AE in M+E treated patients was also similar across groups. In the Met Dx- group, Grade ≥3 AEs on M+E were higher than on P+E (56% vs. 35%), but the rate was similar to that observed for Met Dx+ pts on M+E (57%) or P+E (53%). The number of AEs leading to death was highest in Met Dx- pts on M+E (n=5), whereas the number of AEs leading to treatment discontinuation was highest in Met Dx+ pts on M+E (n=6); no consistent patterns were observed for either. The rate of tumor growth was not significantly different between treatment arms or Met sub groups. 55% of Met Dx+ pts progressed with new lesions vs 43% of Met Dx- (P+E), but the addition of M had no effect on this rate. The power to detect a difference is limited by the number of subjects in the study, i.e., 65 with Met Dx+ (35 on M+E and 30 on P+E) and 56 with Met Dx- (27 on M+E and 29 on P+E).
Conclusion: Combination with MetMAb did not appear to substantially alter the safety profile of erlotinib and differences in AEs do not clearly explain the PFS and OS outcomes observed in Met Dx subgroups on M+E. Furthermore, the addition of M to E in Met Dx- patients did not appear to alter tumor growth rates or patterns of disease progression
Keywords: NSCLC, cMet, MetMAb, erlotinib

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P3.168 TOLERANCE AND EFFICACY OF PEMETREXED-CISPLATIN FOR ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER A GALICIAN LUNG CANCER GROUP STUDY

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Background: Advanced stage non-small cell lung cancer (NSCLC) represents a 80% all lung cancer. Recently a noninferiority phase III study was proved that in adenocarcinoma and large-cell carcinoma histology advanced NSCLC, cisplatin/pemetrexed provides better efficacy than cisplatin/gemcitabine. This was the first prospective phase III study in NSCLC to show survival differences based on histologic type. We conducted a multicenter study in advanced NSCLC to evaluate the tolerance and efficacy of first-line pemetrexed-cisplatin in non-epidermoid carcinoma.
Methods: Patients with advanced NSCLC and non-epidermoid carcinoma received pemetrexed (500 mg/m2 day 1) and cisplatin (75 mg/m2 day 1) every 21 days (PC) with restaging after 3 and 6 cycles. The primary end point was to evaluate the overall response rate.
Results: Ninety-four patients with non-squamous carcinoma were accrued from seven centers across Galicia. Overall response rate was 42.9% (1.4% of complete response and 41.4% of partial response). Median overall survival was 12.6 months (95% confidence interval, 6.76 to 18.43); progression-free survival was 4.17 months (95% conficence interval, 3.3 to 5). The treatment was well tolerated, with the most common treatment-related side effects being grade 1 and 2 asthenia (58.55%), anemia (44.94%) and nausea (30.34%). Grade 3 and/or 4 toxic reactions were neutropenia (7.86%, 4.49% with fever), vomiting (5.62%), anemia, nausea and asthenia (2.25%).
Conclusion: Combination with pemetrexed-cisplatin is well tolerated and has activity in advanced adenocarcinoma and large-cell carcinoma lung cancer, as previous publications have demostrated.
Keyword: pemetrexed, cisplatin, non-squamous

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P3.169 DOES A HISTORY OF TOBACCO CHEWING IMPACT THE RESPONSE TO GEFITINIB?

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Background: Response and clinical outcome following therapy with an EGFR tyrosine kinase inhibitor is markedly different in smokers as compared to never-smokers. There is some evidence that tobacco chewing increases the risk for lung cancer, although the degree of risk as compared to cigarette smoking is unknown. There is no data as to the incidence of EGFR-activating mutations in patients with a history of tobacco chewing and the activity of EGFR-TKIs in this patient population. We evaluated the efficacy of Gefitinib in patients with adenocarcinoma of the lung, who were non-smokers, but had a history of tobacco-chewing and the incidence of EGFR-mutations in this population of patients.
Methods: An audit of all patients in the thoracic medical oncology OPD at Tata Memorial Hospital, with adenocarcinoma lung, who were started on Gefitinib over the preceeding 6 months, was done. All patients who were never-smokers were included in the analysis and a history of tobacco chewing was elicited. Baseline imaging (CT scan or PET/CT scan) was performed and Gefitinib 250mg orally once daily was prescribed. Clinical evaluation was done monthly and repeat imaging was done every 2 months. QOL questionnaire was collected every two months. Analysis was done with simple percentages. EGFR mutation analysis is being done on the paraffin blocks with direct sequencing.
Results: Of a total of 74 patients started on Gefitinib, 59 were never-smokers (25 males and 34 females). Of the 25 males who were never-smokers, 8 were tobacco-chewers and 17 were non-smokers and non-tobacco-chewers. Of the 34 females who were never-smokers, 4 were tobacco-chewers and 30 were non-smokers and non-tobacco-chewers. Thus, there were a total of 12 patients who were never-smokers, but were tobacco-chewers, and a total of 47 patients who were never-smokers and non-tobacco-chewers. The response rate to Gefitinib assessed at 2 months follow-up, in patients who were never-smokers and non-tobacco users was 28% (13/47), with a disease stabilization rate of 28% (13/47). In patients who were never-smokers, but had a history of tobacco-chewing, the response rate to Gefitinib assessed at 2 months, was 33% (4/12) and the stable disease rate was 62.5% (5/12). The median followup is 2 months. Followup is too short to assess survival results at present
Conclusion: A history of tobacco chewing does not appear to adversely impact the response rate to EGFR TKI compounds. The number of patients who are non-smokers, but are tobacco-chewers is small. Data regarding the EGFR mutation analysis in tobacco chewers will be presented at the meeting.
Keywords: gefitinib, NSCLC, tobacco chewing

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P3.170 BIWEEKLY DOCETAXEL-CISPLATIN IN CHEMO-NAïVE PATIENTS WITH ADVANCED SQUAMOUS CARCINOMA OF THE LUNG: A GALICIAN LUNG CANCER GROUP PHASE II STUDY

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Background: Advanced stage non-small cell lung cancer (NSCLC) represents a 80% all lung cancer. Schemes of polychemotherapy have meant a small improvement in overall survival and quality of life. We conducted a multicenter study in advanced stage squamous NSCLC to evaluate the efficacy of first-line biweekly docetaxel-cisplatin.
Methods: Patients with advanced NSCLC and epidermoid histology received biweekly docetaxel (50 mg/m2 days 1, 14) and cisplatin (50 mg/m2 days 1,14) every 28 days (DC) with restaging after 3 and 4 cycles. The primary end point was to evaluate the

progression-free survival.
Results: Forty-five patients with epidermoid carcinoma were accrued from six centers across Galicia. Overall response rates were 45.9%, all them had a partial response. Median overall survival was 12.6 months (95% confidence interval, 10 to 15.2); progression-free survival was 4.7 months (95% confidence interval, 3.9 to 5.5). The treatment was well tolerated, with the most common treatment-related side effects being grade 1 anemia (48.8%), asthenia (32.5%), nausea (30.2%) and anorexia (27.91%). Grade 3 and/or 4 toxic reactions were neutropenia (20.9%, 11.6% with fever), diarrhea (4.6%), mucositis and neuropathy (2.3% both).
Conclusion: Biweekly docetaxel-cisplatin is active and well tolerated in patients with advanced stage squamous NSCLC.
Keyword: non-squamous, cisplatin, docetaxel

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P3.171 CLINICAL CRITERIA THAT EXCLUDE METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS FROM PARTICIPATING IN CLINICAL TRIALS: RETROSPECTIVE ANALYSES IN A COMMUNITY-BASED HOSPITAL

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Background: Clinical trials are one of the cornerstones of clinical research and have been increasingly incorporated into our daily clinical practice. Nevertheless, we noticed poor accrual into some of these trials. To identify which factors excluded patients from participating in clinical trials, we retrospectively studied all stage IV NSCLC patients submitted in the past four years to one of our lung cancer units.
Methods: NSCLC patients submitted from January 2007 to December 2010 were identified from the lung cancer registry and the basic clinical data were analysed. The most common mandatory exclusion criteria in first-line chemotherapy trials were used to elaborate the results.
Results: A total of 182 patients with stage IV disease susceptible of analysis were examined: 155 males and 27 females, with a median age of 65 years (range: 36-84). The following table displays the breakdown of exclusion criteria, indicating the number and percentage of patients potentially eligible for accrual after applying them successively:

EXCLUSION CRITERIA	Nº (%)	Nº REMAINING (%)
Other malignancies within 5 years	20 (11%)	162 (89%)
ECOG 2-4	78 (43%)	84 (46%)
Intracranial metastases at diagnosis	17 (9%)	67 (37%)
*Tumour tissue sample not available	16 (9%)	51 (28%)

*Diagnosis was cytology-based or formalin-fixed, paraffin-embedded tumour tissue sample was not available

Conclusion: In our community-based hospital, a significant percentage of stage IV NSCLC patients have clinical characteristics that preclude them from participating in clinical trials, mainly due to poor performance status. Patient accrued in most clinical trials may not reflect the patient distribution in the community. More trials are needed in the group of patients with poor PS and unfavorable clinical characteristics.

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P3.172 LONG TERM SURVIVORS WITH ADVANCED NSCLC TREATED WITH ERLOTINIB: THE IMPORTANCE OF RASH

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Background: At present there are two main objectives in treating patients with advanced NSCLC: life prolongation and control of symptoms. Erlotinib has an established role in both of them. Here we focus on the first one; we present the characteristics of long term survivors treated with erlotinib.
Methods: Between 2007 and 2009, 189 patients with

stage IIIB/IV NSCLC were treated at our Institute, of whom 57 (30.1%) survived more than a year after starting treatment with erlotinib. Patents received erlotinib until disease progression or unacceptable toxicity. We collected data on their characteristics, response to therapy, toxicity profile and outcome.
Results: The average age of long term survivors was 62.7 years (range 36-81), 34 (59.6%) were females and 37 (65%) patients were in good condition (ECOG performance status 0 or 1); the remaining had PS 2 or 3. 28 (49.1%) were former or current smokers, other 29 (50.9%) were non smokers. With 51 cases (89.5%), adenocarcinoma was the prevailing histologic type; squamous, large cell and NSCLC unspecified accounted for 2 (3.5%) each. EGFR mutational analysis was not performed before the beginning of therapy, because the testing was not available. All patients received a standard dose of erlotinib (150 mg/day); half of them received it in the first, 30% in the second, 2% in third line and 7% as mainteinance therapy. Six patients (10.5%) received erlotinib intermittently with gemcitabine/cisplatin chemotherapy as part of an ongoing clinical trial. All patients developed rash (24.6% CTC grade I, 43.9% grade II, 29.8% grade III, and one patient grade IV). Diarrhoea was present in 33% of patients, 5 patients had paronichia and 2 had conjunctivitis (all grade I or II). Because of intolerable side effects dose lowering was necessary in 12 (21%) and treatment was discontinued in 5 (8.7%) patients. Response to erlotinib therapy was complete remission in 5 (8.8%), partial remission in 31 (54.4%) and stable disease in 21 (36.8%) of patients. Median PFS and OS from the start of erlotinib therapy were 17 months (C.I.10.5-23.4) and 26 months (C.I. 22-29.9) respectively.
Conclusion: Long term survivors do not differ much in their clinical characteristics from other patients with advanced NSCLC treated with erlotinib, except for the frequency of rash. In the analysis that we performed on all 189 patients that received erlotinib, only half of them developed rash and a third developed rash grade II or III, while in the group of long term survivors all developed rash and in two thirds of them rash was grade II or III. Development of rash may possibly predict long-term survival in advanced NSCLC treated with erlotinib.
Keywords: rash, NSCLC, long term survivors, erlotinib

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P3.173 INDIVIDUALIZED CHEMOTHERAPY (CT) IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: A possible way to improve the treatment efficacy of advanced NSCLC lies in preliminary selection of patients for individualized CT using objective prognostic criteria for tumor susceptibility to current antineoplastic chemicals. This study was aimed at comparative assessment of CT efficacy between the standard regimen and an individual choice of effective cytostatics in patients with NSCLC.
Methods: From December 2005 till November 2010, 46 patients with NSCLC were examined (mean age 58): squamous cell - 24 pts (IIIA- 3 pts, IIIB - 18 pts, IV - 3 pts), adenocarcinoma - 22 pts (IIIA - 1 pt, IIIB - 17 pts, IV - 4 pts). Prior to the CT course, patient's blood was tested in vitro response for cytostatics in different doses (Etoposide 80-100-120 mg/m^2, Cisplatinum 50-75-100 mg/m^2, Carboplatinum 250-350-450 mg/m^2, Doxorubicin 30-50-70 mg/m^2, Mitomycin C 3-6-9 mg/m^2, Gemcitabine 800-1000-1200 mg/m^2, Vinorelbine 20-30 mg/m^2, etc.). The response was evaluated based on the dynamics of thiol-disulfide ratios (TDR) in blood in vitro. This method included whole blood incubation with various cytostatics in aliquots corresponding to different therapeutic doses, five determinations of TDR in blood (before and in the process of 24-hour incubation), and then a selection of one or several optimal agents from those tested. The CT regimen in the study group (n = 23) was based on a combination of 2-3 cytostatics, with susceptibility to them being tested preliminary using TDR. In the control group (n = 23), the empirical standard regimen CT (EP, EPD, GP, VP, EMP, etc.) was used.
Results: Objective responses following 2 CT courses were obtained in 7 (30%) pts in the study group

[(PR - 7 (30%) pts, SD - 14 (61%) pts, PD - 2 (9% pts] versus 4 (17%) pts in the control group [(PR - 4 (17%) pts, SD - 9 (40%) pts, PD - 10 (43%) pts]. Subsequently, the patients continued to receive the repeated courses of CT with 4-8 week intervals depending upon clinical necessity and tolerance. An average number of courses administered made up to 8 (in a range of 4 to 10) in the study group and 5 courses (in a range of 3 to 8) in the control group. In the study group, median survival was 2, 1 times as long (20, 6 months versus 9, 8 months in the control group).

Conclusion - Results: Objective responses following 2 CT courses were obtained in 7 (30%) pts in the study group [(PR - 7 (30%) pts, SD - 14 (61%) pts, PD - 2 (9% pts] versus 4 (17%) pts in the control group [(PR - 4 (17%) pts, SD - 9 (40%) pts, PD - 10 (43%) pts]. Subsequently, the patients continued to receive the repeated courses of CT with 4-8 week intervals depending upon clinical necessity and tolerance. An average number of courses administered made up to 8 (in a range of 4 to 10) in the study group and 5 courses (in a range of 3 to 8) in the control group. In the study group, median survival was 2, 1 times as long (20, 6 months versus 9, 8 months in the control group).

Keyword: Individualized, Chemotherapy, NSCLC,

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P3.174 EFFECT OF GEFITINIB ON CLINICALLY SELECTED NON-SMALL CELL LUNG CANCER AND EGFR MUTATION RATE – EXPERIENCE FROM A SINGLE CENTER FROM INDIA

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Background: Gefitinib is an important drug in the management of NSCLC. It has been found to be effective in patients who are clinically selected. It has better activity in patients with EGFR mutations. It is commonly used in patients in first and second line setting. We retrospectively analyzed our prospectively collected data to assess the efficacy and safety of gefitinib in these patients. Mutation analysis was done on the paraffin blocks available by direct sequencing.

Methods: The record of patients receiving Gefitinib was retrieved from the data entry done prospectively. Source document of these patients were the hospital file. These patients received Gefitinib treatment for the NSCLC. Patients were followed up every 2 months with scan, clinically and QOL to assess the efficacy. Patients were also evaluated for side effects. Skin side effects and loose motions were specially documented. Scan was evaluated by radiologist who was designated for the same.

Results: There were 54 patients who received Gefitinib. There were 31 females and 23 males. Median age was 54 (range 30-80 years). Response rate was evaluated in all 54 patients. 17/54 patients had PR, 18/54 had stable disease and rest of them had progressive disease at 2 months. 12/31 females had partial response, 10/31 females had stable disease. 5/23 male patients had PR, 8/23 had stable disease and rest had progressive disease. 25/54 patients had skin side effects. Rash: 9/25, Itching: 1/25, Abscess: 2/25, Boils on Face or Skin : 2/25, Blackish Discoloration of skin : 3/25, Rash + Itching : 6/25, Pustules + Boils on legs : 1/25, Skin Ulcers : 1 /25. Diarrhea occurred in 2/54 patients.6 patients had interruption in taking Gefitinib because of skin toxicity. 1 patient had to permanently stop due to skin toxicity. In patients with skin toxicity 10/25 patients had PR. We will be presenting EGFR mutation data at the time of presentation.

Conclusion: Gefitinib is an effective drug in the management of NSCLC. Clinically selected patients benefit more with this drug. Skin toxicity correlates with the response rate.

Keywords: NSCLC, non-smoker, gefitinib

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.175 PREDICTION OF TREATMENT RESPONSE TO EGFR TYROSINE KINASE INHIBITORS BY DIRECT SEQUENCING METHOD FOR EGFR MUTATION IN NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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Background: It has been proven that non-small cell lung cancers with epidermal growth factor receptor (EGFR) mutation are highly sensitive to EGFR-tyrosine kinase inhibitors (TKIs). Direct sequencing is known to be the standard for detecting EGFR mutations, however it has limited sensitivity. This retrospective study was aimed to evaluate predictive value of direct EGFR sequencing for the treatment response to EGFR-TKIs in a university affiliated hospital.
Methods: Direct EGFR sequencing from exon 18 to 21 of EGFR was done in 89 paraffin-embedded nonsquamous non-small cell lung cancer biopsy specimens without a tumor cell-enrichment procedure. The associations of the clinicopathologic features and EGFR genotypes were analyzed. If the patients were treated by EGFR-TKIs during their clinical courses, the clinical outcomes were assessed according to the EGFR genotypes.
Results: The analyzed cases were composed of 81 (91.0%) adenocarcinomas, 2 (2.2%) large cell carcinomas, and 6 (6.7%) unspecified non-small cell carcinomas. The EGFR mutation rate was 29.2%. The mutation rates were significantly different according to sex (40.0% in female vs. 18.2% in male, p=0.024) and smoking status (42.3% in non- or light smoker vs. 10.8% of heavy smoker, p=0.001). EGFR-TKIs were administered to 42 patients, and the response could be evaluated in 36 patients (24 patients treated with gefitinib 250mg/day and 12 patients with erlotinib 150mg/day). The response rates were significantly different depending on the EGFR genotypes (54.5% in mutant EGFR vs. 20.0% in wild type EGFR, p=0.038). The disease control rate was 72.7% vs. 28.0% (mutant vs. wild type EGFR, p=0.012). The progression free survival of EGFR-TKIs treatment was 8.3 months vs. 1.4 months (mutant vs. wild type EGFR, p=0.020). There was no significant difference in response rate between gefitinib and erlotinib treatment groups (33.3% vs. 25.0%, p=0.609). 45.5% of the EGFR-TKIs responders had been reported to have wild type EGFR by the direct sequencing method.
Conclusion: EGFR mutations guaranteed the good clinical outcomes during the treatment of EGFR-TKIs. However, 20% of non-squamous non-small cell lung cancer patients with wild type EGFR decided by direct sequencing method responded to EGFR-TKIs. Therefore, clinical decision making whether to administer the drugs based on the mutation test result should be very cautious if the test, such as direct DNA sequencing, has limited sensitivity.
Keywords: Non-small cell lung cancer, EGFR, Sequencing

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P3.176 THE INFLUENCE OF GASTRIC SECRETION INHIBITORS ON GEFITINIB THERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Gefitinib is orally available, selective EGFR tyrosine kinase inhibitor used in patients with non-small cell lung cancer (NSCLC), especially harboring EGFR activating mutations. Pharmacokinetic study revealed absorption of gefitinib was affected by the pH in stomach. However, cancer patients in advanced stage are frequently administered gastric secretion inhibitors, such as proton pump inhibitors (PPIs) and H2 blockers (H2Bs). We hypothesized that gastric secretion inhibitors might suppress the efficacy of gefitinib therapy. We studied the influence of PPIs/H2Bs on the efficacy of gefitinib therapy in patients with NSCLC.
Methods: From Apr 2004 to Aug 2009, 100 patients with NSCLC received gefitinib in our hospital. We retrospectively analyzed the correlation between use of PPIs/H2Bs and efficacy or toxicity of gefitinib therapy.
Results: 65%(65/100) patients who received

gefitinib administered PPIs/H2Bs simultaneously. Patients with PPIs/H2Bs(PPIs/H2Bs group) had similar response rate compared with patients without PPIs/H2Bs(non PPIs/H2Bs group) (55.4% vs 40.0%, p=0.09). We observed similar disease control rate in each group(66.2% vs 60.0%, p=0.47). Progression free survival (144days vs 101days, Log-rank test p=0.687) and overall survival (555days vs 857, Log-rank test p=0.435) were similar between two groups. Interstitial lung disease(ILD) occurred more frequently in non PPIs/H2Bs group (4.6 vs 20%, p=0.03).

Conclusion: Gastric secretion inhibitors didn't affect the efficacy of gefitinib treatment. ILD occurred more frequently in non PPIs/H2Bs group. We speculate the correlation between development of ILD and blood concentration of gefitinib.

Keywords: gefitinib, gastric secretion inhibitors

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P3.177 PROSPECTIVE OBSERVATIONAL COMPARISON OF OUTCOMES IN AFRICAN AMERICAN AND CAUCASIAN PATIENTS RECEIVING SECOND-LINE TREATMENT WITH PEMETREXED FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Few prospective studies have evaluated the impact of race and ethnicity on clinical outcomes, during lung cancer treatment. This prospective observational study evaluated the impact of ethnicity on disease control rate (DCR) in patients (pts) with NSCLC treated with second-line pemetrexed (P).

Methods: Eligibility criteria included stage IIIB or IV NSCLC pts receiving single-agent P for second-line therapy in routine clinical practice. Sites were selected to ensure high minority representation. Due to persistent challenges in achieving desired enrollment of Hispanic and Asian pts, the focus of the study was narrowed to a comparison of pts self-reporting as Caucasian (C) and African American (AA). This report describes findings regarding the primary endpoint of the study, DCR. Some pts remain under observation—full characterization of survival will be available in early 2011. Non-inferiority was evaluated using logistic regression analysis for DCR controlling for predefined covariates: age, gender, income, marital status, insurance type, smoking status, ECOG performance score, disease stage, histology, comorbidities, time from end of first-line until initiation with P, prior exposure to first-line platinum, first-line paclitaxel, and number of first-line cycles. The DCR of AAs was considered non-inferior to Cs if the upper 95% confidence bound on the adjusted odds ratio (OR) for Cs vs AAs was less than 1.78, corresponding to a difference in proportion of 14% assuming Cs to have a DCR of approximately 50%. The bound was chosen to be one-half of the anticipated difference between treatment and no second-line treatment.

Results: The unadjusted DCR was 43.4% (116/267) for C and 45.8% (27/59) for AA (unadjusted OR=0.91). The adjusted OR for the comparison of C to AA in the final logistic regression model was 0.79 (95% CI, 0.41, 1.51). This upper 95% confidence bound was within the pre-specified acceptable bound of 1.78.

Conclusion: Based on pre-specified analyses, DCR of AAs was non-inferior to Cs. Hence, ethnicity is not considered a significant predictor of disease control following second-line treatment with P.

Keywords: Pemetrexed, NSCLC

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P3.178 COMPARISON OF 2ND LINE TREATMENTS FOR NON SMALL CELL LUNG CANCER AT THE EXETER ONCOLOGY CENTRE

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Background: In the UK last year there were 40860 new cases of Non Small Cell Lung Cancer representing a significant proportion of the cancers

treated at the Exeter Oncology Centre. In 2008 the National Institute for Clinical Excellence (NICE) in the UK recommended Erlotinib as an alternative to Docetaxel chemotherapy as second line treatment for patients with NSCLC. We present a review of 105 patients initiated on Docetaxol and Erlotinib over a three year period (2007- 2010) at the Exeter Oncology Centre.

Methods: Patients receiving Docetaxol or Erlotinib outside a clinical trial were identified through chemotherapy records. Notes were reviewed retrospectively. Data were collected on age, gender, histology, smoking status, duration of treatment, reasons for stopping treatment, toxicities and survival from time of diagnosis.

Results: 105 patients receiving either Docetaxol or Erlotinib were identified. 35 patients received Docetaxol and 70 patients received Erlotinib. In the Docetaxol group 13 patients (37%) were female and 22 patients (62%) were male. Of the 70 patients in the Erlotinib group 37 (52.9%) were female and 33 (47.1%) male. Median age was similar in both groups. Following NICE recommendations in 2008 the total number of patients receiving 2nd line treatment for NSCLC increased by 70% due to a large rise in patients commenced on Erlotinib. Pre 2008 23 patients received Docetaxol and 16 patients received Erlotinib. Post 2008 12 patients received Docetaxol and 54 received Erlotinib. Mean duration of Docetaxol treatment was 54 days (3 weekly cycles). Mean duration of Erlotinib treatment was 72 days. Median survival from diagnosis was 20 months in patients receiving Docetaxol and 13 months for patients receiving Erlotinib. However in this sample size the survival difference was not statistically different. The above figures and data on histology are summarised in the table below and will be updated prior to presentation.

	Docetaxol	Erlotinib	Total
Population	35	70	105
Pre NICE recommendation	23	16	39
Post NICE recommendation	12	54	66
Adenocarcinoma	13	45	58
Squamous Cell	13	11	24
NSCLC NOS	9	14	23
Median Duration of treatment (Days)	54	72	
Median Survival from initial diagnosis (months)	20	13	

Conclusion: We found that in our series overall survival was good in both groups. The 2008 NICE recommendation of Erlotinib as an alternative agent has enabled a larger number of patients to receive 2nd line therapy for NSCLC. Erlotinib is now increasingly prescribed due to its ease of administration, efficacy and good toxicity profile. However Docetaxol continues to be used with a positive effect on survival, particularly for patients with squamous cell carcinoma.

Keywords: Non small cell lung cancer, erlotinib, Docetaxol

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P3.179 REAL LIFE OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN 1ST LINE NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): A EUROPEAN PILOT STUDY ANALYSING BEVACIZUMAB-BASED VERSUS NON-BEVACIZUMAB-BASED TREATMENTS

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Background: Bevacizumab has been used in first line NSCLC in Europe since its regulatory approval in 2007 and has demonstrated significantly improved overall survival and/or progression free survival in two randomized phase III trials. However, HRQoL outcomes have not been reported and real life outcomes have been assessed only in the US. Objectives: To investigate, in two European countries, the Time to Progression (TTP) and the comparative HRQoL of patients receiving bevacizumab-based therapy versus non-bevacizumab-based therapy in 1st line non-squamous NSCLC.

Methods: Data were drawn from the Adelphi NSCLC Disease Specific Programme, a large cross-sectional study of patients in France and Germany in 2010. Physicians provided retrospective information regarding disease status and treatment patterns. TTP

was defined as time from start of treatment to physician-reported disease progression or two weeks before the start of second-line therapy. A log rank test was applied to test for differences between the two comparison groups. Cox Proportional Hazard Models were fitted to the data. Sensitivity analyses were run to analyse if age was a prognostic factor for treatment benefit between the two groups. For the HRQoL assessment, patients were invited to complete a questionnaire including the EQ-5D and FACT-L instruments. Propensity scoring methods were used to match the two comparison groups on confounding variables including age, performance status and time since diagnosis. A t-test was used to assess the relationship between current treatment and quality of life.
Results: 895 non-squamous patients were included in the TTP analyses, of whom 421 had experienced disease progression. 301 patients received bevacizumab-based treatment and 594 patients received a non-bevacizumab treatment first line. Bevacizumab-treated patients were younger (mean age 58.6 years versus 63.3 years). The median time to progression for bevacizumab-treated patients was 8.5 months compared with 6 months in the non-bevacizumab treated group ($p<0.001$). The Hazard ratio relating to the treatment effect (bevacizumab-based versus non-bevacizumab based) was 0.65 (95% CI 0.52 to 0.81). The differences in TTP remain significant between the two first-line therapy groups even after controlling for age. HRQoL was assessed for 363 non-squamous patients receiving first line treatment of whom 132 were currently receiving bevacizumab-based therapy and 231 were currently receiving non-bevacizumab-based therapy. The HRQOL scores using the FACT-L instrument (total scores) were 77.3 for bevacizumab patients (95% CI 73.7 to 81.0) compared with 74.1 for non-bevacizumab patients (95% CI 70.9 to 77.33), $p=0.19$. The EQ-5D scores for Progression-Free Survival were 0.68 for the bevacizumab group (95% CI 0.63 to 0.74) and 0.66 for the comparative patients (95% CI 0.62 to 0.71), $p=0.57$.
Conclusion: This real life pilot study demonstrated extended TTP for bevacizumab-based versus non-bevacizumab therapy and showed that bevacizumab-based therapy does not have any detrimental effect on HRQoL as measured by the EQ-5D and the FACT-L. The TTP results were consistent with findings of two phase III trials and real life outcomes from a US study.
Keywords: Non-small cell lung cancer, Time To Progression, Health Related Quality of Life, bevacizumab

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P3.180 TOLERANCE AND EFFICACY OF CHEMOTHERAPY WITH PLATINUM AND PEMETREXED IN ELDERLY PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: An increasing number of elderly patients are diagnosed with lung cancer. A recent study has demonstrated a benefit of a platinum-based doublet (carboplatin and paclitaxel) in elderly patients with non-small cell lung cancer.
Methods: Our objective was to determine the tolerance and efficacy of the platinum-pemetrexed doublet in elderly patients with advanced non-squamous NSCLC, compared with younger patients. We retrospectively reviewed the files of all patients treated by chemotherapy for an advanced non-squamous cell NSCLC in our department between January 2008 and August 2010.
Results: Forty-five patients with a stage IIIb-IV non-squamous NSCLC were treated with platinum-pemetrexed as a first line chemotherapy. Thirteen were 75 years old or older. Drugs were administered according to standard doses and protocols. The initial Performance Status in elderly patients was: 0-1 in 77% and 2 in 23%, and was similar in the younger patients' group. In the elderly patients' group, the response rate was 33%, and the stabilization rate was 33% (versus 44% and 28% in the younger patients' group, $p=0.85$). The progression-free survival (PFS) was not statistically different between the 2 groups, with a median at 3 months (IQR 18 days – 4.3 months) in the elderly patients' group (versus 1 month in the younger patients' group (IQR 20 days – 3.6 months), $p=0.49$). The hematological toxicities (all grades) in elderly patients were: anemia (incidence: 31%), thrombocytopenia (15%), neutropenia (38%); the grade 3-4 hematological toxicities in this group were: thrombocytopenia (8%) and neutropenia (15%). One patient suffered from febrile neutropenia. The most frequent non-hematological toxicities (all grades) in the elderly

patients' group were: fatigue (54%), mucositis (15%), loss of weight (15%), nausea-vomiting (8%); the grade 3-4 non-hematological toxicities were: fatigue (31%), mucositis (8%), dysphagia (8%). No toxic death occurred. There was no statistical difference in the side-effects between the 2 groups, except less frequent weight loss (p=0.048) and nausea-vomiting (p=0.02) in the elderly patients' group compared with the younger patients' group. No elderly patient received erythropoietin (EPO), compared with 34% of younger patients (p=0.02). Use of G-CSF in elderly patients was more frequent than in younger patients (62% vs 19%, p=0.005). The treatment was stopped because of toxicity at a similar rate in the 2 groups (15%). Co-morbidities and weight loss (of more than 10%) were not associated with grade 3-4 toxicities.

Conclusion: In patients with non squamous NSCLC treated with the platinum-pemetrexed doublet as a first line chemotherapy, the response rate and PFS are similar in elderly and younger patients. The tolerance of this doublet appears to be acceptable in elderly patients with less frequent weight loss and digestive side-effects than in younger patients.

Keywords: elderly patients, Advanced Non-Small Cell Lung Cancer, non-squamous carcinoma, Pemetrexed

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P3.181 COMPARISON OF MICRORNA PROFILE IN PLASMA VERSUS BRONCHOALVEOLAR FLUID CITOLOGY IN PATIENTS WITH LUNG ADENOCARCINOMA

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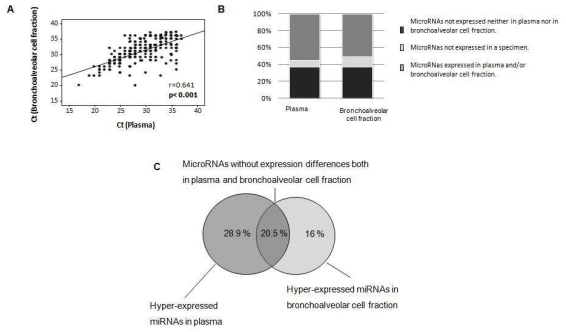
Background: The discovery of microRNAs (miRNAs) has revealed an unexpected and spectacular role for the regulation of cell gene expression. Evidence supports the use of miRNAs as disease-specific biomarkers. Several recent reports show circulating miRNAs in biological fluids such as sputum, serum and plasma, among others, can be protected from endogenous RNase activity in exosomes, helping to transfer genetic material in the human body. The identification of miRNAs is necessary to validate new less invasive biomarkers for improving the detection and prognostic of patients with lung cancer. The present study aimed to obtain miRNA representative signatures in patients with lung adenocarcinoma from plasma and bronchoalveolar cell fraction.

Methods: Plasma and bronchoalveolar cell fraction were collected in six patients who had required flexible bronchoscopy. Taqman Low Density Arrays (TLDAs) were used to assess the expression level of 381 miRNAs. MicroRNA hyper-expression was defined as a 5-fold or greater increase in plasma in contrast with the bronchoalveolar cell fraction and vice versa.

Results: Our goal was to compare patterns from circulating plasma miRNAs with the bronchoalveolar cell fraction derived miRNA. Patients (4 men and 2 women) had a median age of 59.5 [range, 54.7-68.0] years. All had lung adenocarcinoma stage III or IV. To determine the degree of correlation between the expression levels of 381 miRNAs of plasma samples and bronchoalveolar cell fraction, the miRNA Ct values of plasma were compared with respect to the Ct values of bronchoalveolar cytology in patients. Pearson´s correlation factors were in a range between 0.636 and 0.794, with p-values lower than 0.001 for all patients. In addition, we found that only around 50% miRNAs were comparable between plasma and bronchoalveolar cell fraction and 20 % of miRNAs showed similar expression in both samples (figure 1). The profiles are not comparable; however, there is a similarity in the relative expression in a subset of miRNAs (miR-17, miR-19b, miR-195 and miR-20b) between both biological samples in all patients. These results show a lack of association of miRNA signatures between plasma and bronchoalveolar.



Conclusion: Our data reflects that there is an absence of association between expression pattern in the circulating plasma miRNAs and the bronchoalveolar cell fraction-derived miRNAs from the same patient. Only a small subset of miRNAs (from 18% to 27%) is commonly represented in both samples, and this considering 5 fold differences as equal in the expression levels.

Keywords: plasma, microRNA profile, bronchoalveolar fluid cytology, Adenocarcinoma

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P3.182 PEMETREXED IN THE SECOND LINE CHEMOTHERAPY OF NON SMALL CELL LUNG CANCER. A MULTICENTRE PROSPECTIVE ANALYSIS OF DATA FROM CLINICAL PRACTICE.

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Background: Non small cell lung cancer (NSCLC) is one of the most aggressive tumours with unsatisfactory prognosis and extremely high mortality. Pemetrexed became one of the standard chemotherapeutic options in advanced NSCLC. It is recommended both in the 1st line and in the 2nd line.

Methods: Results of the second line therapy in NSCLC with pemetrexed monotherapy were evaluated in 10 centres. The first line chemotherapy was platinum based regimen. Data of consecutive out-patients were prospectively collected from January 2008 to december 2010. Demographics, tolerance of treatment and prognostic factors were discussed.

Results: The series consisted of 389 patients (pts), 247 men and 142 women, mean age was 61 years (28 -80), 77 were non-smokers, 134 ex-smokers and 175 smokers. PS was 0 in 71 pts, 1 in 278 pts, 2 in 40 pts. Adenocarcinoma was present in 236 pts, squamous cell carcinoma in 83 pts, non specified NSCLC in 51 pts, large cell carcinoma in 19 pts. According to TNM classification 17 pts were in stage I, 14 pts in stage II, 140 pts in stage III, 214 pts in stage IV, 4 pts were not classified. Side effects of treatment (Gr 3, 4) appeared in 113 (29.0%) pts, leucocytopenia in 49 pts, neutropenia in 43 pts, anaemia in 33 pts, trombocytopenia in 13 pts, fatigue in 22 pts, nausea/vomiting in 9 pts, infection in 8 pts, rash in 5 pts. Therapeutic response: CR in 5 pts, PR in 43 pts, SD 136 pts and PD in 144 pts. Overall disease control was achived in 47.4%. The median of overall survival (MOS) from the pemetrexed application was 9.8 months (8.0 m -11.6 m). It was 9.7 m in men, 9.9 m in women (p 0,081), 7.9 m in smokers and 11.8 m in non-smokers (p 0.048), 11.4 m in adenocarcinoma and 9.4 m in squamous cell carcinoma (p 0.048). MOS according to PS: NA in PS 0, 9.6 m in PS 1, 4.1 m in PS 2 (p 0.001). MOC according to stages: 10.6 m in stage I+II, 12.0 m in stage III and 9.2 m in stage IV (p 0.163). Median of progression free survival (PFS) was 2.7 m (2.4 m – 3.0 m), it was 2.6 m in men and 2.8 m in women (p 0.729), 2.5 m in smokers and 3.3 m in non-smokers (p 0.246), 2.6 m in adenocarcinoma and 3.1 m in squamous cell carcinoma (p 0.996). PFS according to PS: 3.6 m in PS 0, 2.6 m in PS 1, 1.4 m in PS 2 (p 0.001). PFS according to stages: 5.1 m in stage I+II, 2.8 in stage III and 2.4 in stage IV (p 0.157).

Conclusion: In present study pemetrexed was effective and well tolerable drug used in the second line chemotherapy of NSCLC treatment. MOS was significantly longer in PS 0 and 1 than in PS 2, in adenocarcinoma than in squamous carcinoma and in non-smokers than in smokers. PFS was not influenced by any evaluated parameter except of PS.

Keywords: Pemetrexed, Advanced NSCLC, second line chemotherapy

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P3.183 PHASE II TRIAL OF NAB-PACLITAXEL PLUS CARBOPLATIN IN PATIENTS WITH ADVANCED NSCLC AT RISK OF BLEEDING FROM VEGF DIRECTED THERAPIES

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Background: Platinum-based chemotherapy is standard for patients (pts) with advanced NSCLC. When added to chemotherapy, bevacizumab (Bev) improves response rate, progression free survival and overall survival (RR, PFS and OS), but pts with squamous histology or hemoptysis are excluded. nab-Paclitaxel (nanoparticle albumin bound paclitaxel) has been safe in phase I/II studies. A phase III study comparing paclitaxel/carboplatin (carbo) to nab-paclitaxel/carbo was reported to have met its primary endpoint of response rate. The objective of this trial is to determine the efficacy of nab-paclitaxel/carbo in pts ineligible for bevacizumab (Bev).
Methods: Chemo-naïve pts with advanced NSCLC ineligible for Bev therapy (squamous histology, thrombotic or embolic events within 6 months, hemoptysis, cavitary lung lesions) were included. Controlled brain metastases were allowed. Treatment with nab-paclitaxel 300 mg/m^2 (decreased to 260 mg/m^2 after the first 40 pts) and carbo AUC 6 was given every 21 days (up to 6 cycles). We used a 2-stage design; the 1st stage enrolled 27 pts and the 2nd stage will enroll 36 pts. The primary endpoint is RR by RECIST. Secondary objectives include PFS and OS. Correlative studies include blood miRNA analysis to evaluate for predictive biomarkers of response.
Results: 52 (of 63 planned) pts have been enrolled in this ongoing trial. After the first 27 pts were enrolled, there were 8 confirmed PRs (30%) and 9 SD (33%), thus, second stage was initiated. 81% of pts are Caucasian, with a median age of 64 years. All pts have been smokers (mean 49 pk-yrs). Histology includes 37 squamous cell, 8 adenocarcinoma, 2 adenosquamous, and 5 NSCLC (NOS). Grade 3/4 toxicity experienced by more than 2 patients is listed in table 1. Grade 3 neuropathy is significantly higher than seen in prior studies despite being dosed at the MTD in combination with carbo. After the first 40 pts, in consultation with the sponsor, we decreased the dose of nab-paclitaxel to 260 mg/m^2 because of neurotoxicity and have seen no Gr3/4 neuropathy in the subsequent 12 pts. Four patients died during the first or second cycle of therapy related to sepsis, febrile neutropenia and dehydration.

Table 1: Toxicity	Gr3 n (%)	Gr4 n (%)
Hematologic		
· Neutropenia	4 (8%)	8 (15%)
· Thrombocytopenia	5 (10%)	1 (2%)
· Anemia	2 (4%)	1 (2%)
Non-Hematologic		
· Sensory Neuropathy	13 (25%)	0
· Neutropenic Fever	7 (13%)	2 (4%)
· Infection without Neutropenia	5 (10%)	5 (10%)
· Hyponatremia	7 (13%)	0
· Hypoxia	1 (2%)	2 (4%)
· Dyspnea	7 (13%)	2 (4%)
· Dehydration	6 (12%)	3 (6%)
· Fatigue	10 (20%)	0

Conclusion: *nab*-Paclitaxel and carbo on a 3 week schedule offers a reasonable treatment option for pts with advanced NSCLC with squamous histology who are ineligible for Bev. This study was approved and funded by the National Comprehensive Cancer Network (NCCN) from general research support from Celgene.
Keywords: bevacizumab ineligible, nab-paclitaxel, squamous carcinoma, neuropathy

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P3.184 IN A PHASE IIB TRIAL GTX-024 OVERCOMES THE NEGATIVE IMPACT OF >8% WEIGHT LOSS ON OVERALL SURVIVAL IN NON-SMALL CELL LUNG CANCER (NSCLC) SUBJECTS

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Background: NSCLC represents greater than 80% of newly diagnosed lung cancer with over three quarters of patients being diagnosed with Stage III or IV disease. Due to the advanced stage of cancer at the time of diagnosis, 5 and 10 year survival rates are poor. At diagnosis, 60% of lung cancer patients have substantial weight loss, increasing to >80% prior to death from malignancy. Much of this weight loss is attributed to muscle wasting leading to a decline in physical function and other detrimental consequences early in the course of a patient's malignancy. Studies have demonstrated that NSCLC patients with weight loss at diagnosis are less likely to tolerate chemotherapy, have worse treatment outcomes and shorter overall survival. The negative impact of muscle wasting on the patient and caregiver underscore the importance of preventing and treating this condition early in the course of therapy. We conducted a Phase IIb, randomized, double blind, placebo controlled, multi-center study to evaluate the effect of GTx-024 on muscle wasting and physical function in patients with cancer.
Methods: Subjects (n=159) were randomized to oral GTx-024 (1 or 3 mg) or placebo daily for 16 weeks. Subjects were males >45 y and postmenopausal females, had experienced ≥2% weight loss in the 6 months prior to randomization, had a BMI <35 and either NSCLC, colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia or breast cancer. The primary endpoint was change in total lean body mass (muscle). We report on overall survival in the entire study population and NSCLC cohort based on weight loss of > or ≤8% in the 6 months prior to randomization.
Results: In placebo subjects in the ITT population, overall survival was significantly (P=0.003, log rank) reduced in subjects with >8% weight loss compared to subjects with ≤8% weight loss. Among NSCLC subjects (n=61) placebo subjects with >8% weight loss demonstrated a similar survival disadvantage (P=0.04); 4 month Kaplan-Meier estimates 100% vs 49% ±14.8%. In GTx-024 treated subjects in both the ITT and NSCLC groups, increased weight loss did not negatively affect survival.
Conclusion: Preceding weight loss among NSCLC patients not treated with GTx-024 is predictive of decreased overall survival. In this 16 week Phase IIb trial, NSCLC subjects randomized to placebo with >8% weight loss at baseline were 2 times more likely to die than subjects with ≤8% weight loss. In the GTx-024 group weight loss was not predictive of overall survival. These data suggest that GTx-024 treatment may overcome the negative prognostic effect of >8% weight loss. Further research is needed to assess the effect of GTx-024 on overall survival.
Keywords: GTx-024, muscle wasting, Cachexia, survival

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P3.185 PHASE I CLINICAL TRIAL OF ADENOCARCINOMA CELLS TRANSFECTED WITH HLA A1 AND GP96-IG HEAT SHOCK PROTEIN IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: This is a phase I clinical trial to determine the safety, immunogenicity, and clinical response to our allogeneic gp96-Ig heat shock tumor vaccine for NSCLC patients (pts) with advanced disease who have failed at least one line of standard chemotherapy and erlotinib.
Methods: Allogeneic, cultured lung adenocarcinoma cells transfected with HLA A1 and gp96-Ig were irradiated and injected intradermall. Three dose-schedule 107 cells administered by 9´combinations were considered (total of 4.5 biweekly (DS1), 18 weekly (DS2), or 36 twice weekly (DS3) injections). Immune response to vaccination was measured by

determining adenocarcinoma-specific CD8 CTL frequencies in ELI-spot assays for interferon-γ (IFN-γ) and by measuring the frequency of FoxP3+ CD4+ Tregs. If pts had a clinical benefit: (CR, PR or SD), they continued with the next course of vaccinations for up to 3 courses.
Results: 19 pts have been enrolled. Median age was 65 years; most of the pts were Hispanic females. Data is available from 18 pts: 12 pts were treated in DS1 cohort, four in DS2 and three in DS3. None of the pts experienced serious adverse events (SAE) related to vaccine. Grade I: rash, skin induration and skin erythema were the most common AEs in the 3 cohorts. There was not an increment of AEs with the increase in the frequency of vaccinations. Six pts have achieved transitory disease stabilization (SD). Most of the pts had an immunological response (CD8 CTL) determined by ELI-spot, and the frequency of FoxP3+ CD4+ Treg decreased.
Conclusion: Minimal toxicity and immunologic response have been seen so far in this very advanced population of NSCLC pts
Keywords: NSCLC, immunotherapy, heat shock protein gp96

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P3.186 A PHASE I STUDY OF MM-10-001 IN ADVANCED NSCLC

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Background: MM-10-001 is a bioactive agent exported from Shiitake Mycelium in aqueous medium. The MM-10-001 contains a triple helix beta-glucan, isolated from the cell walls of the shiitake mushroom (Lentinula edodes), with potential immunostimulating activity. The beta-glucan in MM-10-001 binds to a lectin site within the complement receptor 3 on leukocytes, priming the receptor to trigger cytotoxic degranulation of leukocytes when leukocyte CR3 binds to iC3b-opsonized tumor cells. This phase I study was designed to assess the feasibility and toxicity of therapy with beta-glucan MM-10-001. Secondary endpoints included exploratory analysis of the effect of MM-10-001 on the innate immune compartment (in particular NK cell activation and effector status) and the cytokine profile of the patients as well as antitumor efficacy and patient reported functional status.
Methods: Patients with advanced NSCLC for which standard curative or palliative measures do not exist or are no longer effective received orally escalating doses of MM-10-001 (5mg, 10 mg and 20 mg); a cycle consisted of 28 days. The blood samples for correlative studies were collected pre-study and weeks 1, 5, 9, 13. Serum cytokine levels were measured with 30-plex cytokine/ chemokine/growth factor multiplex panels (Invitrogen), and analyzed using a FLEXMAP-3D instrument (Luminex).
Results: To date, 20 patients (7M/13F) have been treated (MM-10-001 5 – 20 mg). The median age was 72 (range 43-88), with 9 ECOG 0, and 11 ECOG 1. All patients were evaluable for toxicity. No grade 3+ treatment related adverse events were noted. Grade 2 adverse events reported are fatigue (3 pts), anorexia (1 pt), Alk Phos (1 pt), and joint pain (1 pt), each with an attribution of "possible". Median time to treatment failure was 3.5 months (range 1-13+ months). Correlative studies on 19 cytokines in addition to immunoglobulins (A, M, G), WBC, hemoglobin, PLT, ANC, C-reactive protein, and serum complements C3 and C4 were conducted on 18/20 subjects. Significant cytokine increases were noted in three patients concurrent with progression, resulting in a positive trend in several cytokines over time. Subset analysis, excluding those patients, suggested a possible decrease in IL-12 as a function of both time and dose ($p=0.01, 0.02$ respectively), along with a decrease in MIP1b as a function of dose ($p=0.03$). These results were not significant when adjusting for multiple comparisons. However, after accounting for multiple comparisons, low IL-2R was associated with improved survival ($p<0.05$, log-rank).
Conclusion: At the time of interim analysis, the MTD has not been reached and study will continue with escalating doses of MM-10-001. The preliminary data indicates potential immunostimulating activity of MM-10-001.

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P3.187 LUNG CANCER IN NEVER SMOKERS: A MONO-ISTITUTIONAL EXPERIENCE

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Background: Lung cancer in never smokers seems to represent a distinct disease entity with its own distinct tumorigenesis, clinical characteristics, and response to therapy. From May 2003 to January 2011, 123 never smoker lung cancer stage IV patients (pts) were followed at our Istitution
Methods: Patients' Characheristics: F/M 73/50 (59,3/40,7%). Median age was 61yrs (range 29-78). All of them had a good PS (ECOG 0-1). Histology: squamous/adenocarcinoma/NoS 9/95/19 (7,3/77,2/15,4%). Number of metastatic sites: single/ multiple 57/56 (54,5/45,5%). EGFR mutation (sequencing of exons 18-21) was performed in 87 pts (70,7%) with 47,1% mutated and 52,9% wild type. K-RAS mutation (sequencing of exon 2) was performed in 85 patients (69,1%) with 8,2% mutated and 91,8% wild type. 4/20 (20%) EGFRwt and K-RASwt pts scored positive at the EML-ALK traslocation analysis by FISH and 3 more pts known to be EML4/ALK positive were referred to our Institution . Treatment: 111 pts received first line chemotherapy: 102 (91,8%) with a platinum doublet and 9 (8,2%) mono-chemotherapy with gemcitabine. 94 pts (76,4%) received an EGFR TKI in either line of treatment. 86 pts (77,4%) were treated with both chemotherapy and an EGFR-TKI. 64 pts (52%) received at least one further line of chemotherapy (median 2-4). Response rate, PFS and OS were evaluated for the overall population as well as for EGFR mutated (EGFR mut) versus wild-type pts (EGFR wt).
Results: ORR to first line chemotherapy was 43,8% (EGFR wt: 52,3% vs EGFR mut: 48,5%) 90 out of the 94 treatments with an EGFR-TKI (in 82 patients) were evaluable for response. 69/82 pts had a known EGFR mutational status (24 pts EGFR wt, 45 pts EGFR mut). ORR to EGFR-TKIs was 46,3% (EGFR wt: 29,1 % vs EGFR mut: 55.5%). PFS and OS in the overall population (123 pts) were respectively 6,1 and 31,6 months (mo). Median OS for TKI treatment (ever/never) was 35 vs 14.4 mo (p=0,002 Log rank test) PFS/OS in the 87 pts with a known EGFR mutational status were respectively: all (6,7 mo/40 mo) ; EGFR wt (6,5 mo/36 mo); EGFR mut (7 mo/43,6 mo). The difference in OS between EGFR mutated and wild-type pts was statistically significant (p< 0,09).
Conclusion: This analysis confirmed that adenocarcinoma is the most common histology subtype in lung cancer of never smokers, with female preponderance. In line with literature data, 47,1% of the population tested EGFR mutation positive. In our experience, EGFR mutation positive status do confers a survival advantage even if it does not predict for better response rate to chemotherapy.
Keywords: Lung cancer, never smoker

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P3.188 CLINICAL RESPONSES TO GEFITINIB RETREATMENT IN NON-SMALL-CELL-LUNG-CANCER ADENOCARCINOMA PATIENTS WHO BENEFITED FROM PRIOR EFFECTIVE GEFITINIB THERAPY: A RETROSPECTIVE ANALYSIS

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Background: Gefitinib, an EGFR tyrosine kinase inhibitors have been widely used in non-small-cell-lung-cancer (NSCLC).Gefitinib is most effective in patients with women, never smoked, pulmonary adenocarcinomas, and patients of Asian origin.

There are some treatment options for NSCLC adenocarcinoma patients who responded to gefitinib initial administration and demonstrated tumor progression. Re-administration of gefitinib in a suitable is one choice. The study is to evaluate the efficacy and toxicity of the re-challenge gefitinib.
Methods: We retrospectively evaluated the clinical charts of 17 NSCLC adenocarcinoma patients who had obtained a partial response (PR) or stable disease (SD) with gefitinib treatment and were re-treated with gefitinib after failure of the initial gefitinib treatment.
Results: All of the 17 patients were adenocarcimoma of the lung and treated with gefitinib as the 2nd EGFR-TKI. One patient (5.8%) showed CR, 8 (47%) achieved SD, and 8 (47%) had progressive disease. The disease control rate was 53% and the median progression-free survival was 3months (range from 1month to 29months). The median overall survival from the beginning of the first gefitinib were 32months (range from 11months to 51months). The median overall survival from the beginning of the 2nd gefitinib were 11months(range from 5months to 40months). The toxicities associated with the 2nd gefitinib were mild.
Conclusion: Our results indicate that patients with NSCLC adenocarcimona may still be expected to have prolonged survival if they once responded to gefitinib and then received different treatments followed by readministration of gefitinib.
Keyword: gefitinb; NSCLC; adenocarcinoma; readministration

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P3.189 PHASE II RANDOMIZED, OPEN-LABEL STUDY OF CETUXIMAB (CET) AND BEVACIZUMAB (BEV) IN COMBINATION WITH PACLITAXEL (P) AND CARBOPLATIN (C) IN PATIENTS WITH STAGE IIIB/IV NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Cet, a monoclonal antibody (mAb) that blocks binding of epidermal growth factor (EGF) to EGF receptor (EGFR) or Bev (anti-VEGF mAb) has been combined with chemotherapy in advanced NSCLC cancer trials with acceptable toxicity profiles and improved survival compared to chemotherapy alone. In previous trials, Cet and Bev were combined separately with chemotherapy and were generally well tolerated. This study aims to evaluate the efficacy of Cet plus Bev combination with chemotherapy in the survival of stage IIIB or IV NSCLC patients.
Methods: Patients with stage IIIB or IV NSCLC (n=120) were randomized to receive Cet (400 mg/m^2 on day 1 as initial dose and weekly thereafter at 250 mg/m^2) plus Bev (15 mg/kg on day 8 of each 3-week cycle) for 6 cycles in combination with either 6 cycles (arm A) or 3 cycles (arm B) of P (200 mg/m^2) and C (AUC=6) on day 1 of each 3-week cycle. Patients who demonstrate complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD) after six cycles of therapy on either arms A or B may continue on weekly Cet monotherapy until PD or other withdrawal criteria are met. The primary objective is to estimate progression free survival (PFS) separately for arm A and B. Secondary objectives include estimation of overall survival, tumor response rate, duration of response, safety and tolerability, and quality of life assessment, for each treatment arm. Based on available tumor tissue, EGFR expression will be analyzed and relationships between PFS, and overall survival will be explored.
Results: Planned enrollment was 120 patients. Results for PFS, overall survival, response, toxicity, and quality of life will be reported.
Conclusion: Conclusions will be reported later.
Keywords: Non-small cell lung cancer (NSCLC), cetuximab (Cet), bevacizumab (Bev), stage IIIB/IV

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.190 EXPLAINING THE INCREASED USE OF FIRST-LINE CHEMOTHERAPY IN NSCLC PATIENTS IN NORTHERN IRELAND BETWEEN 2004 AND 2007

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Background: Systemic anti-cancer chemotherapy (SACT) is recommended for patients of good performance status (PS) with advanced or metastatic non-small-cell lung cancer (NSCLC). The literature supports the use of SACT for selected PS2 patients to improve quality of life. We reviewed all patients with NSCLC treated with first-line SACT in Northern Ireland from 2004-2007 demonstrating a year on year increase in the number of patients treated mainly due to increasing treatment of patients with PS=2.
Methods: The patient records of all patients with NSCLC referred to oncology services in Northern Ireland from 2004 to 2007 were retrospectively reviewed; patients treated with first-line SACT were selected for analysis. Clinical characteristics including patient age, sex, tumour type, PS, smoking history, weight loss and comorbities were reviewed. Kaplan Meier survival curves with 95% confidence intervals were generated for the whole study population and patients with PS=2. Median survival from the time of first chemotherapy and 1 year overall survival times were calculated and compared to literature standards.
Results: 434 patients with NSCLC were treated with first-line SACT in Northern Ireland from 2004 to 2007. The numbers of patients treated were 78 in 2004, 100 in 2005, 108 in 2006 and 148 in 2007. This corresponded to an increase in the percentage of all NSCLC patients from 15% in 2004 to 27% in 2007. A rise in the number of patients treated with poorer PS was the greatest factor driving the increase in SACT use, with PS 2 patients numbers increasing from 18 in 2004 (23.1% of treated patients) to 51 in 2007 (34.4% of treated patients). The median survival time of the study population was 8.3 months with 1 year overall survival of 35%. On univariate analysis PS ($p<0.0001$), stage ($p=0.004$) and weight loss ($p<0.0001$) were significantly associated with survival, but symptomatic comorbidity score, age ≥ 70, gender, pathological subtype and year of cohort were not. For PS2 patients the median survival was 7.2m and 1 year overall survival 31%. These results are comparable to published prospective clinical trials.
Conclusion: There has been a clear increase in the use of systemic palliative chemotherapy for NSCLC in Northern Ireland. The biggest increase has been in patients with poorer performance status (PS2), followed by elderly patients and patients with significant comorbidities. Such patients may previously have been excluded from chemotherapy but recent evidence has given increasing confidence that they can be treated effectively and safely. The outcomes of patients treated in Northern Ireland compare favourably to published literature standards.
Keywords: NSCLC, Chemotherapy

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P3.191 THE ANALYSIS OF INFLUENCE OF CLINICAL PREDICTORS ON THE RESULTS OF TREATMENT WITH ERLOTINIB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Erlotinib is a tyrosine-kinase inhibitor (TKI) used for the treatment of patients with non small cell lung cancer (NSCLC) in Czech Republic since 2005. Wide use of erlotinib in patients with NSCLC enables to collect a robust data in Czech Tarceva patients registry, where are recorded all the patients treated with erlotinib in 10 centers of excellence in Czech Rep. Objective of this

retrospective analysis is to compare treatment efficacy in the subgroup of patients outside the clinical studies and try to find factors influencing the treatment effect.
Methods: Retrospective analysis of all data from the Tarceva registry was performed. In this analysis, the influence of particular clinical factors on the treatment results and the survival data were evaluated.
Results: : In total, the complete data of 1735 patients (median age 65 years; 64,4% women and 35,6% men; 21,6% nonsmokers, 39,5% stop-smokers and 38,9% current smokers; 63,9% PS 0/1, 36,1% PS 2/3) were available at the date of evaluation (19 January, 2011). The most frequent histological types were adenocarcinoma (42,3%) and squamous cell carcinoma (39,2%). Highly significant ($p < 0,001$) correlations in treatment outcomes determined using Pearson Chi-square test were found in all the evaluated clinical factors, such as gender, occurrence of treatment adverse effect generally and rush in particular, smoking status and performance status. Surprisingly, the histological type was found as the weakest, however still significant predictor of treatment response ($p = 0,046$) with mOS – $p = 0,016$ and mPFS – $p = 0,082$).
Conclusion: The analysis of a non-selected group of NSCLC patients treated with erlotinib in real life practice showed the most powerful factors influencing the treatment results and survival. In our group, the general clinical factors were more powerful predictors of the result of treatment as the histological type of tumor. In global picture of these results we have to bare in mind, that all the clinical factors that we have evaluated are considered much more prognostic than predictive factors.
Keywords: NSCLC, erlotinib, clinical predictors

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P3.192 EFFICACY AND SAFETY OF FIRST LINE BEVACIZUMAB PLUS CHEMOTHERAPY IN NON SQUAMOUS NON SMALL CELL LUNG CANCER (NSCLC)

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Background: First line bevaizumab plus chemotherapy improves outcomes in pts with advanced or recurrent NSCLC, as proven in two pivotal phase III trials (E4599 and AVAiL).This multicentric, single-arm study aimed to further assess the efficacy and safety profile of first-line bevaizumab -based therapy in unresectable NSCLC
Methods: Between 2008 to 2010 Inoperable non-squamous NSCLC with ECOG PS 0;2, life expectancy 40 years;3 months and adequate bone marrow, hepatic and renal function were enrolled in the study with informed consent. The dosing regime was bevaizumab 7.5 mg/kg plus chemotherapy for up to 6 cycles,followed by sequential local radiotherapy with 60 Gy in 30 fractions with 3DCRT followed by single-agent bevaizumab until progression. Exclusion criteria included evidence of CNS metastases, even if previously treated, major blood vessel invasion, haemoptysis (MORE than;2.5mL red blood), history of coagulation disorders, uncontrolled hypertension, clinically significant cardiovascular disease and gastrointestinal perforation within 6 months of enrolment. Primary endpoint was safety; secondary endpoints included TTP and OS
Results: The intent-to-treat population (n=14) was: male 8, female 6; mean age 56 years; past or active smokers 6; stage IV disease 9/14. Median number of bevaizumab cycles was 9, with 12/14 of pts receiving ;7 Bv cycles. Incidence of clinically significant adverse events (AEs) was low. 11/14 pts had an AE of special interest of any grade (G), the most common being G ;2 proteinuria (4/14) and epistaxis (3/14). AEs of special interest were reported in only 1/14 of pts and included proteinuria, hypertension , epistaxis . Only one G 1 CNS bleeding events were reported, among the 2 pts who developed CNS metastases during therapy. No G ;3 wound-healing complications or congestive heart failure events were reported. Bevaizumab was infrequently interrupted due to AEs in 4/14 patients. Efficacy outcomes were remarkable: overall response in 12/14; median TTP 8.3 months; median OS 18.9 months
Conclusion: The safety and remarkable efficacy of first-line bevaizumab plus chemotherapy followed with local RT was confirmed in this small pilot trial with advanced non-squamous NSCLC. These findings are consistent with those of the overall population in the pivotal phase III trials, E4599 and AVAiL. No new safety signals were reported in this analysis.
Keywords: NSCLC, Advanced, bevacizumab, Non-squamous

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P3.193 THERAPY BEYOND SECOND LINE IN NON-SMALL CELL LUNG CANCER: CLINICAL FEATURES AND SURVIVAL IN A REAL-WORLD SCENARIO

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Background: Despite recent advances in non-small cell lung cancer (NSCLC) treatment, so far there are only three approved lines for clinical use and no third-line cytotoxic drug considered standard of care. To date, there is limited clinical data suggesting survival benefit for third-line cytotoxic treatment and beyond. Therefore, the treatment choice in this setting has been a matter of individual decision. This retrospective study reports the clinical characteristics and outcome for cytotoxic treatment administered in third-line and beyond in a real-world scenario of a developing country.
Methods: Medical charts from patients with metastatic NSCLC treated between 1999 to 2010 in a private oncology center in Brazil, were retrospectively reviewed. Patients with documented exposure to third-line and beyond cytotoxic treatment were identified and followed. The aim was to assess the clinical features and survival of this subgroup and compare them to the subgroup that did not receive cytotoxic therapy beyond second-line. Patients were excluded if there was insufficient data. Statistical analyses were performed using the SPSS 17.0 software.
Results: Two hundred thirty-nine patients presenting with advanced disease were included. Thirty-five patients (14.6%) received third-line, 14 patients (5.8%) received fourth-line and 5 patients (2.1%) received fifth-line treatment. Most common cytotoxic treatments administered in third to fifth line were: pemetrexed (31.4%), docetaxel (25.7%), the carboplatin-paclitaxel combination (11.4%), vinorelbine (8.6%), and gemcitabine (5.7%). The performance status (PS) was 0-1 in 91.7%, and there was a predominance of adenocarcinoma hystologic subtype (65.7%). Only 12.5% were never-smokers and 57.1% had a history of weight lost. The disease stage at presentation, according to AJCC 6th edition was: I-IIIB 11.4% and wet IIIB-IV 88.6%. Of note, none of these characteristics was statistically different from the subgroup that was not treated beyond second-line treatment in comparison to the best supportive care (BSC) group. Patients receiving third-line or greater were significantly younger, with median age 58 years vs. 64 years, respectively (p=0.016). Notably, median overall survival for patients receiving third-line cytotoxic treatment and greater compared to BSC was 22.7 (95% CI, 15.8-29.5) months vs. 9 (95% CI, 7.6-10.5) months, respectively (p=0.002).
Conclusion: This retrospective study identified a subgroup of patients that was treated outside of predefined guidelines. The wide array of cytotoxic treatment utilized in third-line and beyond betrays a lack of pattern in the therapy selection. There was a small group of remarkably long-lived survivors, despite no major clinical differences from patients receiving BSC. The association of this survival with chemotherapy requires further evaluation.
Keywords: Advanced Non-Small Cell Lung Cancer, third-line treatment, Chemotherapy

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.194 META-ANALYSIS OF THE EGFR-TKI VERSES CHEMOTHERAPY FOR NSCLC PATIENTS BY DIFFERENT SELECTIONS.

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Background: EGFR TKI has been the most perspective treatment in advanced non-small cell lung cancer in the past ten years. Several clinical trials have shown gefitinib and erlotinib is not as

good as the chemotherapy in all the NSCLC patients. Some trials treated the patients with TKI according to the clinical characters such as pathological type, gender, smoking history or ethnicity. A few studies chose only EGFR mutation patients for TKI therapy. We want to find out how to select the proper patients for TKI or chemotherapy.

Methods: We did a meta-analysis of all randomized controlled trials involving patients with advanced NSCLC treated with chemotherapy or TKI by different selections. Efficacy outcomes of interest were objective response rate (ORR), disease control rate (DCR) based on the Response Evaluation Criteria in Solid Tumors (RECIST) and 1 year survival of each treatment arm.

Results:

12 randomized studies comparing chemotherapy versus TKI in advanced non-small cell lung cancer were selected. 8 trials enrolled NSCLC patients without selection and randomized to receive TKI or chemotherapy. Two trials selected patients by clinical selection of gender and smoking history in Eastern Asia. Three trials chose EGFR mutation patients for TKI or chemotherapy randomizely. By different selections the RR of ORR was .8(9%CI .66-.) of without selection, .76(9%CI .67-.86) of clinical selection favor TKI and .(9%CI .6-.6) of mutation selection favor TKI, respectively.The RR of DCR was .(9%CI .9-.8) of without selection, not available of clinical selection and .9(9%CI .8-.97) of mutation selection favor TKI, respectively. The RR of year survival was .8(9%CI .97-.) of without selection, .96(9%CI .9-.) of clinical selection and .76(9%CI .9-.97) of mutation selection favor TKI, respectively.

Table 1 Characters of the eligible trials

Author	Year	Pts	Treatment Arm	Control Arm
Without Selection				
Cufer, T. (SIGN)	2006	141	Gefitinib	Docetaxel
Maruyama, R. (V-15-32)	2008	490	Gefitinib	Docetaxel
Lilenbaum, R.	2008	103	Erlotinib	Paclitaxel+ Carboplatin
Crino, L. (INVITE)	2008	196	Gefitinib	Vinorelbine
Kim, E. S. (INTEREST)	2008	1466	Gefitinib	Docetaxel
Lee, D. H. (ISTANA)	2010	161	Gefitinib	Docetaxel
Vamvakas, L.	2010	327	Erlotinib	Pemetrexed
Agarwal, S.	2010	35	Gefitinib	Gemcitabine+Carboplatin
Clinical Selection				
Lee, J.S. (First-SIGNAL)	2009	309	Gefitinib	Gemcitabine+Cisplatin
Mok, T.S. (IPASS)	2009	1217	Gefitinib	Paclitaxel+ Carboplatin
Molecular Selection				
Mitsudomi, T. (WJTOG3405)	2010	177	Gefitinib	Docetaxel+Cisplatin
Maemondo, M. (NEJSG)	2010	230	Gefitinib	Paclitaxel+ Carboplatin

Conclusion: For NSCLC patient without selection the TKI is not superior to the chemotherapy. When choose the patients with clinical characters the ORR of TKI is better than the chemotherapy, thouth the 1 year survival is similar. For EGFR mutation patients the ORR, DCR and 1 year survival is better than chemotherapy significantly.

Keywords: Chemorherapy, target therapy, EGFR mutation

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P3.195 LOW DOSE ASPIRIN AND EGFR-TKI-INDUCED DIARRHOEA: NEED FOR A RANDOMISED TRIAL?

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Background: Gefitinib and Erlotinib, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) are increasingly used for the treatment of metastatic non-small cell lung cancer. Diarrhoea is the second most common side effect of EGFR-TKI. In the ISEL and BR-21 studies, Gefitinib and Erlotinib were respectively responsible for 27 and 55% of diarrhoea, all National Cancer Institute Common Toxicity Criteria grades combined (1,2). Reduction in EGFR-TKI dosage is an option when diarrhoea does not improve with symptomatic treatment, yet carries the risk of decreased efficacy of anti-cancer therapy. In the BR-21 study, which led to Erlotinib approval, diarrhoea was the second most frequent cause of dose reduction (5%) and treatment interruption (6%). Certain patients can be prescribed with EGFR-TKI for a year or even longer. For patients facing the prospect of long-term EGFR-TKI therapy, poor tolerance can significantly alter quality of life. Yamaguchi et al. demonstrated that certain platelet-related factors were elevated in Japanese patients receiving gefitinib, postulating that certain gefitinib toxicities could be related to platelet activation (3). In 2006, Kanazawa et al. hypothesized that aspirin could decrease toxicity induced by EGFR-TKI (4). In a prospective non-controlled study, they report a decrease in global (skin and digestive) gefitinib-induced toxicity when adding low-dose aspirin to gefitinib treatment. To our knowledge, no other experimental study has been

published in the English literature on the possible decrease in EGFR-TKI-induced diarrhoea with aspirin.
Methods: This is a non controlled prospective study.
Results:

Age/Sex (year-old)	EGFR status of the tumour	TKI/dosage (mg/day)	Length of treatment with EGFR-TKI (months)	Diarrhoea grade before aspirin	Diarrhoea grade with aspirin
77/Female	Mutated	Erlotinib / 100	9	Grade 2 to 3	Grade 0 to 1
91/Female	Mutated	Gefitinib / 250	0.5	Grade 1	Grade 0
54/Female	Mutated	Erlotinib / 50	10	Grade 2 to 3	Grade 0
71/Female	Mutated	Erlotinib / 125	6	Grade 1 to 2	Grade 0
74/Female	Mutated	Erlotinib / 100	18	Grade 2 to 3	Grade 0
71/Female	Non mutated	Erlotinib / 150	1	Grade 1	Grade 0
78/Female	Mutated	Erlotinib / 100	23	Grade 1 to 2	Grade 0

Conclusion: According to our experience, although limited to seven consecutive Caucasian patients who experienced grade 1 to 3 EGFR-TKI-induced diarrhoea, despite adequate use of anti-diarrhoeal drugs, introduction of aspirin (75 mg/d) induced a dramatic, rapid and sustained improvement. A randomised controlled study is required in order to confirm that low dose aspirin improves TKI-EGFR-induced diarrhoea without decreasing its anti-cancer efficacy. References Thatcher et al. Lancet 2005;366:1527-37. Shepherd F et al. New Engl J Med 2005;353:123-32. Yamaguchi K et al. J Clin Oncol 2005 ;23 (Suppl) :244s. Kanazawa S et al. Anti-Cancer Drugs 2006;17:423-7.
Keywords: TKI-EGFR, diarrhoea, aspirin

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P3.196 ERLOTINIB AS SECOND-LINE TREATMENT FOR PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER AND NON-SQUAMOUS HISTOLOGY: A GALICIAN LUNG CANCER GROUP STUDY (GGCP041/09).

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Background: Erlotinib is an orally available, potent, selective and reversible inhibitor of EGFR TK activity, providing significant survival benefits as monotherapy for the treatment of patients with locally advanced or metastatic non-small-cell carcinoma (NSCLC), after failure of at least one previous chemotherapy regimen. The results reporting the general practice use of erlotinib (TRUST study), superimposed to those obtained in the pivotal BR.21 study; in this trial, clinical predictors of response included adenocarcinoma histology, even though erlotinib had a significant effect on overall survival (OS) in all subgroups of patients. Here it is reported the efficacy of erlotinib in the 2nd line of patients with non-squamous cell carcinoma in a clinical practice setting.
Methods: Unselected patients with advanced NSCLC and non-squamous histology were treated with 150 mg/day of erlotinib as 2nd line therapy until unacceptable toxicity or progressive disease in 4 Galician institutions. Primary endpoint is progression-free survival (PFS), and the sample size of the study is 70 patients.
Results: At the time of the analysis, 31 patients were included in the dataset. Baseline characteristics: median age: 61.9 yrs. (range: 38-81); 75% male; 68% adenocarcinoma; 78.4% stage IV; 71.4% performance status ECOG 0-1. Amongst evaluable patients, ORR was 19.2% (95% CI: 5.5-33.7), and the disease-control rate 46.1% (95% CI: 21.9-57.8). With a median follow-up of 5.9 months, median PFS was 5.3 months (95% CI: 2.6-8.0), for a remarkable median OS of 10.3 months (95% CI: 7.7-13.0) Toxicity was mild and manageable: 39.3% patients experienced grade 1/2 cutaneous toxicity; 14.3% asthenia and anaemia. 4 patients developed grade 3/4 adverse events (rash, diarrhoea and asthenia). 3 patients transiently interrupted the therapy, while 5 patients underwent dose reduction. No patient needed drug discontinuation.
Conclusion: Data reported from this study on unselected patients with advanced NSCLC and non-squamous cell carcinoma confirm the efficacy and safety of 2nd line erlotinib in routine practice, with a remarkable OS above 10 months. The study is ongoing and the analysis will be updated, including a higher number of patients. EGFR mutations are currently well established positive predictive factor for EGFR efficacy. Data from the mutational status of the patients will be also presented.
Keywords: Non-Small-Cell Lung Cancer, EGFR-TKI, Non-squamous histology

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P3.197 ERLOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT

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Background: Erlotinib is a tyrosine kinase inhibitor approved as second and third-line therapy in advanced NSCLC. This target molecule has shown an impact on median survival and quality of life. There are factors that predict a better response to erlotinib and include: female gender, Asian ethnicity, adenocarcinoma histology, non-smoking status and mutational status (MS) of epidermal growth factor receptor (EGFR).

Methods: Analysis of an observational study was performed in patients that received erlotinib as second and third-line therapy between 2006 and 2010. Parameters: age, sex, smoking habits, histologic type, TNM stage at presentation, prior chemotherapy regimens, mutational status and overall survival according to MS. Assessment of response to erlotinib and survival according to MS.

Results: A total of 104 patients were enrolled, 57 (54.8%) males and 47 (45.2%) females. Forty-eight (46.2%) were non-smokers, 31 (29.8%) ex-smokers and 25 (24.0%) smokers. Mean age of 67.2 ± 12.8 yrs. Histologic types: adenocarcinoma in 66 (63.5%) patients, squamous in 18 (17.3%) and undifferentiated carcinoma in 20 (19.2%). We found 43 (41.3%) patients in stage III, 52 (50.0%) in stage IV and the remaining 9 (8.6%) in early stages at diagnosis. first-line chemotherapy regimens used were platinum + gemcitabine (51.0%), platinum + vinorelbine (11.5%), platinum + paclitaxel (11.5%) and platinum + pemetrexed (8.6 %). In patients in whom erlotinib was third-line therapy, second line regimens most commonly used were: pemetrexed (61.1%) and taxotere (30.6%). EGFR mutation was performed in 82 patients and was positive in 22 cases (26.8%). In assessing the overall survival (excluding patients in early stage and IIIA), the EGFR-positive vs negative patients had an overall survival of 47 vs 22 months respectively (p = 0.038). Response rate to erlotinib: 12.1% had a partial remission (PR), 40.7% showed stable disease – SD (disease control rate of 51.8%) and 47.2% experienced progressive disease.Response rate among EGFR-positive patients: 15.0% had PR, 50.0% showed SD (disease control rate of 65.0%) and 35.0% experienced PD. The response to erlotinib among EGFR-positive patients was associated with better control of the disease (OR 1.651, 95% CI 0.566 to 4.817) versus EGFR-negative patients. The estimated survival after erlotinib in EGFR-positive versus EGFR-negative patients was 14 and 6 months respectively (p = 0.003).

Conclusion: Our study demonstrates that the presence of EGFR mutation is associated with better overall survival (prognostic factor independent of therapy) and better response to erlotinib (predictive factor of response)

Thus, since January 2010, determining the EGFR mutation status has become a routine test in all patients with NSCLC in our unit.

Keywords: erlotinib, Non-small cell lung cancer, EGFR, mutational status

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.198 IMPACT OF ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER SYMPTOMS ON PATIENT DAILY LIVING AND HEALTH RELATED QUALITY OF LIFE.

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Background: Health Related Quality of Life

(HRQoL) in oncology patients is directly related to symptoms. The aim of the study was to assess the impact on daily living and HRQoL of the symptoms of advanced non-small cell lung cancer (NSCLC).
Methods: An observational prospective study was carried out in 32 Spanish institutions, and included 257 patients. Patients had stage IIIB NSCLC with pleural or pericardial effusion or stage IV NSCLC and were about to initiate second-line treatment at the time for enrolment. HRQoL and disease-related symptoms were assessed with the lung-specific Functional Assessment of Cancer Therapy questionnaire (FACT-L) and the Lung Cancer Symptom Scale (LCSS), respectively. An ad hoc specific questionnaire correlating the impact of NSCLC symptoms on daily life was also evaluated.
Results: Preliminary baseline data for 257 patients are presented; 56,4% had adenocarcinoma and 23.7% squamous cell carcinoma; the median (SD) age was 65.0 (10.0) years; 79.4% were males, 96.5% Caucasian, and 83.5% current/ever smokers. ECOG performance status was 0/1/2/3: 15.2%/56.4%/21.8%/5.4%. At the basal visit the mean (SD) LCSS score was 34.2 (19.0) points and the mean (SD) FACT-L score (SD) was 80.9 (23.2) points. Patients who discontinued the therapy or experienced progressive disease showed a significant worsening of symptoms. Impact of LC symptoms on daily life shows a high correlation with HRQoL assessed according to FACT-L questionnaire (r=0.82).
Conclusion: The presence of symptoms and their impact on the daily life was related with a major impact on HRQoL. Final analysis showing the QoL and symptoms of patients and the correlation with second line therapy will be presented.
Keywords: NSCLC-related symptoms, Health Related Quality of Life, Non-Small-Cell Lung Cancer, Second line treatment

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P3.199 SECOND AND FURTHER LINES OF THERAPY IN ADVANCED NSCLC AFTER FAILURE OF CHEMOTHERAPY WITH BEVACIZUMAB – A RETROSPECTIVE STUDY.

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Background: There are only limited data about the effectiveness of the second and further lines of therapy in patients with advanced non-squamous NSCLC (NSQ NSCLC) after failure of first line chemotherapy with bevacizumab. Chemotherapy and EGFR TK inhibitors have been used commonly in practice, however, without any phase III trial aimed specifically on advanced metastatic NSCLC pretreated with bevacizumab. Purpose of this study was to evaluate the second and further lines of therapy in this group of patients.
Methods: Patients with advanced metastatic NSQ NSCLC treated with the first line chemotherapy and bevacizumab between July 2007 and March 2010, and with further systemic therapy due to disease progression were eligible for this retrospective study.
Results: Altogether 39 patients were included (male/female: 19/20, median age: 56 yrs, range: 33–76). EGFR TK inhibitor was used in the second line treatment in 22 patients (erlotinib: 21, gefitinib: 1), chemotherapy was used in 17 patients (pemetrexed: 13, docetaxel: 2, gemcitabine and carboplatin: 2). Response rate: PR: 5% (95%CI: 1–17), SD: 51% (95%CI: 36–66), PD: 44% (95%CI: 29–59). Progression free survival (PFS) in 39 patients – median: 3 months (95%CI: 1.5–4). Estimated overall survival (OS) – median: 5 months. There was no difference in the PFS or OS between the patients treated with EGFR TK inhibitor or chemotherapy in the second line. EGFR mutation status was unknown in 20 patients and known (positive for sensitizing mutations) in 2 patients. These 2 patients achieved PFS 16 and 10+ months. Third line chemotherapy was administered in 17/32 patients with PD after the second line treatment. Erlotinib was used after the previous chemotherapy most often – in 9/11 patients. Docetaxel or pemetrexed were used after the 2nd line EGFR TK inhibitor in 4/6 patients, other chemotherapeutics in 2 patients. There was an impressive difference in OS (from the start of the 2nd line therapy) between the patients in which

it was possible to administer the third line therapy comparing with those without further therapy – MST (median survival time): not reached yet, but will be over 9 months vs 1.5 months. Fourth line treatment was administered in 6/12 patients with the PD after the 3rd line therapy. MST in the group with vs without the 4th line therapy was 13 vs 6.5 months. Two patients received 5th line chemotherapy (oral vinorelbine or etoposide), OS is 30+ and 18+ months in these patients. There were no unexpected toxicities or serious adverse events (excluding those connected with the NSCLC PD) in the whole group of 39 patients.

Conclusion: Second and further lines of systemic therapies may improve survival of patients with NSCLC PD after the first line chemotherapy and bevacizumab. Choosing the right time for these therapies, i.e. starting treatment in time without any unneeded delays seems to be one of the key issues.

Keywords: Chemotherapy, NSCLC, bevacizumab, second line

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P3.200 DELIVERY OF SYSTEMIC TREATMENT IN CASES OF METASTATIC NON SMALL CELL LUNG CANCER AT A SINGLE CANADIAN INSTITUTION

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Background: Despite many innovations in treatment and increased emphasis on prevention with smoking cessation programs, lung cancer continues to cause extensive morbidity and mortality worldwide. Most patients present with advanced unresectable disease and are candidates only for palliative treatment. Since the late 1990s, platin based doublets have been the mainstay of palliative chemotherapy regimens for metastatic disease and are associated with a 10-12 month median overall survival (MOS) in phase III clinical trials. However, the toxicity associated with cytotoxic chemotherapy can adversely affect quality of life limiting the applicability of such treatments to the general NSCLC population. In addition, poor performance status patients do not necessarily benefit from such treatment. With a median age at presentation approaching 70, many patients are well into their 8th decade and are less tolerant of the many side effects of cytotoxic drugs. Furthermore, given the prevalence of significant, often smoking related co-morbidities many patients are not candidates for such treatment. We set out to ascertain what proportion of stage IV NSCLC patients received palliative systemic chemotherapy at our institution. For the remaining patients, we determined which of the above mentioned factors contributed to the decision not to treat systemically.

Methods: After ethical approval was obtained, demographic details, clinical variables and outcome data were gathered on patients diagnosed at the Tom Baker Cancer Centre (TBCC) from 2003 to 2006 using the Glans-Look Lung Cancer Database. Treatment modalities delivered (cytotoxic treatment, anti-epidermal growth factor receptor (EGFR) treatment, palliative radiation, etc) were documented. Charts were reviewed to ascertain reasons for choice of treatment. Statistical analysis was performed using the Kaplan-Meier method, multivariate analysis and Spearman's rank correlation.

Results: 832 patients were diagnosed with stage IV NSCLC at the TBCC in 2003-2006. While the majority (72.1%) received palliative radiation, only 23.3% received systemic treatment while 18% received no palliative treatment at all. The proportion who received systemic treatment was related to age with 46% of the under 50yr old group receiving systemic treatment vs 17% for the 70-80yr and 3% for the over 80 age group. Palliative radiation was not associated with a survival benefit. However, MOS of those who received systemic treatment was 11.2 vs 2.9 months for those who received none. MOS improved with additional lines of treatment: 8.6 vs. 14.4 vs. 27.7 months for 1st line, 2nd line and 3rd line of systemic treatment respectively.

Conclusion: The proportion of patients who receive systemic treatment for metastatic NSCLC is low, and likely a result of poor performance status, advanced age and multiple co-morbidities. However, for patients at our institution who were well enough to receive systemic therapy, MOS approached 12 months, comparable to Phase III trials. Clearly, new strategies are needed to increase the uptake of systemic treatment in metastatic NSCLC. Detailed analysis of reasons for not receiving systemic chemotherapy will be presented.

Keywords: Metastatic Disease, Non small cell lung cancer, Chemotherapy

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P3.201 WEEKLY PACLITAXEL APPEARS ACTIVE AND WELL-TOLERATED IN THIRD AND FOURTH-LINE ADVANCED NSCLC PATIENTS

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Background: Weekly paclitaxel has been evaluated in Phase II studies in second-line metastatic NSCLC (Chang, 1998) but not widely in the third and fourth-line setting. The aim of this study was to evaluate the activity and toxicity of single-agent paclitaxel administered weekly to heavily pretreated patients with non-small cell lung cancer (NSCLC).
Methods: Patients with Stage IV NSCLC who have received ≥ 2 prior lines of therapy are eligible. Patients receive paclitaxel (60-80mg/m^2) delivered for 3 consecutive weeks on a 4-week cycle. CT scans are performed every 2 cycles. Patient data is collated from the Royal Marsden NHS Foundation Trust electronic patient record. The null hypothesis will be rejected if ≥ 3/20 (15%) RECIST responses are seen.
Results: To date, 12 patients (median age 65 years; range, 47-73) have commenced treatment. Patient demographics including gender, NSCLC histological subtype, ECOG performance status and lines of prior treatment are detailed in Table 1. No patient to date has had an EGFR mutation although all patients have received prior erlotinib. Five patients have had a CT scan after 2 cycles (8 weeks of treatment) with 2/ 5 achieving a PR (in both these patients the response has been confirmed with a second CT scan after a further 2 cycles). No Grade 3/4 toxicities have been reported to date. 10 patients continue on treatment at present.

Patient no.	Age (median 65)	Gender	Histology	PS	Lines of prior treatment
1	68	F	Adenocarcinoma	1	2 (P- PEM; E)
2	69	F	Adenocarcinoma	2	2 (P-PEM; E-capecitabine)
3	62	F	Adenocarcinoma	2	3 (paropanib- PEM; E-capecitabine; D)
4	80	M	Squamous	2	3 (V; E; MVCarbo)
5	61	M	Adenocarcinoma	1	2 (P-PEM; E)
6	47	F	Adenocarcinoma	1	4 (PV, E; BIBW/ placebo; P-PEM)
7	72	M	Squamous	1	2 (PV; BIBW PT)
8	73	M	NA	1	3 (P/G; D; BIBW PT)
9	64	F	Adenocarcinoma	2	2 (P-PEM; E)
10	68	M	Adenocarcinoma	1	3 (PV; E; PV)
11	66	F	Adenocarcinoma	2	2 (PV; E)
12	73	F	Adenocarcinoma	1	3 (E; PEM; D)

P = platinum chemotherapy; PEM = pemetrexed; E = erlotinib; D = docetaxel; MVCarbo = mitomycin, vinblastine and carboplatin; Vin = oral vinorelbine; T- paclitaxel; G = gemcitabine

Conclusion: Single agent paclitaxel administered on 3 consecutive weeks out of 4 at a dose of 60-80mg/m^2 is well-tolerated in heavily pretreated NSCLC patients and demonstrates encouraging preliminary clinical activity. References Chang A, Boros L, Asburg R et al. Weekly moderate-dose paclitaxel (P) in stage IV non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 1998;17:420a.
Keywords: NSCLC, 3rd and 4th line therapy, Weekly paclitaxel

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.202 NUTRITIONAL PARAMETERS IMPROVE SURVIVAL OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER DURING CHEMOTHERAPY TREATMENT.

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Background: Lung cancer is one of the most common type of cancer worldwide and is the leading cause of cancer death. Malnutrition is frequent in patients with non small cell lung cancer (NSCLC). Early identification and treatment of nutritional deficiencies can lead to improved outcomes including survival. Non invasive techniques are needed to evaluate changes in body composition, nutritional status and prognosis in these patients. The aim of the study was to investigate the prognostic role of nutritional parameters in advanced non small lung cancer (NSCLC) patients under first line chemotherapy
Methods: 119 advanced NSCLC patients naive to treatment were included prospectively, anthropometric and biochemical like serum albumin level, platelets/ lymphocytes index (P/L), body mass index (BMI) and bioelectrical impedance analysis (BIA) including phase angle was obtained; Overall Survival was calculated with Kaplan Meier method and Cox proportional hazard models were constructed to evaluate multivariate prognostic effect.
Results: 55 females and 64 males were included, mean age was 60.5±12.5 years, IMC =24.8±4.5mg/

m^2, patients weight loss average was 8.4% and phase angle media was 5.8. Patients with malnutrition parameters showed significantly lower overall survival: BMI<20 mg/m^2 (p>0.001); Subjective Global Assessment (SGA) results as well nutrition vs moderate or severe malnutrition(p=0.002); phase angle <5.8 (0.014); and platelet/lymphocytes index <150 (p=0.032). After multivariate analysis phase angle remain significative (table 1).
Table 1. Overall Survival Multivariate analysis

Nutritional parameter	RR	IC 95%	p
BMI<20	1.48	(0.287-1.377)	0.246
Albumin<3.5 mg/dl	2.55	(0.955-6.811)	0.062
Phase angle	1.99	(0.999-3.985)	0.050
P/L	1.47	(0.698-3.123)	0.308
SGA	0.17	(0.763-4.328)	0.177

Conclusion: Malnutrition parameters are independent prognostic indicators of poor survival in advanced NSCLC. Phase angle value was the most significant parameter as reported in similar recent studies. Nutritional interventions could improved body weight, BMI, albumin and phase angle and potentially lead to an improved survival in patients with advanced NSCLC.
Keywords: survival, Body Mass Index, Malnutrition

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P3.203 ADVANCED NEVER SMOKER ADENOCARCINOMA OF THE LUNG: REPORT OF PAIRED NORMAL AND TUMOR WHOLE GENOME SEQUENCING

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Background: Recent technological advances in the form of Whole Genome Sequencing (WGS) technologies now provide us with platforms to interrogate entire human genomes at a fraction of the time and cost compared to more traditional sequencing technologies. For the first time, next-generation sequencing (NGS) offer us the ability to survey the global somatic landscape of cancer. It is now possible with NGS to re-sequence, analyze, and compare the matched normal and tumor genes of an individual patient's entire genome. As part of a prospective pilot study at our institution, we report the results of WGS of paired normal and tumor specimens collected from a female never smoker with advanced adenocarinoma of the lung.
Methods: After informed signed consent and confirmation of study eligibility (KPS ≥ 80, adequate renal, hepatic, and hematologic labs, advanced incurable cancer progressed on ≥ 1 prior systemic therapy), a CT guided biopsy of a lung metastasis and whole blood was collected for WGS analysis on the Illumina HiSeq2000 system. Data compiled will include somatic coding point mutations and frameshift mutations including mutations in important domains or motifs (kinase, ligand binding, etc), genes mapping within focal high level amplicons or homozygous deletions, genes involved in translocations/fusions, rank order of expressed genes, and/or germline mutations or SNPs involved in drug metabolism. RNA sequencing of these specimens is also ongoing.
Results: A 61 year old woman initially presenting with stage 4 adenocarinoma of the lung, was previously treated with the following regimens: carboplatin and paclitaxel, pemetrexed, and erlotinib. After progressing on erlotinib, she underwent a lung tumor biopsy and whole blood collection. NGS began the first week of January 2011 and as of January 31, 2011, a minimum of 23X genome coverage on both normal and tumor samples was completed. Preliminary results show a TP53 somatic mutation, and the absence of EGFR and KRAS mutations and EML4/ALK translocation. RNA sequencing is in process. Analysis is ongoing and final results will be presented at the meeting.
Conclusion: In the first prospective NGS pilot study for advanced cancer patients, we successfully completed WGS of a paired normal and tumor sample in non-small cell lung cancer. With improved infrastructure and decreased costs, we anticipate that WGS using NGS techniques will become more commonplace and has the potential to identify

unique tumor aberrations at an unprecedented depth.
Keywords: Whole genome sequencing, next generation sequencing, never smoker, advanced adenocarcinoma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.204 MID-TERM RESULTS OF INTRAPLEURAL PERFUSION HYPERTHERMIC CHEMOTHERAPY FOR THE PATIENTS WITH MALIGNANT PLEURAL SEEDING AND EFFUSION IN NON-SMALL CELL LUNG CANCER

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Background: Chemotherapy is considered as the mainstay treatment for non-small cell lung cancer (NSCLC) diagnosed with pleural seeding or malignant pleural effusion. However, the reported median survival of this subgroup entity is only 6-9 months. Intrapleural perfusion hyperthermic chemotherapy (IPHC) may be used for local control of pleural disease but the clinical effect has to be established. The aim of this study is to evaluate the safety and feasibility of IPHC in the treatment of lung cancer with pleural metastases.
Methods: From June 2003 to August 2010, 29 patients who were diagnosed with pleural seeding or occult malignant effusion underwent IPHC. Twenty one patients underwent IPHC after pulmonary resection and 8 patients for recurred lung cancer without distant metastasis were also applied. We examined perioperative complications, pleural disease progression free survival, distant metastasis free survival, and overall survival.
Results: The mean age was 61.3 years (15 male and 14 female). Twenty eight patients were adenocarcinoma and 1 squamous cell carcinoma. All the patients had no intraoperative adverse events. Postoperative acute renal insufficiency occurred in 3 patients (10.3%). One patient progressed to chronic renal failure and the others returned to normal creatinine within 2 months. All patients received adjuvant intravenous chemotherapy. Median hospital stay after IPHC was 7 days (R: 5-27 days). During the follow-up period, pleural metastasis was controlled in 21 (72.4%) patients and was aggravated in 8 (27.6%) patients. Distant metastasis occurred in 19 (65.5%) patients. The median time to pleural disease progression and distant metastasis were 12.0 and 12.8 months, respectively. Median survival was 24.6 months and 3 year survival was 52.5%.
Conclusion: IPHC is the safe and simple procedure. Our results suggest that IPHC is the highly effective local control modality in patients with malignant pleural seeding or occult effusion resulting from lung cancer who also undergo pulmonary resection of their primary lesions. These findings may affect the prolongation of survival.

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P3.205 SINGLE NUCLEOTIDE POLYMORPHISMS IN DNA REPAIR GENE ERCC1 PREDICT CLINICAL RESPONSE TO PLATINUM-BASED CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Background: to assessed whether single nucleotide polymorphisms (SNP) of DNA-repair genes ERCC1 predict efficacy and prognosis of non-small-cell lung cancer (NSCLC) patients treated with platinum-based chemotherapy
Methods: A retrospective dataset of 117 patients with NSCLC were routinely treated with cisplatin or carboplatin based regimens as first- or second-line chemotherapy. The allelotyping of DNA-repair genes polymorphisms were determined via PCR-RFLP using genomic DNA obtained from peripheral WBC.
Results: ERCC1 (Asn118Asn) genotype was significantly associated with response to treatment. Patients with either one or two C alleles (C/C, C/T) at Asn118Asn were more likely to respond to platinum-based chemotherapy compared with those without the C allele (Odds ratio=0.19 95% CI 0.041-0.872 P = 0.033, by binary logistic regression). There was a significant association between the ERCC1

C8092A polymorphism and OS (P =0.001, by log-rank test), with median survival times of 9 (C/C) and 16 (C/A or A/A) months, respectively, suggesting that any copies of the A allele were associated with an improved outcome. Cox's multivariate analysis suggested that the joint effect of ERCC1 polymorphic variants (C8092A and N118N) (Odds ratio, 4.37; 95% CI, 1.26-15.23 P =0.021) was independent prognostic factors for OS in advanced NSCLC patients treated with platinum-based chemotherapy.
Conclusion: Assessment of genetic variations of ERCC1 could predict platinum-based chemotherapy outcome in advanced NSCLC.
Keyword: Single nucleotide polymorphisms ; DNA repair gene ; Non-small cell lung caner ; Chemotherapy

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P3.206 PEMETREXED CHEMOTHERAPY AFTER SECOND LINE PALLIATIVE CHEMOTHERAPY IN METASTATIC NON SMALL CELL LUNG CANCER (NSCLC)

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Background: Pemetrexed (P) is currently indicated only for first, maintenance and second line treatment of non squamous NSCLC. There are currently no data for its use after second line treatment. Due to funding restrictions in Cyprus (P is not reimbursed for any indication in patients with NSCLC), P was used in selected patients when most other therapeutic options had been used (ie post first line gemcitabine platinum doublet, second line docetaxel and third line erlotinib).
Methods: Ten patients are included in this retrospective study. Four patients received this as 3rd line, five as 4th line and one as 5th line (previous treatments as above and also Vinorelbine). Patients had regular Chest x-rays (every 2 cycles) and CT scans (every 3-4 cycles) and assessment of their toxicity with CTC criteria every 3 weeks.
Results: 6 males / 4 females, with 3 patients still alive and on treatment. Mean age 56 years (range 49-77), 5 never smokers, performance status WHO1 for 7 patients and WHO2 for 3 patients, histology adenocarcinoma in 7 patients, mixed adenocarcinoma/BAC in 3. They received a median 4.5 /mean 8.7 cycles of chemotherapy (range 2-34). Only 2 patients had grade 2 malaise, the rest was grade 1 or no toxicity. 7 patients had symptomatic improvement. 2 patients had a partial response, 3 patients minor response, 2 patients stable disease and 3 patients progressive disease. Median progression-free survival from the date of starting P was 196 days (95% CI 117 - 462 days). Median overall survival from starting P was 556 days (95% CI 34 - 1078 days). Median overall survival from initial treatment was 1175 days (95% CI 846 to 1504 days).
Conclusion: In well selected patients with preserved performance status and non squamous NSCLC, P after 2nd line chemotherapy can result in very meaningful palliation of symptoms and prolongation in survival.
Keywords: Pemetrexed chemotherapy, metastatic NSCLC

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P3.207 CORRELATION OF TIMING AND CLINICAL BENEFIT FROM TREATMENT WITH PEMETREXED IN METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Pemetrexed is increasingly being used in the treatment of advanced stage, non-squamous NSCLC. Pemetrexed is introduced mainly as a combination therapy for first line treatment or a single agent in second line. However, there is little data on the efficacy of pemetrexed in later lines of treatment.
Methods: In a retrospective single institution study, we reviewed the outcome of treatment with pemetrexed in patients with advanced stage, metastatic NSCLC. We evaluated clinical benefit and toxicities among patients who received the treatment at 1st through 5th line of chemotherapy. Patient and disease characteristics included age and ECOG performance status (PS) at the time of

initiating pemetrexed, gender, ethnicity, smoking history, stage at the time of diagnosis of lung cancer, tumor histology, number and location of metastatic involvement at the time of initiating pemetrexed, and toxicities. Details of chemotherapies prior to and after pemetrexed were also collected.
Results: 135 patients received pemetrexed between 2004 and 2008. Pemetrexed was given as a single agent (85%) or in combination with other anti-tumor agents (15%) and in 1st (7%), 2nd (59%), 3rd (20%), and 4-5th (13%) line of therapy. Except for age(median age 74 years for 1st line vs 60-65 years in 2nd-5th line, p=0.04) , there was no statistically significant difference in demographic or disease-related characteristics between lines of therapy. The median number of delivered cycles of pemetrexed, grade III/IV toxicities, overall response rate (ORR) and rate of stable disease > 6 months (SD), progression free survival (PFS), and overall survival (OS) were not significantly different between groups. Across all lines of treatment, single vs combination use of pemetrexed or choice of prior treatment did not significantly differ regarding ORR, SD, PFS or OS. Across all lines, metastasis to bone (p=0.008) and liver (p=0.03) were associated with significantly worse ORR and SD, and also worse PFS and OS in bone (p= 0.03, p= 0.04 respectively) and liver (p<0.001, p=0.02 respectively). In multivariate analysis among all lines of treatment, age ≤65 years (p=0.02) and ≤ 2 sites of extra-pulmonary metastasis (p=0.002) were associated with better ORR and SD. Longer survival was associated with PS≤1 (p<0.001), never smoking history (p=0.01) and longer (≥ 18 months) interval from diagnosis to initiation of pemetrexed treatment (p=0.02).
Conclusion: In this cohort of patients, pemetrexed appeared to be equally safe and effective earlier or later in the course of management of metastatic NSCLC. Clinical predictors of benefit from pemetrexed therapy are not influenced by the timing of this treatment or by choice of prior therapies. These findings however will need to be validated in an independent cohort of patients.
Keyword: non-small cell lung cancer, advanced stage, pemetrexed

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P3.208 THE CHANGES IN PATTERNS AND OUTCOMES OF PALLIATIVE CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS DURING THE 2000S : A SINGLE CENTER EXPERIENCE FOR 7 YEARS.

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Background: Platinum-based doublets have been the standard care in advanced non-small cell lung cancer (NSCLC) patients since the 1990s. During the 2000s, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors(TKIs) and an antifolic agent pemetrexed were introduced and showed efficacy in NSCLC patients, expanding options for palliative chemotherapy beyond second line. The purpose of this study is to describe the changes in patterns and outcomes of palliative chemotherapy for NSCLC patients after the advent of the new agents in nonselected NSCLC patients in clinical practice.
Methods: 1,569 patients were diagnosed with metastatic NSCLC and received palliative chemotherapy at Samsung Medical Center, Seoul, Korea between Jan 2002 and Dec 2008. 1,540 patients with available data were included in retrospective analysis, with a follow-up until Dec 2010.
Results: 65.6% (n=1,011) had adenocarcinoma, and 19.4% (n=299) had squamous cell carcinoma. Since 2006, adenocarcinoma started to increase in incidence and during 2006-2008 incidence of adenocarcinoma was higher (70.1%) than during 2002-2005 (59.9%) (p=0.001). 79.4% received platinum based chemotherapy as the first line. Of the 1,540 patients, 61%, 55%, and 25% received a second-, third-, and fourth-line chemotherapy. Recently diagnosed NSCLC patients (during 2005-2007) proceeded to more lines of chemotherapy with 36.1% (n=234) of more than the fourth line, compared with only 24.1% of the patients diagnosed during 2002-2005 (p<0.001). The main change in patterns of palliative chemotherapy was the introduction of pemetrexed and TKIs. Until

2005, these agents consisted 25.7% of second line chemotherapy, in contrast to 64.4% since 2006. The median overall survival(OS) was 12.9 months (95% C.I. 12.1-13.7 months), with 2.0 months increase during 2005-2008 (n=1066,median OS 13.6 months, 95% C.I. 12.7-14.5 months) compared with during 2002-2004 (n=474,median OS 11.6 months, 95% C.I. 10.4-12.8 months)(p<0.001). In subgroup analysis according to histology, the increased survival was significant only in patients with adenocarcinoma (median OS 16.3 months during 2005-2008 vs. 13.0 months during 2002-2004, p=0.006)
Conclusion: TKIs and pemetrexed has been increasingly administered as second- or third- line chemotherapy for metastatic NSCLC patients, and more patients are being treated with more lines of chemotherapy. Overall survival was significantly increased especially in adenocarcinoma patients. With the recent approval of these agents as the first-line chemotherapy, further changes are expected.
Keywords: Chemotherapy, Non-small cell lung cancer, Third-line therapy, second-line therapy

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P3.209 A COMPARATIVE CLINICAL AND COST-EFFECTIVENESS EVALUATION OF GEFITINIB AND ERLOTINIB IN THE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Gefitinib and erlotinib improve response rates, progression-free survival and quality of life (QOL), when compared to chemotherapy, in the first line treatment of patients with advanced NSCLC who have activating EGFR mutations. Pooled data from retrospective series and a small prospective study (total=2400 patients), suggest that gefitinib and erlotinib are equivalent in Asian populations. After chemotherapy failure in unselected patients, erlotinib improves overall survival while gefitinib does not.
Methods: A decision-analytic model was developed to determine the comparative clinical efficacy and cost-effectiveness (CE) of gefitinib versus erlotinib. After testing, patients with activating EGFR mutations receive erlotinib vs. gefitinib in the 1st-line setting followed by chemotherapy. Patients without activating mutations receive 1st-line chemotherapy and 2nd-line erlotinib; while those in the gefitinib arm go on to best supportive care (The model assumes that while further chemotherapy may be used, benefits and costs would be similar in both arms). Clinical data are derived from available literature and assume that gefitinib does not improve survival in patients without activating EGFR mutations while erlotinib does, as extrapolated from ISEL and BR21. Societal costs were obtained from cancer centers in Singapore. Health effects were expressed as life-years (LY) and quality-adjusted life years (QALY) gained. All costs and incremental cost-effectiveness ratios (ICER) are in 2010 Singapore Dollars (SGD) [1.3SGD=1USD]. Sensitivity analyses were conducted to test for different clinical and cost scenarios (The base case assumes a mutation prevalence of 40%).
Results: In the base case, treatment with erlotinib generated an incremental 0.066 LY and 0.037 QALY. At listed prices, in which erlotinib is approximately 50% more expensive than gefitinib per daily dose, incremental cost was SGD 17,460; generating an ICER of SGD 265,000/LY and SGD 468,000/QALY. Sensitivity analyses showed that when 10% of patients have activating mutations, erlotinib generates an increment of 0.099 LY and 0.056 QALY, an added cost of SGD 17,860 and ICERs of SGD 180,000/LY and SGD 319,000/QALY. After discussions with the authors, and realizing its market share in Singapore was 30% or less, Roche decided to provide erlotinib at a discount that brings it to the same cost per dose as gefitinib. With this changed assumption, this model calculates that the ICERs for erlotinib when compared to gefitinib would be SGD 164,000/LY and SGD 289,000/QALY, bringing it closer to (but still beyond) generally accepted thresholds for oncology medications. Of note, when both drugs have the same price, the ICERs represent an assessment of the CE of erlotinib in the treatment of EGFR negative patients.
Conclusion: Erlotinib improves clinical efficacy when compared to gefitinib but it is not cost-effective at full listed price in Singapore. At discounted price, it is not cost-effective in the treatment of

mutation negative patients but it is equivalent to gefitinib in the treatment of patients with mutations. Comparative efficacy and cost effectiveness models may help assess the relative clinical and economic value of therapeutic interventions and may be used as a tool in determining drug prices and in increasing access to new innovative cancer drugs and their economic value to society.

Keywords: Lung cancer, gefitinib, erlotinib, Cost-effectiveness

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P3.210 AUDIT OF LUNG CANCER CHEMOTHERAPY FOR PATIENTS OF POOR PERFORMANCE STATUS.

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Background: Systemic chemotherapy is a recommended treatment for patients with advanced NSCLC of good performance status (WHO 0-1) with trials demonstrating both a survival advantage and improvement in quality of life. The treatment of patients of performance status (PS) 2 is contentious. The aim of this study is to review the outcomes of patients of poor PS treated with chemotherapy in our unit.

Methods: This is a retrospective review of all lung cancer patients treated at the Kent Oncology Centre between 1.7.09 and 30.6.10. All patients planned for chemotherapy were identified from an electronic action sheet database. Patients of poor PS (WHO 2-3) were identified and individual case notes analysed recording diagnosis, PS, age, line of treatment, planned chemotherapy and survival from decision to treat.

Results: 199 patients with lung cancer were planned for chemotherapy. 23 patients were of poor PS (PS2=21, PS3=2). 17 patients were diagnosed with non-small cell lung cancer (NSCLC), 4 small cell lung cancer and 2 mesothelioma. Of the 17 patients with NSCLC 12 were adenocarcinoma cell type, 4 squamous cell and 1 unspecified NSCLC. The median age was 66 years (range 41-79 years). 6 patients were planned for doublet chemotherapy, 8 single agent chemotherapy and 3 treatment with a tyrosine kinase inhibitor. 9 patients received first line treatment and 8 second line treatment. The median survival was 42 days (range 11-251 days). There was no clinically significant difference between patients treated first line v second line (31days v 47 days). 6 patients never started treatment. 5 patients died within 30 days of treatment. 2 patients lived longer than 16 weeks. The median survival of the patients with SCLC was 506 days. The median survival of the patients with mesothelioma was 591 days.

Conclusion: Our data suggest that poor PS patients with NSCLC do not benefit from treatment with systemic chemotherapy and early referral to palliative care specialists would seem more appropriate. Treatment with targeted biological therapy needs further evaluation in this group of patients. The outcomes for poor PS patients with SCLC and mesothelioma treated with chemotherapy are significantly better.

Keywords: Chemotherapy, performance status, NSCLC

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P3.211 CA(N) AND R497K ARE ASSOCIATED WITH PFS TO EGFR TKIS IN THE ADVANCED NSCLC PATIENTS HARBORING ACTIVATING MUTATION OF EGFR.

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Background: In non-small cell lung cancer (NSCLC) pts harboring activating mutations of EGFR (mutEGFR) treated with EGFR tyrosine kinase inhibitors (EGFR TKIs), 70~80% of objective tumor response are reported, however, the rest (20~30%) of the pts barely responds to EGFR TKIs. Meanwhile, even in the NSCLC pts having wild type

EGFR. favorable tumor response to EGFR TKIs is sometimes observed. We investigated the mutation status and genotype of genetic polymorphisms of EGFR gene in NSCLC pts receiving EGFR TKIs and analyzed an association between them and clinical outcomes and toxicities.
Methods: In 165 advanced or metastatic NSCLC pts receiving gefitinib or erlotinib, we assayed EGFR mutation in paraffin embedded tumor tissue using direct sequencing and genotyped six different SNPs in genomic DNA extracted from peripheral blood; promotor 191C>A, 216 G>T, intron 1, CA repeat number (CA)n, exon 13, R497K, exon 20, 2607G>A, and exon 25, D994D.
Results: Sex ratio (M: F) was 80:85 and mean age was 63.1. All pts were stage III or IV and histological subtype was as follows: adenocarcinoma 136, squamous cell carcinoma 22, miscellaneous 7. The objective response rate (CR+PR) was 38.2% (65 pts) and SD was 31.5% (52 pts). mutEGFR was associated with (CA)n (≤36 vs.>36) with statistical significance (p=0.018). Statistical correlation existed between objective tumor response and (CA) n (p=0.05). In both all pts and mutEGFR group, mutant type (RK/KK) of R497K showed much more prolonged PFS (4.2 vs.15.9 mo, p=0.002) and OS (10 vs. 32 mo, p=0.007) when compared with wild type (RR). Of 143 pts assessed for skin toxicities, G2607A was statistically correlated with skin rash (p=0.04).
Conclusion: Taken together, shorter (CA)n (≤36) is associated with favorable tumor response to EGFR TKIs as well as mutEGFR. RK/KK mutants of R497K located on EGFR exon13 might be a pharmacogenetic biomarker to predict prolonged PFS and OS in the NSCLC pts harboring mutEGFR who are treated with EGFR TKIs.
Keywords: NSCLC, EGFR TKI, CA repeat, R497K

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P3.212 MUTATION OF EPIDERMAL GROWTH FACTOR RECEPTOR GENE IN SQUAMOUS CELL CARCINOMA OF LUNG

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Background: The epidermal growth factor receptor (EGFR) gene mutation has been reported as an important predictive factor for EGFR-tyrosine kinase inhibitor (TKI) efficacy in NSCLC. In "The Lung Cancer Diagnosis and Treatment Guideline published by The Japan Lung Cancer Society 2010 edition", the EGFR gene mutation is strongly recommended to be analyzed in deciding the treatment policy of advanced NSCLC. In addition, it is known that the EGFR gene mutation is frequently observed in adenocarcinoma (Ad), but very rare in squamous cell carcinoma (Sq). Efficacy of EGFR-TKI in EGFR gene mutation positive Sq has not examined enough.
Methods: We obtained tumor samples from 27 patients diagnosed as Sq (excluded Ad-Sq carcinoma) by two or more pathologists between January 2008 to December 2010. The EGFR mutation status was determined by PCR-Invader assay (BML Incorporation) and direct sequencing method.
Results: EGFR mutations were detected in 2 of 27(7.4%) samples. Common characteristics of two patients were male, elderly, high level of CEA, and good PS. One patient was a non-smoker, and the other was a heavy smoker. Exon 21 point mutations (L858R) were observed in both patients. Gefitinib was administered to one patient (non-smoker), and the partial response was observed.
Conclusion: The frequency of the EGFR gene mutation in Sq was low. However, it was suggested that gene mutation positive Sq is responded to EGFR-TKI. It is necessary to analyze the EGFR gene mutation in Sq.
Keywords: EGFR, NSCLC, squamous cell carcinoma, gefitinib

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P3.213 CHEMOTHERAPY IN NON SMALL CELL LUNG CANCER PATIENTS WITH BRAIN METASTASES

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Background: The prognosis of non small cell lung cancer which has metastasised to the brain is very poor and the expected survival without treatment is about one month. Steroids and radiotherapy are used for symptom control, but the role of chemotherapy in these patients is not well established. There are some small single institution non randomised studies which suggest that fit patients with brain metastases due to non small cell lung cancer that have chemotherapy, do as well as other stage IV non small cell lung cancers without brain metastases getting chemotherapy.
Methods: From March 2005 to May 2007, at James Cook university hospital, Middlesbrough, UK, we treated 9 patients with brain metastases from non small cell lung cancer with carboplatin and gemcitabine chemotherapy. Seven of these patients had WHO PS of 1, while 2 patients were WHO PS 2. Four of the nine patients had extracranial metastases while 5 patients had just brain metastases and no other extrathoracic metastases. The median age of the patients was 66 years (range 49 - 74 years).
Results: Four patients had a partial response to chemotherapy (44%), 4 had stable disease (44%) and one had progressive disease on chemotherapy. The median survival was 8 months (range 2 - 13 months). There were 2 patients (22%) who survived over a year. Chemotherapy was generally well tolerated in these patients. There were only three episodes of hospital admissions with grade III or worse haematological toxicity and neutropaenic fever (of a total of 24 cycles of chemotherapy). There were no chemotherapy related deaths. Four of nine patients had radiotherapy after chemotherapy, three patients had radiotherapy prior to chemotherapy and two had no radiotherapy. Of the 2 patients with WHO PS 2, one progressed on chemotherapy and the other survived for 6 months.
Conclusion: Though this is a small study, we think this is significant because the median survival of patients in this small study is comparable to stage IV non small cell lung cancer without brain metastases. Chemotherapy in non small cell lung cancer patients with brain metastases is not standard practice, but we think in a selected group of patients with WHO PS 1 or better, combination chemotherapy may improve survival without causing much toxicity.
Keywords: Non small cell lung cancer, brain

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P3.214 A PRONOSTIC SCORE BASED ON CLINICAL FACTORS AND BIOMARKERS FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Survival of patients diagnosed of advanced stage non-small cell lung cancer (NSCLC) is poor. Several studies have demonstrated that the performance status (PS), tumour stage and treatment are independent prognostic factors for survival. Other studied variables include age, histology, CNS metastases, serum tumour markers, LDH, albumin Il-6 and PCR. The objective of the present study is to determine the prognostic impact of clinical factors and biomarkers in patients with advanced stages of NSCLC and establish a prognostic classification of these patients.
Methods: A prospective study of 130 patients with non-operable NSCLC stages IIIA-IV with follow-up until death of all patients. CEA, CA125, CYFRA 21-1, albumin, LDH, VSG and leucocytes levels were determined.
Results: Multivariate analysis showed PS (ECOG) >1 HR=2.4 (95% CI, 1.5-3.9), stage IV HR=2.23 (95% CI, 1.4-3.4), no treatment HR=2.5 (95% CI, 1.5-4.1), CA125>35U/mL HR=2.4 (95% CI, 1.5-3.7), CYFRA 21-1>3.6ng/mL HR=1.9 (95% CI, 1.2-2.9) and leucocytes >10000/μL HR= 1.77 (95% IC, 1.1-2.7) as independent prognostic factors for survival. One point was assigned for each adverse prognostic factor (APF) except for treatment. Patients were classified into three groups according to the number of APF: "low risk" 0-1 APF; medium risk 2-3 APF (HR= 2.8; 95% CI, 1.6-4.9) and high risk 4-5 APF (HR=9.2; 95% CI, 4.8-17.9). Mean survival of patients was 15 months (95% CI, 6.2-23.8) in group 0-1, 6 months (95% CI, 5.5- 6.5) in group 2-3 and 2 months in group 4-5 (95% CI, 1.1-2.9). When classifying patients according to whether or not they had received chemotherapy, both groups presented similar results to the total group as higher numbers of APF correlated with shorter survival.

Conclusion: The application of a SCORE which includes clinical data and biomarkers may improve the prognostic classification of these patients. Further prospective validation studies are needed to confirm these results.

Keywords: prognostic factors, tumor markers, score, multivariate analysis

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P3.215 EXPERIENCE OF USING ERLOTINIB FOR TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Selection of lung cancer patients with mutation of EGFR tyrosine kinase in their cancer cells is critical for management of their treatment strategy. The clinical dose setting of erlotinib was determined as its maximum tolerated dose (MTD). Erlotinib is expected of its effectiveness whether or not lung cancer cells have EGFR mutations. We don not have enough data of effectiveness of erlotinib in Japanese lung cancer patients.
Methods: To analyze the treatment outcome of erlotinib, we retrospectively investigated the background, effectiveness, adverse events of 39 patients (pts) of advanced NSCLC treated with erlotinib from January 2008 to May 2010 in our hospital.
Results: Patients background was follows; median age 66 (range 31 - 85 years old), ratio of male/ female = 15/ 24, smoking history +/ - = 24/ 15, PS 0/ 1/ 2 = 2/ 24/ 9, tissue type adenocarcinoma/ squamous cell carcinoma/ others = 27/ 6/ 2, number of previous regimen 0/ 1/ 2/ over 3 = 2/ 25/ 11/ 1, previous usage of gefitinib +/ - = 7/ 32, mutation of EGFR gene +/ -/ unknown = 18/ 16/ 5. The best response rate; CR/ PR/ SD/ PD/ NE = 0/ 11/ 18/ 9/ 1. In seven patients who had previously treated with gefitinib, the best response rate SD/ PD = 5/ 2. Response rate (RR) in all patients was 28.2%, and disease control rate (DCR = CR + PR) was 74.3%. Overall survival (OS) was 27.2 months and progression free survival (PFS) was 5.5 months in all patients. In sub analysis, the progression free survival (PFS) in population with positive EGFR mutation was significantly longer than that of negative EGFR mutation. PFS of patients with adenocarcinoma was longer than that of other tissue types, but there was no difference in PFS between male and female. Pts with skin rash had significantly longer PFS than those without it. The past history of gefitinib intake did not affect PFS. The each number of adverse events over grade 3 was three pts of skin rash, two of diarrhea, two of liver injury respectively. There was no patient of drug-induced interstitial pneumonitis.
Conclusion: The effectiveness of erlotinib in our hospital was as alike as that reported previously. Erlotinib was effective in some pts of negative EGFR mutation.

Keywords: erlotinib, Advanced Non-Small Cell Lung Cancer, gefitinib, retrospective study

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.216 CLINICAL PATTERNS AND OUTCOMES FOR THE BEVACIZUMAB MAINTENANCE POPULATION IN THE ECOG E4599 STUDY OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): RESULTS OF AN EXPLORATORY ANALYSIS

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Background: Bevacizumab's mode of action supports continued use until progressive disease

(PD). In clinical settings, such as colorectal and ovarian cancer (eg, BRiTE, ARIES, GOG-218), and in preclinical lung cancer models, continuous VEGF suppression with bevacizumab has been shown to be key to tumor control. The E4599 study that specified bevacizumab treatment to progression demonstrated significant survival benefits in NSCLC patients. Because current data on single-agent bevacizumab maintenance in NSCLC are limited, we conducted a retrospective analysis of clinical characteristics and outcomes for the maintenance population in E4599.
Methods: E4599 included patients with advanced, metastatic, or recurrent non-squamous NSCLC treated with 6 cycles of induction carboplatin-paclitaxel (CP) ± bevacizumab (15 mg/kg q3w). Patients with an objective response or stable disease (SD) after 6 cycles of CP + bevacizumab (CP+B) then continued on single-agent bevacizumab maintenance until PD or unacceptable toxicity. Response rates, progression-free survival (PFS), overall survival (OS), and 1-year survival rates were assessed using Kaplan-Meier methods for patients in the CP+B arm receiving ≥1 infusion of bevacizumab maintenance without PD before start of maintenance (maintenance non-progressor population) and patients in the CP alone arm without PD after 6 cycles of CP + 21 days (CP non-progressors).
Results: In the CP+B arm, 258 of 429 patients (60.1%) completed 6 cycles of CP+B, and 207 (48%) patients received bevacizumab maintenance without prior PD. Baseline characteristics for the maintenance population were similar to the overall CP+B population, except for a higher percentage of patients with weight loss ≥5% in the CP+B arm. Best responses in the bevacizumab maintenance population for the entire treatment period (induction + maintenance) were complete response (1.9%), partial response (55.6%), SD (30.4%), and unknown (12.1%); median exposure to bevacizumab (induction + maintenance) was 12 cycles. The main reasons for bevacizumab discontinuation were PD (72.5%) and toxicity (9.7%). No significant differences in the safety profile were observed between the maintenance population and the overall CP+B population. In the maintenance population, the median PFS and OS from day 1 of cycle 7 were 4.4 months (95% confidence interval [CI]: 3.88–5.42) and 12.4 months (95% CI: 11.30–15.57), respectively. The median OS from start of treatment was 17.3 months, with a 1-year survival rate of 74.9% (155/207). In the CP alone arm, 194 of 440 patients (44.1%) completed 6 cycles of induction therapy. Best responses for CP non-progressors at 6 cycles of chemotherapy + 21 days (n=134) were complete response (2.3%), partial response (31.3%), SD (42.0%), and unknown (24.4%). For CP non-progressors, the median PFS and OS were 2.8 months (95% CI: 2.10–3.12) and 11.2 months (95% CI: 9.17–13.57), respectively. The median OS from start of CP treatment was 16.1 months, with a 1-year survival rate of 67.9% (91/134).
Conclusion: Although retrospective and non-comparative, these analyses from E4599 show that patients in the bevacizumab maintenance population had a long median OS of 17.3 months, including a median PFS and OS of 4.4 and 12.4 months beyond induction, respectively.
Keywords: Non-small cell lung cancer, bevacizumab, maintenance, survival

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P3.217 CLINICAL CHARACTERISTICS, TREATMENT OUTCOMES, AND SAFETY OF EGFR TYROSINE KINASE INHIBITON IN ADVANCED NSCLC PATIENTS POSSESSING AN EGFR MUTATION: THE ALBERTA, CANADA EXPERIENCE

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Background: In three large phase III trials, conducted primarily in selected Asian populations, first-line gefitinib monotherapy is associated with significant progression-free survival (PFS) in advanced non-small cell lung cancer (NSCLC) patients who possess epidermal growth factor receptor (EGFR) activating mutations. We hypothesized that clinical characteristics portending EGFR mutation status, treatment outcomes, and toxicity with first-line EGFR tyrosine kinase inhibition (TKI) would compare favorably in a North American population.
Methods: A population-based, retrospective, chart review was conducted on treatment-naïve, advanced, non-squamous, NSCLC patients referred for EGFR mutation analysis between March 1, 2010 and

March 1, 2011 in Alberta, Canada. Baseline clinical characteristics, mutation status, treatment, response rate (RR), and toxicity data were collected.
Results: To date, 120 patients have been analyzed for EGFR mutational status analysis. 31 (25.8%) harboured EGFR activating mutations: 21 (68%) with exon 19 in-frame nucleotide deletion, 7 (23%) with exon 21 L858R point mutation, and 3 (10%) with both exon 19 and 21 mutations. Clinical characteristics associated wtih EGFR mutations were never-smokers or former light-smokers (OR: 9.8; 95% CI, 3.2 - 30.3), and Asian ethnicity (OR: 3.0; 95% CI, 1.0 - 9.2). Gender and age were not associated with the EGFR mutation. Of the EGFR mutation positive patients, 24 (77%) received first-line gefitinib, 3 (10%) received systemic chemotherapy, and 4 (13%) received best supportive care only. One of the 20 evaluable patients receiving gefitinib had a CR (5%), 12 patients had a PR (60%), and 7 patients displayed stable disease (35%). Treatment was well tolerated with only one patient having to discontinue gefitinib due to grade 3 liver transaminitis.
Conclusion: This study demonstrates that in an Albertan population of non-squamous advanced NSCLC patients, EGFR mutations occur at an incidence of 25.8%. Smoking status and ethnicity were strongly associated with the presence of EGFR mutations within this population. Response rates compare similarly to Asian populations treated with first-line EGFR tyrosine kinase inhibition. Further analysis of survival data are ongoing.
Keywords: Non-small cell lung cancer, Non-squamous, Epidermal growth factor receptor, gefitinib

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P3.218 USING DURING-RT PET TO INDIVIDUALIZE ADAPTIVE RT FOR PATIENTS WITH STAGE III NSCLC: A MULTICENTER PLANNING STUDY

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Background: With concurrent chemoradiation, RTOG0117 concluded 74 Gy in 7-8 weeks as the maximum tolerated radiation (RT) dose for stage III Non-Small Cell Lung Cancer (NSCLC). We hypothesized that RT dose can be further escalated with a shortened treatment duration by individualized adaptive RT.
Methods: Two consecutive prospective dose escalation trials have been conducted to test the hypothesis. The prescription dose of the first trial was set individually to correspond to a 15% risk of RT-induced lung toxicity (RILT) according to a normal tissue complication model. RT dose was further escalated in the second trial by adapting dose individually to the residual metabolic volume on PET obtained during-RT so that the residual metabolic volume would receive the maximal dose while keeping a tolerable risk of normal tissue toxicities. The treatment was to be completed in 30 daily fractions, with 5 fractions a week for both trials. Fraction size, total equivalent dose at 2 Gy fraction size (ED_2), and biologic equivalent dose (BED) ranged from 2 to 3.8 Gy, 66 to 100 Gy, and 79.2 to 120 Gy, respectively. Carboplatin and paclitaxel were given concurrently and adjuvantly. Mature data from the first and the interim results from the second trial are reported.
Results: The median ED_2 were 66 Gy (range 66-100) and 100 Gy (range 80-100) ($P<0.01$) for trial #1 and #2, respectively. Of 18 patients treated on trial #1, with a minimum follow-up of 50 months, the median and 5-year overall survivals were 30 months and 33%, respectively. 12 patients died: 5 from local failure, 3 distant metastasis, 3 heart diseases, and 1 radiation pneumonitis. 6 patients were alive: 1 with local progression and 5 with no evidence of disease at the last follow-up. Patients treated to higher dose had significantly better survival ($P=0.02$). For toxicity, 5 (22%) patients had grade ≥ 2 RILT and 10 (55%) grade ≥ 2 radiation esophagitis. A total of 33 patients enrolled on trial #2, 18 of them with a minimum followed up of 6 months were included in this analysis. All 18 patients had tumor reduction during-RT and received at least 74 Gy ED_2 within 6 weeks; 10 received the maximum trial dose of 100 Gy ED_2. Overall, 1 had grade 3 RILT and 7 had grade ≥2 esophagitis. With a median follow-up of 10 (range 6-26) months, there were 2 deaths, one from GI bleeding at 6 months, the other at 20 months with unknown etiology without evidence of disease progression. None of the patients had local regional failures at this time.

Conclusion: Local failure was the major cause of death in trial #1 with most patients not receiving high dose RT due to estimated RILT limitations in patients with stage III NSCLC. An adaptive RT treatment, using during-RT PET, allowed higher RT dose delivered with concurrent chemotherapy, achieved promising local regional control in this limited series. RTOG 1106 will validate this promising results and compare it with conventionally fractionated 74 Gy RT.

Keywords: Non-small cell lung cancer, Adaptive dose escalation, conurrent chemoradiation

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P3.219 DOSE ADJUSTMENTS ARE PROBLEMATIC IN COMMON TOXICITIES OF BEVACIZUMAB

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Background: Bevacizumab is used in non-small cell lung cancer (NSCLC), colon cancer, glioblastoma, renal cell carcinoma, and breast cancer. Whether there are differences in incidence or severity of toxicity across these diseases is unknown. Bevacizumab has been associated with life threatening toxicities including hemorrhage and thrombosis along with common toxicities of hypertension (HTN) and proteinuria occurring in more than 20% of patients. While close monitoring for these toxicities can prevent excess morbidity and mortality, recommendations for monitoring and dose reduction are vague. In landmark studies, the dose was held for hemorrhage, proteinuria greater than 2 g/L, and grade 4 hypertension. We examined the incidence of bevacizumab common toxicities and determined if dose adjustments or discontinuation occurred across diseases.

Methods: A retrospective chart review was conducted of patients receiving at least one dose of bevacizumab at Methodist University Hospital between January 1, 2008 and December 31, 2010. Patients receiving ophthalmic therapy or with incomplete data were excluded. Toxicities listed above were defined and graded according to the Common Toxicity Criteria v4.0.

Results: 149 patients were included in analysis. Baseline characteristics are shown (table 1). Hypertension and proteinuria occurred in 62% and 18% of patients respectively (table 2). There were 3 reports of DVT within 3 weeks of bevacizumab administration; 2 occurring in colon cancer patients and 1 occurring in an ovarian cancer patient . One peritoneal hemorrhage occurred in a colon cancer patient.

Table 1: Demographics	
Baseline characteristics (n = 149)	
Gender Female	57%
Ethnicity African American Caucasian Other	72% 24% 4%
Median age	60 (range 27-85)
Disease state Non-small cell lung cancer Breast cancer Colon cancer Glioblastoma Renal Other	28% 13% 47% 2% < 1% 10%
Past medical history HTN Renal failure	49% 1%
Current medications Antihypertensives Antiplatelet agents Anticoagulants	47% 2% 11%
Bevacizumab dose range Median dose Median number of doses	600 mg (range 190-3050 mg) 2 (range 1 – 22)

Table 2. Incidence of HTN, proteinuria, and no dose adjustment/discontinuation for toxicity			
HTN			
Disease state(n)	N (%)	Grade 3/4, n (%)	No dose delay, adjustment or discontinuation, n (%)
NSCLC (41)	22 (54)	6 (15)	4 (67)
Colon (70)	47 (67)	19 (27)	10 (53)
Breast (19)	11 (58)	5 (26)	3 (60)
Glioblastoma (3)	1 (33)	1 (33)	1 (100)
Renal (1)	1 (100)	1 (100)	-
Other (15)	11 (73)	3 (20)	2 (67)
Total (149)	93 (62)	35 (23)	20 (57)
Proteinuria			
Disease state (n)	N (%)	Grade 2 – 4, n (%)	No Dose delay, adjustment or discontinuation, n (%)
NSCLC (41)	5 (12)	2 (5)	-
Colon (70)	16 (23)	11 (16)	2 (18)
Breast (19)	3 (16)	1 (5)	1 (100)
Glioblastoma (3)	1 (33)	1 (33)	-
Renal (1)	-	-	-
Other (15)	2 (13)	1 (7)	-
Total (149)	27 (18)	15 (10)	3 (20)

Conclusion: The incidence of grade 3/4 HTN and grade 2 – 4 proteinuria was higher than reported in the literature. This may be a refection of the large number of African-American patients in our cohort. Blood pressure monitoring was routine, however, grade 3/4 hypertension had little documentation of dose adjustment, delay, or discontinuation. Monitoring of proteinuria was variable. Standard

algorithms need to be implemented for dosing adjustments in these common toxicities
Keywords: bevacizumab, hypertension, proteinuria

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P3.220 ANALYSIS OF CROSS-OVER PORTION OF ENCORE-401, A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY OF ERLOTINIB WITH AND WITHOUT ENTINOSTAT, A CLASS 1 ISOFORM SELECTIVE HISTONE DEACETYLASE INHIBITOR (HDAC) IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Drug resistance in cancer therapy represents a significant hurdle for improving clinical outcome with both targeted agents as well as cytotoxic chemotherapy .ENCORE-401 was conducted based on preclinical data demonstrating that epigenetic modifiers can delay and/or reverse tolerance to epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment. The primary efficacy data and preliminary subset analysis for ENCORE-401 demonstrated that in the unselected patient population no added clinical benefit was observed with the addition of entinostat while in a group of patients with high e-cadherin (3+, IHC) levels at time of diagnosis, improvement was observed in both PFS (3.7 mos vs 1.9 mos; HR 0.55 (95% CI 0.22-1.37 p=0.19))and OS (9.4 mos vs 5.4 mos; HR 0.36 (95% CI 0.14-0.94 p=0.03))[1]. The results of the cross-over portion of the study are presented here.
Methods: 132 patients with previously treated stage IIIB/IV NSCLC, no-prior erlotinib, PS ≤ 2, and tissue available for biomarker assessment, were randomized (1:1) to erlotinib 150 mg PO QD days 1-28 plus entinostat 10mg PO or placebo days 1 and 15 Q 28 days [= 1 cycle] for a maximum of 6 cycles. Treatment was unblinded upon documentation of both disease progression and the patient's desire to continue on study in the open label crossover study phase should they have been on placebo.
Results: 132 patients were enrolled to achieve 110 evaluable. All patients have completed the double-blind study phase as well as exploratory cross-over option. 16 patients elected to participate in the cross-over option and entinostat was added upon erlotinib progression. 5 of 16 (31%) patients had disease stabilization >60 days (range 61-139); 2 of 16 (13%) had disease stabilization < 60 days; 4 of 16 (25%) had progressive disease and 5 of 16 (31%) could not be evaluated. The median PFS for the 16 patients on erlotinib alone was 1.97 months and an additional 1.78 months in the cross-over portion with entinostat. Summary of EGFR sequence, EGFR copy number, KRAS status, Veristrat classification and E-cadherin IHC protein expression for the cross-over patients will be presented.
Conclusion: A randomized, placebo controlled phase II trial of erlotinib+ entinostat or erlotinib + placebo has been completed with exploratory analysis of biomarkers selected for analyzing the potential for epigenetic therapy to overcome EGFRi drug resistance identifying a subset of patients that have high e-cadherin expression levels at time of diagnosis deriving the greatest clinical benefit from the combination of entinostat and erlotinib. Results from the cross-over portion further demonstrate that select patients with resistance to erlotinib therapy may derive clinical benefit with the addition of entinostat. Future studies are planned to confirm the role of tumor phenotype in determining sensitivity to erlotinib – entinostat combination therapy.
Keywords: EGFR-TKI resistance, histone deacetylase, erlotinib, Phase 2

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P3.221 EFFICACY AND SURVIVAL DATA FROM A PHASE II STUDY OF HISTOLOGY-GUIDED CHEMOTHERAPY IN STAGE IIIB/IV NON-SMALL CELL LUNG CANCER WITH PEMETREXED PLUS PLATINUM FOR NON-SQUAMOUS AND TAXANE PLUS PLATINUM FOR SQUAMOUS AND NON-SQUAMOUS CARCINOMAS

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Background: Pemetrexed/platinum has become one of the standard regimens in treatment of non-squamous non-small cell lung cancer (NSCLC). This study aimed to examine efficacy of pemetrexed/platinum in treating Thai NSCLC patients comparing to the taxane/platinum regimen.
Methods: Two platinum-doublet regimens were assigned for newly-diagnosed stage IIIB (malignant pleural effusion)/IV NSCLC patients. For non-squamous carcinomas, 16 patients were categorized to receive 500 mg/m2 of pemetrexed in combination with platinum (cisplatin 80 mg/m2 or carboplatin AUC = 5) and 16 patients with 175 mg/m2 of paclitaxel or 75 mg/m2 of docetaxel in combination with platinum. Eight patients with squamous cell carcinoma were allocated to taxane and platinum. Cycles were repeated every 3 weeks until disease progression with 6 cycles maximum. Response evaluation was performed every 2 cycles.
Results: From December 2009 to February 2011, 37 NSCLC patients gave consent. Five patients were excluded from the analysis (early death before treatment, co-primary cancers, unmet liver function, each, and consent withdrawal (2)). Among 32 eligible patients, 28 patients had non-squamous whereas 4 patients were squamous histology. Fifteen patients in the non-squamous group received pemetrexed/platinum and 13 patients received taxane/platinum. Responses in each group were: non-squamous (pemetrexed/platinum): 2 (13.3%) PR and 13 (86.7%) SD; non-squamous (taxane/platinum): 1 (8.3%) PR and 11 (91.7%) SD; squamous (taxane/platinum): 1 (25%) PR and 3 (75%) SD. Median progression-free survival time were 191 days in the non-squamous group and 188 days in the squamous group. Median overall survival has not been reached in both groups.
Conclusion: Pemetrexed/platinum given to the non-squamous NSCLC patients provides better response than taxane/platinum regimen in Thai patients. Taxane/platinum regimen remains standard in squamous NSCLC with comparable progression –free survival benefit to the non-squamous group.
Keywords: histology, Pemetrexed, taxane, platinum

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P3.222 NOVEL EGFR ANTIBODIES WITH INCREASED ACTIVITY TOWARDS MUTANT EGFRS AND POTENTIALLY REDUCED TOXICITY

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Background: Non-small cell lung cancers (NSCLC) driven by ligand-independent activating mutations in epidermal growth factor receptor (EGFR) often respond to treatment with EGFR tyrosine kinase inhibitors (TKIs). About half of acquired resistance to EGFR-TKI therapy results from a secondary point mutation in the EGFR tyrosine kinase domain at amino acid position 790 (T790M). T790M mutants also display reduced sensitivity to Cetuximab treatment in preclinical models.
Methods: We have investigated the molecular mechanism responsible for the reduced Cetuximab sensitivity and found that T790M mutant receptors primarily exist and signal as monomers. We have exploited this characteristic of the T790M mutant to isolate novel EGFR inhibitory antibodies with activities against all EGFR variants.

Results: 12D03 monoclonal antibody presents high binding toward EGFRL858R/T790M and potently down-regulates this receptor. In vivo tumor growth inhibition was demonstrated in various tumor models, driven by either EGFRL858R/T790M, EGFRvIII or overexpressed wtEGFR. As opposed to other EGFR inhibitory antibodies, these novel antibodies have reduced ligand binding inhibitory activity and minimal inhibitory effect on EGF induced human primary keratinocyte proliferation, suggesting a potentially reduced skin toxicity profile.
Conclusion: The broad activity profile, combined with potentially reduced skin toxicity, suggests that these antibodies will have great potential for combinability with other therapeutic agents.

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P3.223 WHEN WAIT FOR MORE EVIDENCE? REAL OPTIONS ANALYSIS IN PROTON THERAPY

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Background: Trends suggest that cancer spending growth will accelerate. One method for controlling costs is to examine whether the benefits of new technologies are worth the extra costs. However, especially new and emerging technologies are often more costly, while limited clinical evidence of superiority is available. In that situation it is often unclear whether to adopt the new technology now, with the risk of investing in a suboptimal therapy, or to wait for more evidence, with the risk of withholding patients their optimal treatment. This trade-off is especially difficult when it is costly to reverse the decision to adopt a technology, as is the case for proton therapy. Real options analysis (ROA), a technique originating from financial economics, assists in making this trade-off.
Methods: We examined whether to adopt proton therapy, as compared to stereotactic body radiotherapy, in the treatment of inoperable stage I non-small cell lung cancer. Three options are available: adopt without further research; adopt and undertake a trial; or delay adoption and undertake a trial. The decision depends on the expected net gain of each option, calculated by subtracting its total costs from its expected benefits.
Results: Adopt and trial was the preferred option, with the highest expected net gain for a sample size of 200 patients. Increase of treatment costs abroad and costs of reversal altered the preferred option.
Conclusion: We have shown that ROA provides a transparent method of weighing the costs and benefits of adopting and/or further researching new and expensive technologies.
Keywords: proton therapy, cancer care, innovation, decision-making

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P3.224 SERUM SIALYL LEWISX PREDICT BRAIN METASTASIS IN PATIENTS WITH STAGE I NON-SMALL CELL LUNG CANCER

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Background: Surgical treatment is the most efficient therapy for early non-small lung cancer (NSCLC). However, even after radical surgery (R0) many patients relapse or progress to systemic disease. Recurrence has been detected in approximately 30-40% of patients with NSCLC, even in stage I. Brain metastasis is critical metastasis site. Developments of whole brain radiotherapy and/or molecular-targeting therapies (mainly EGFR inhibitor) progress the survivals of these patients, therefore it is important to detect the early brain metastasis to improve their survivals. The aim of this study is to determine the predictors of brain recurrence preoperatively; we compared SLX with two widely used tumor markers, CEA and CYFRA 21-1 in patients with stage I NSCLC.
Methods: The study involved 213 patients (132 male, 81 female; median age 69 years; range 44-93 years) with completely resected stage I NSCLC.

Our study excluded patients with any other cancers and those who underwent neoadjuvant therapy. Among the 213 patients, we identified 48 with recurrence within 3 years. The patients were divided into three groups with regard to the recurrence site: no recurrence within 3 years (n=165); recurrence without brain metastasis (n=34); and recurrence with brain metastasis (n=14). The duration of the free-from-recurrence period was measured from the date of operation until the first evidence of recurrence on an imaging study, or the last date of follow-up for patients who remained alive and without recurrence.
Results: The mean follow-up period for the entire study population was 54 months. On pathologic examination, 146 patients had adenocarcinoma (included 8 BAC), 47 had squamous cell carcinoma, 4 had large cell carcinoma, and 5 had adenosquamous carcinoma. 113 patients were in stage IA, 100 in stage IB. The 3-and 5-year survival rates in total patients were 89%, and 79%respectively. The 3-year survival rates in patients with three groups (no recurrence, recurrence without brain metastasis, and recurrence with brain metastasis) were 96%, 65%, and 61%, respectively. The medians and ranges of serum concentration of SLX in patients with no recurrence were 23.6 ng/mL (10.6–51.7 ng/mL); for those with recurrence without brain metastasis was24.5 ng/mL (10.0–85.4 ng/mL), and for those with recurrence with brain metastasis 36.2 ng/mL (15.9-57.6 ng/mL), respectively (Kruskal-Wallis test; $P < .001$). The concentrations of SLX were significantly higher in patients with brain metastasis than in those with recurrence without brain metastasis (Mann-Whitney U-test; $P = .0047$). No significant difference for serum CEA and CYFRA concentration was evident among the three groups.
Conclusion: The concentration of SLX in serum can predict the risk of brain recurrence in stage 1 NSCLC. Follow-up evaluation included brain MRI and adjuvant therapies should be considered to improve prognosis in patients with high concentration of SLX.
Keywords: SLX, Lung cancer, stage 1, Brain Metastasis

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P3.225 CISPLATIN-ETOPOSIDE COMBINATION IN THE ADJUVANT THERAPY FOR NON-SMALL CELL LUNG CANCER – A BRAZILIAN EXPERIENCE

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Background: Adjuvant chemotherapy is generally recommended in most patients with resected non-small cell lung cancer (NSCLC), with some restrictions according to tumor stage and size. However, different cisplatin-doublets were used in phase III trials, and the best choice remains unclear. The purpose of this study is to describe the Brazilian National Cancer Institute (INCA) experience with the cisplatin-etoposide (Cis-Vp) combination in this situation, with special interest to survival data.
Methods: We retrospectively evaluated the medical charts of patients receiving adjuvant treatment for NSCLC at INCA between 2004 and 2008. The primary outcome was overall survival (OS) and prognostic factors were analyzed using log-rank.
Results: Fifty-one patients were included, all treated with Cis-Vp. Median age was 61 years (40-76), and 53% were female. Adenocarcinoma was the most frequently reported histological subtype (57%), while squamous cell carcinoma was detected in 33%. Forty percent of patients were diagnosed with pathologic stage I, 33% with stage II, and 27% with stage III. Lobectomy was the predominant surgical procedure (80%), whereas pneumectomy was performed in 14%, and bilobectomy in 6%. The median number of cycles was 4 (1-4). Fifty-nine percent of patients received 80 mg/m2 of cisplatin and 76% received 300 mg/m2 of etoposide at the first cycle. Eleven patients (22%) were also treated with adjuvant radiation therapy. After 31 months median follow-up, the median OS was 57 months. In the univariate analysis, survival was inferior in advanced stage (III vs. I-II; median 34 vs. 57 months, respectively; p=0.22) and after RT (median 19 vs. 57 months; p=0.001). No difference was detected for OS according to gender (p = 0.70), histology (p =

0.33), or platinum dose (p = 0.13).
Conclusion: The outcomes described in our institution are in line with those reported in the early IALT study publication, in which 57% of patients received Cis-Vp. Nevertheless, recent data suggest more consistent results with cisplatin in combination with novel-generation agent vinorelbine, especially after long-term follow-up. These data support the need for long follow-up in the adjuvancy.
Keywords: Survival analysis, Lung neoplasms, Adjuvant chemotherapy

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P3.226 EVALUATION OF CLINICAL N1 NON SMALL CELL LUNG CANCER PATIENS TO ELUCIDATE PATHOLOGICAL N2 SUBGROUP.

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Background: Introduction: For a clinically diagnosed as N1 disease (cN1), there exist the different cases of the pathologic stage of a disease. The mixture of the patients of pathologically proven ipsilateral N2 involvement (pN2) in particular may diminish the prognosis of this group. This study was conducted to evaluate the clinical N1 disease and to elucidate predictors for pN2 disease.
Methods: We reviewed 1,080 the clinicopathological records and CT films and/or PET films of consecutive patients who underwent complete resection for non–small cell lung carcinoma in Kyoto University Hospital for ten years from January, 2000 to December, 2009. We examined the histological typing, T factor, location of the main tumor (hilum or peripheral), CYFRA value, CEA value, and status of lymph nodes involvement (single station or multi station) as prognostic factor and /or predictive factor of pN2 involvement.
Results: Among 1,080 patients 73 patients (6.8%) were diagnosed as cN1 with 55.9% five year over all survival. Five year survival rate of pN0 (n=24, 33%), pN1 (n=31, 42%) and pN2 (n=18 25%) were 73.5%, 53.8% and 19.0% respectively. The tumor histological typing of these 73 patients were adenocarcinoma in 27 patients (37%), squamous cell carcinoma in 35 patients (47.9%) and others 11 patients (15%), and higher proportion of squamous cell carcinoma patients were observed. It was disposed that the patients with squamous cell carcinoma had better prognosis than that of the patients with other histological types, and also that the patients with right upper lobe location of primary tumor had better prognosis than Those with other locations. In the multivariate analysis by the proportional hazard model the number of station of lymphadenopathy on CT (single or multi) was the only prognostic factor (relative risk 2.54, p=0.05). When the CYFRA value exceeded the standard value, the possibility that was pN1 or more was high. (χ square test, p=0.048).
Conclusion: Patients with cN1 disease were proved to have unexpected pN2 involvement in high incidence. CYFRA value can be a possible predictor of pN2 involvement.
Keywords: Non small cell lung cancer, Clinical N1, Pathological N2

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P3.227 AN UPDATE OF THE PHASE III STUDY OF ADJUVANT VINORELBINE PLUS CISPLATIN (NP) VERSUS NP PLUS ENDOSTAR (NPE) IN PATIENTS WITH COMPLETELY RESECTED STAGE IB-IIIA NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Adjuvant chemotherapy demonstrated a 5-15% benefit in 5-year survival in early-stage NSCLC. However, it is clear that current therapies are far from satisfying. Endostar, a recombinant human Endostatin, could inhibit tumor angiogenesis. In a phase III trial, the addition of Endostar to NP regimen resulted in higher response rate, clinical benefit rate and longer median time to progression compared with NP alone in advanced NSCLC patients. In this study, we tried to investigate adjuvant NP regimen with or without Endostar in early-stage NSCLC patients.
Methods: Completely resected patients (stage IB-IIIA) were randomized to receive adjuvant NP plus Endostar (arm A, Vinorelbine 25mg/m^2 on d1 and d8 plus Cisplatin 80 mg/m^2 intravenously, plus Endostar 7.5mg/m^2 per day, iv, for 14 consecutive days. Every 21 days as one cycle, for 4 cycles) or NP regimen alone (arm B). The randomization was stratified by gender, stage and histology. The primary endpoint was overall survival (OS) and the secondary endpoints were relapse-free survival (RFS) and safety.
Results: 905 patients (arm A: 449; arm B: 456) from 43 centers in China were enrolled between 9/2007 and 12/2010. Two arms were well-balanced with regard to age, gender, histology, stage, and resection type. 80 patients in arm A and 91 patients in arm B had relapsed disease. The median RFS was 27.7 months in arm A and 24.6 months in arm B (p=0.6009). 80.3% of patients in arm A finished 4 cycles of treatment and 77.8% of patients in arm B received 4 cycles of chemotherapy. Median survival time was not available at this moment because only very few patients had died. Grade 3/4 toxicities in arm A included leukopenia (58.4%), neutropenia (77.4%), anemia (13.1%), nausea (12.4%). Grade 3/4 toxicities in arm B included leukopenia (35.5%) neutropenia (61.6%), anemia (8.5%) and nausea (8.5%). It is worth noting that the incidence of cardiac toxicities in arm A (28.0%) was higher than that in arm B (21.1%).
Conclusion: The preliminary result showed that patients in arm A experienced a longer median relapse-free survival time than in arm B (27.7 months vs. 24.6 months), although the difference was not statistically significant until now. The toxicity profiles for both arms were tolerable in this study. The patient follow-up is ongoing.
Keywords: Endostar, Vinorelbine, Cisplatin, Non-small cell lung cancer (NSCLC)

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P3.228 EVALUATION OF CLINICAL CHARACTERS COMBINED WITH COMPUTED TOMOGRAPHY SIGNS IN DIAGNOSING SOLITARY PULMONARY NODULE

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Background: To evaluate the feasbility of clinical characters combined with computed tomography(CT) signs in diagnosing solitary pulmonary nodule(SPN) in the civil servants of Nanjing in P.R. China.
Methods: All the cases received chest X-rays when they took their routing health examinations. If SPN was detected, then the patient was confirmed by spiral CT scan and all the clinical characters and CT signs were recorded .The patients could receive fiberbronchoscopy, percutaneous aspiration lung biopsy, video assisted thoracoscopic sugery(VATS) , thoracotomy or just follow- up-visited according to the advises of clinical Doctors. Totally 431 cases of SPN were found in civil servants of Nanjing in the routing health examinations from January 2004 to April 2010 in the medical examination center of our hospital. Excepting 21 cases of lost-follow up, 410 patients were enrolled in the test, of which 189 malignant cases and 207 benign cases were diagnosed by pathology and 14 cases were clinically diagnosed of benignity because the nodules had no changes in the at least two-year follow-up visiting. 60 cases of malignancy and benignity were randomly taken from pathologic detected patients respectively. Comparing the clinical characters and CT signs of the two groups, four clinical characters and nine CT signs were found to have significant different display between the two group P<0.2), which included the patients' age(<40 year, 40-60 year, or >60year), quantity of smoking(<400/year, 400-800/

year, or >800/year), tumor marks of blood serum(0-2 items higher than normal, 3-4 items higher, or ≥5 items higher), family history of malignant diseases, the size(0.5-1 centimeter, 1-2 centimeter, or 2-3 centimeter), contour(smooth, shallow or deep lobulation) and pattern of calcification of the nodule, spicula sign, vascular convergence sign, bronchi sign, cavity, vacuole sign, and enhancement(<20 hounsfield unit(HU), 20-60HU or >60HU). 2/3 of the 410 patients (malignancy, n=122; benignity, n=151)formed the training set, and the other 137 patients formed the test set(malignancy, n=67; benignity, n=70) Utilizing Bayes analysis Œthe prior odds of malignant SPNs and the likelihood ratios of the 4 clinical characters and the 9 CT signs were taken from the training set which were then used to calculate the probability of malignancy of each patient of the training set and the test set. Patients whose calculated probabilities were≥50% were then judged as malignancy and those with<50% calculated probabilities were judged as benignity.
Results: In the training set, the sensitivity(SEN), specificity(SPE), diagnostic odd ratio(DOR) and positive likelihood ratio(+LR) were 0.85, 0.83, 27.8 and 4.95 respectively; at the same time ,these datum of the test set were 0.85, 0.80, 22.8 and 4.26 respectively.
Conclusion: With the application of Bayes analysis, clinical characters combined with CT signs may be a feasible method in distinguishing between malignant and benign SPNs of civil servants of Nanjing.
Keywords: Solitary pulmonary nodule, diagnosis

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P3.229 A PHASE III STUDY OF CARBOPLATIN/PACLITAXEL VERSUS ORAL URACIL-TEGAFUR AS THE ADJUVANT CHEMOTHERAPY IN RESECTED NON-SMALL CELL LUNG CANCER (NSCLC) – CONDUCTED BY SETOUCHI LUNG CANCER GROUP (SLCG) –

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Background: Recent studies have demonstrated that adjuvant chemotherapy provides a survival benefit in patients with resected NSCLC. We conducted a phase III study of carboplatin/paclitaxel versus oral uracil-tegafur as the adjuvant chemotherapy in resected NSCLC. On November 2010, planned 402 cases were enrolled and registration was completed. Here, we show the characteristics of enrolled patients with survival data of analyzed patients.
Methods: The patients with pathological stage IB-IIIA NSCLC who underwent complete resection were randomized 1:1 to carboplatin (AUC 5) / paclitaxel (175 mg/m^2) every 3 week for 4 cycles (A arm) or uracil-tegafur (250 mg/m^2) daily for 2 years (B arm). The primary endpoint was overall survival (OS) and secondary endpoints were disease-free survival and toxicity. The accrual of 200 patients per arm is required to demonstrate an improvement of OS (15% increase) in the arm A arm compared to B arm.
Results: Between November 2004 and November 2010, 402 patients from 31 Japanese centers were randomized. Median age was 67 (range; 44-82) years. A total of 402 patients consisted of 262 male and 140 female. Two-hundred ninety nine patients had PS of 0, 98 had PS of 1, and 5 had PS of 2. Two-hundred sixty six patients had adenocarcinoma, 100 had squamous cell carcinoma, and 36 had other histologies. Disease stage was IB in 229, IIA in 40, IIB in 81, and IIIA in 52 patients. Toxicities observed during adjuvant chemotherapy were well tolerable. There was no toxic death. The 3-year and 5-year overall survival rates of A and B arms combined was 75.9 % and 62.9%, respectively.
Conclusion: The present phase III trial with carboplatin/paclitaxel or uracil-tegafur is feasible with manageable toxicity.The final result of study is planned to be opened in 2016.
Keywords: Adjuvant chemotherapy, uracil-tegafur, Carboplatin, NSCLC

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P3.230 IS THERE A SURVIVAL DIFFERENCE BETWEEN THE PREVIOUS AND NEW T STAGES OF THE OPERATED N0 NON-SMALL CELL LUNG CANCER PATIENTS ?

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Background: In this study, the survival rates of the operated non-small cell lung cancer patients classified according T factor of the previous and the new TNM staging are compared.
Methods: The medical records and the follow-up data of the patients operated for non-small cell lung cancer between January 2005 and December 2009 is analyzed retrospectively. The pateints are staged according to the previous and the new TNM staging. The survival data of pateints with stages T1N0M0 (n=68), T2N0M0 (n=121) (classified as T2 because of the diameter of the tumor) according to previous TNM staging and the patients with stages T1aN0M0 (n=35), T1bN0M0 (n=33), T2aN0M0 (n=73), T2bN0M0 (n=48), T3N0M0 (n=30) (classified as T3 because of the diameter of the tumor) according to new TNM staging are compared.
Results: There is no survival difference between T1aN0M0, and T1bN0M0, versus T1N0M0 (previous staging) and T2aN0M0, T2bN0M0, and T3N0M0 versus T2N0M0 (previous staging) (p
Conclusion: Subgrouping the operated non-small cell lung cancer patients according to new T factor by the tumor diameter does not result with a significant survival difference when compared to previous TNM staging.
Keyword: lung cancer, staging

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.231 A STUDY OF THE SUCCESSFUL EXECUTION RATE BY THE CDDP+VNB BI-WEEKLY TREATMENT OF THE LUNG CANCER POSTOPERATIVE PATIENT

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Background and Objectives: Poor successful execution rate has been a common feature in clinical trials of cisplatin (CDDP) based adjuvant chemotherapy for NSCLC with only 48% to 69% of patients completing all planned cycles. We evaluated compliance and toxicity of postoperative cisplatin(CDDP) and vinorelbine(VNB) bi-weekly chemotherapy.
Patients and Methods: Patients who received adjuvant chemotherapy after complete resection of NSCLC between January 2008 and December 2010 were analyzed prospectively. Patient demographics, ECOG status, stage, pathologic subtype and type of surgery were recorded. The number of chemotherapy cycles, delays, dose reductions and change of chemotherapy were reported.
Results: Eleven patients were identified. The median age was 66 years (range of 54-75). Eight patients completed all 4cycle treatment under CDDP 40mg/m^2 and VNB 25mg/m^2 bi-weekly. Three patients were reported event of grade four neutropenia and four patients required delays in treatment. There were no toxic deaths. Multivariate analysis showed no effect of age, gender, extent of surgery or ECOG status on compliance, need for treatment modification or toxicity.
Conclusion: Compared to historical trials, adjuvant cisplatin and vinorelbine bi-weekly chemotherapy for resected NSCLC is now accepted by patients and physicians with a high degree of successful execution rate.
Keyword: CDDP VNB chemotherapr postoperation

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P3.232 DIAGNOSIS AND TREATMENT OF ATYPICAL ADENOMATOUS HYPERPLASIA IN LUNG

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Background: The purpose of our study was to analyze the characteristic of atypical adenomatous hyperplasia(AAH) on CT scan, pathology and surgical mode.
Methods: We retrospectively evaluated 10 atypical adenomatous hyperplasias(AAH) that were histologically confirmed and that manifested Male 2 and female 8, median age 54.4. All of the patients had the surgery. We compared the characteristic of CT scan and pathology. 10 patients were following up.
Results: All cases were peripheral nodule which located at left upper lobe 4, left lower lobe 2 and right lower lobe 4. GGO was manifested on thin-section helical CT scans. Diameter from 0.5~1.2 cm. The borderline of GGO was clear and the density was equality. Two of 10 cases had undergone wedge resection and 8 for lobectomy. Postoperative patients recovered quickly without severely complication. Under microscope it manifests local lung alveolus epithelium hyperplasia apparently. The interval slightly incrassation and local fibre cell hyperplasia with slightly nucleus heteromorphism. The follow time was from two months to five years. Now, 10 patients with good life quality are still alive without recurrence and metastasis.
Conclusion: The preoperative diagnosis rate of AAH is improved by high-differentiate enhance CT scan and the CT number histograms, but the finally diagnosis still need the histological evidence. Surgery is one of the most reliable means to treat AAH.
Keywords: high-differentiate CT scan, Surgery, lung atypical adenomatous hyperplasia, pathology

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P3.233 'REAL WORLD' DELIVERABILITY OF ADJUVANT CHEMOTHERAPY IN NON SMALL CELL LUNG CANCER (NSCLC)

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Background: Following a number of large randomized controlled trials describing survival benefit, adjuvant chemotherapy has been adopted into the management of early stage Non Small Cell Lung Cancer (NSCLC).The LACE meta-analysis demonstrated vinorelbine plus cisplatin (VC) to be marginally more effective than other platinum doublets (ref 1). Since 2005, our standard practice has been to treat with VC patients with resected pathological stage II-IIIa . We have audited the deliverability and toxicity of adjuvant VC and measured the impact of adjuvant chemotherapy on survival when compared with patients whose resections predated its introduction.
Methods: All patients (Aberdeen, Scotland) who between 1999-2003 and 2005-2009 underwent a pneumonectomy, lobectomy or wedge resection for non-small cell lung cancer were identified from pathology records. Patient characteristics, surgical procedure and survival analysis were tabulated and compared. All patients were diagnosed received all treatment in one hospital; Aberdeen Royal Infirmary. Case records and clinical databases were interrogated to record demographics (age, gender, performance status, co-morbidity) and clinical characteristics (histology, pathological stage, surgical procedure, length of surgical admission, 30 day surgical mortality rate, 30 day readmission rate, overall survival). Uptake of adjuvant chemotherapy was determined in the 2005 to 2009 cohort. The reasons for non-delivery of chemotherapy were recorded. We reviewed patient outcomes for those patients who underwent adjuvant chemotherapy recording the dosing of chemotherapy delivered (individual drug dosing, number of cycles completed) along with individual toxicity profiles (type, severity,

frequency, number of hospital admissions). Overall survival (date of surgery till date of death/censoring date) was used in the survival analysis. Survival comparisons, using Kaplan-Meier, between the two cohorts (1999-2003 and 2005-2009) were made.
Results: There were 144 patients with resected NSCLC between 2005 and 2009, and 183 between 1999 and 2003. There were no significant differences in terms of patient characteristics, stage or histology between these year groups. Within the 2005-2009 cohort, there were significantly fewer pneumonectomies (Table 1) (X2 13.9, 1df, p<0.005) but duration of surgical admission, 30day readmission rate, and 30 day surgical mortality rate were very similar. Within the 2005-2009 cohort 52 stage II-IIIa cases were identified. Of these, three died within 30 days of surgery. Forty one (84%) patients were referred to Oncology for discussion of adjuvant chemotherapy with an uptake rate of 76% (n=31). Those not treated with chemotherapy were more likely to be older, have significant co-morbidity or to have sustained post-operative complications resulting in a longer surgical admission and a higher 30 day re-admission rate (Table2). The delivery of adjuvant vinorelbine chemotherapy was significantly limited by haematological toxicities. There was one early chemotherapy related death due to neutroenic sepsis. The mean number of cisplatin cycles delivered was 2.7. Haematological toxicity resulted in 40% (n=11) of patients being withdrawn from treatment early. Individual drug dosing and toxicity profiles will be presented. Survival analysis will be formally performed in June 2011 however initial analysis suggests a significantly longer survival in the 2005-2009 cohort (p=0.041) (Figure1).
Conclusion: 1. Favourable uptake of adjuvant chemotherapy 2. Delivery limited by haematological toxicity 3. Significant survival improvement, 2005-2009 cohort
Keywords: Adjuvant chemotherapy, Early Stage NSCLC, Survival analysis, toxicity

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P3.234 FACTORS ASSOCIATED WITH RECURRENCE AND SURVIVAL IN PATIENTS WITH CURATIVELY RESECTED STAGE IA ADENOCARCINOMA OF THE LUNG: LYMPHOVASCULAR INVASION CAN PREDICT RECURRENCE

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Background: Even when meticulously clinically and pathologically studied, completely resected stage IA adenocarcinoma of the lung does recur. However, there are few data regarding the patterns of recurrences and their risk factors in this population. Therefore, this study characterizes cancer recurrence and its risks and assesses recurrence-free survival in patients with curatively resected stage IA adenocarcinoma.
Methods: Between January 1990 and December 2005, a total of 214 patients were given a final diagnosis of pathologic stage IA (UICC-6) adenocarcinoma of the lung. The medical records of these patients were retrospectively reviewed with regard to patient characteristics, tumor pathologic findings and follow up status. Survival was analyzed by the Kaplan-Meier method, log-rank test, and Cox proportional hazards analysis.
Results: The median follow up after curative resection was 66 months. Cancer recurred in 28 patients (13%). Among them, local recurrence occurred in 10 patients (5%), whereas distant recurrence occurred in18 patients (8%). Recurrence earlier and later than 5 years after surgery was in 15 patients (7%) and in 13 patients (6%), respectively, with nearly constant risk. At 5years after index resection, 169 patients (79%) were alive without evidence of cancer recurrence, 27 patients (13%) had experienced recurrence of cancer but still alive and 1 patient had died with non-cancer causes. Recurrence-free 5- and 10-year survival rates were 92.5 and 70.0%, respectively. Univariate analysis revealed five significant prognostic factors: gender (p=0.0177); BAC component (p =0.0007); tumor location (p=0.0099); pleural invasion (p=0.0274) and lymphatic or vascular vessel invasion (LVI) (p< 0.0001). Multivariate analysis revealed BAC

component, tumor location, and LVI as significant factors. Hazard ratios for recurrence were 0.381 for having BAC component (95% CI, 0.147-0.979; p= 0.0451), 0.361 for right sided tumor (95% CI, 0.188-0.692; p= 0.0022), and 2.785 for having LVI (95% CI, 1.392-5.555; p= 0.0038).
Conclusion: Surgically "cured" stage IA adenocarcinoma of the lung recurs. Our analyses indicate BAC component, tumor location, LVI as an independent indicator for cancer recurrence. Identifying high-risk patients for recurrence will simplify decision making for postoperative treatment strategies.
Keywords: adenocarcinoma of the lung, p-stage IA, recurrence, lympphovascular invasion

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P3.235 NEGATIVE PREDICTIVE VALUE (NPV) OF PET-CT IN NODE-NEGATIVE EARLY STAGE LUNG CANCER: IMPLICATIONS FOR NON-SURGICAL MANAGEMENT

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Background: Increasingly, non-surgical methods are utilized for the management of early stage lung cancer. We sought to investigate the accuracy and negative predictive value (NPV) of PET-CT at our center in the nodal staging of clinically node-negative lung cancer.
Methods: All patients treated surgically from January 2005 to December 2008 at Dartmouth-Hitchcock Medical Center who were AJCC 6th edition clinical stage I lung cancer by pre-operative PET-CT staging were included in this analysis. The relationship between both the 6th edition and 7th edition AJCC clinical stage based on pre-treatment PET-CT and true stage based on pathologic dissection was assessed with McNemar's Test.
Results: Of 155 clinically node-negative patients, 135 were pathologically node-negative. The negative predictive value of PET-CT for predicting lymph node involvement was 87%. Based on 6th edition AJCC staging, 92 patients were stage IA and 63 were stage IB via PET-CT. Of the 155 patients in this series, 113 (73%) were correctly staged for both T and N stage via PET-CT based on the 6th edition of AJCC staging: 75% correct for clinical stage IA (McNemar's χ^2= 11.6, $p < 0.001$), 70% correct for clinical stage IB (McNemar's $\chi^2 = 2.13$, $p = 0.2$). Using the 7th edition of AJCC staging, 97 of the 155 patients (63%) were staged correctly with PET-CT: 71% correct for clinical stage IA (McNemar's $\chi^2 = 16.0$, $p < 0.000$), 47% correct for clinical stage IB (McNemar's $\chi^2 = 1.6$, $p = 0.3$). Of the 155 patients in this series clinically staged as IA or IB by PET-CT, 12 patients (8%) were upstaged at pathological dissection due to the presence of N2 disease, 7 of whom also had occult N1 nodal disease. Eight patients had N1 positive nodes in the absence of N2 positive nodes. Thus, 13% of clinically stage I patients in this series harbored occult lymph node metastases. Regarding 6th edition T stage, 22 patients were upstaged, 12 due to visceral pleural invasion, and six patients were downstaged. In the 7th edition, 46 patients were upstaged and 11 were downstaged.
Conclusion: PET-CT has an excellent negative predictive value for predicting the absence of nodal disease in patients with clinical T1-2N0 lung cancer in the AJCC 6th edition. The NPV of PET-CT in nodal staging has implications for non-surgical treatment of lung cancer with stereotactic body radiotherapy where routine pathologic nodal staging is not performed. Identifying radiographic characteristics that correlate with the absence of nodal disease would be helpful in patient selection. For both the 6th and 7th editions, clinical stage IA was more likely to match the pathological stage than was clinical stage IB. In our series, the accuracy of PET-CT in predicting AJCC 7th edition stage is lower than that for the 6th edition.
Keywords: early-stage, pathologic stage, PET-CT

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P3.236 SERUM SIALYL LEWISX LEVEL INDICATES NODAL EXTENSION IN PATIENTS WITH CLINICAL STAGE 1A NON-SMALL CELL LUNG CANCER

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Background: It is well known that nodal extension is diagnosed postoperatively in patients with small-sized non-small cell lung cancer (NSCLC) who exhibit no evidence of nodal extension on chest CT. Nodal extension is a significantly poor prognostic factor. Patients with operable advanced NSCLC are commonly treated with pulmonary resection plus lymph node dissection with pre- or postoperative chemotherapy. Treatments for patients with early-stage NSCLC contain several therapeutic procedures, including lobectomy, segmentectomy, and partial resection, with or without lymph node dissection. The imprecise diagnosis of node-positive NSCLC leads to insufficient treatment, as well as incomplete removal of the lesion. The prediction of nodal extension is therefore particularly important for patients with clinically early stage (but in fact more advanced) NSCLC to receive appropriate treatment.
Methods: We retrospectively analyzed the relationship between pathologically proven nodal extension and the clinicopathologic features in patients with clinical stage 1A NSCLC. From January 2004 to December 2008, 299 patients with NSCLC underwent pulmonary resection with mediastinal lymph node dissection at Osaka City University Hospital (Osaka, Japan). Of these, 131 patients with clinical stage 1A NSCLC were investigated in this study.
Results: The mean age of patients was 67 years (range, 20 to 93 years). There were 72 males and 59 females. There were 113 patients without nodal extension (107 patients with p-stage 1A disease and 6 patients with stage 1B), 6 patients with pathological N1 nodal extension (3 patients with stage 2A disease and 3 patients with stage 2B disease), and 12 patients with pathological N2 nodal extension (all patients with stage 3A disease). The preoperative serum sialyl Lewisx level (SLX, $p = 0.001$) was significantly elevated in patients with compared to those without nodal extension. A ROC curve was constructed to determine if serum SLX levels could be used to differentiate between patients with and without nodal extension. The predictive cut-off value for SLX according to the ROC curve was 26 U/mL. On univariate analysis, being SLX-positive (risk ratio = 3.361, $p = 0.021$) was a significant predictive factor for nodal extension. On multivariate analysis, being SLX-positive was an independent predictive factor for nodal extension (risk ratio = 3.527, $p = 0.021$).
Conclusion: Patients with a serum SLX level of >26 U/mL were likely to have nodal extension. To decide on appropriate postoperative treatment, patients with a positive level of SLX should be treated with conventional pulmonary resection plus mediastinal lymph node dissection to evaluate the disease extent.
Keywords: Non small cell lung cancer, SLX, nodal extension

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P3.237 THE PROGNOSIS OF SURGICALLY RESECTED SPUTUM CYTOLOGY-POSITIVE ADENOCARCINOMA OF THE LUNG

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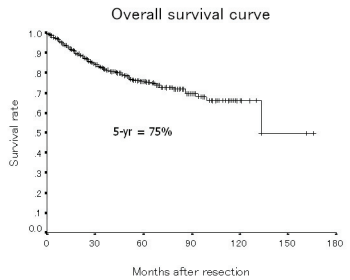
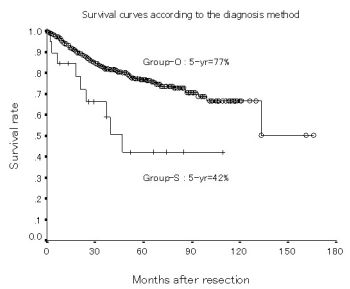
Background: Unlike the representative of central-type primary lung cancer such as squamous cell carcinoma and small cell carcinoma, adenocarcinoma is less often diagnosed by sputum cytology. Recently with the spread of high-resolution computed tomography, cases of screening detected early stage peripheral-type adenocarcinoma of the lung have been increasing, while a few are diagnosed by sputum cytology before surgery. Purpose: We evaluated the prognosis of the patients who had surgical resection of the lung with diagnosis of adenocarcinoma by the pre-operative sputum cytology.
Methods: We retrospectively reviewed 1006 consecutive patients who underwent surgical resection for primary lung cancer at our institution between 1996 and 2010. Preoperative factors and overall survival from surgery to death was assessed. Overall survival was analyzed by the Kaplan-Meier method, and differences in variables were calculated by the log-rank test.
Results: There were 20 patients who were diagnosed with adenocarcinoma by the pre-operative sputum cytology (Group-S). The remaining 986 patients were diagnosed with adenocarcinoma by other diagnostic methods, such as trans-bronchial lung biopsy, trans-bronchial needle aspiration cytology, bronchial washing cytology, CT guided biopsy, VATS biopsy, intra-operative fresh frozen section, and so on (Group-O). Group-S had significantly

larger tumor in size and higher incidence of lymph node metastasis than Group-O. Median follow-up was 22 months (range 1-166). Overall 5-yr survival for the cohort was 75% (Figure 1) . Group-S had significantly worse 5-yr survival of 42% compared with 77% for Group-O (p=0.002) (Figure 2) .





Conclusion: The stage of Group-S was more advanced stage of Group-O. Group-S had a siginificant worse prognosis than Group-O.
It is supposed that patients diagnosed with adenocarcinoma by the pre-operative sputum cytology have biologically higher malignancy in lung adenocarcinoma patients with surgical resection of the lung.
Keywords: surgical resection, sputum cytology, Adenocarcinoma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.238 BETTER ESTIMATES OF SURVIVAL FOR PATIENTS CONSIDERING ADJUVANT CHEMOTHERAPY AFTER SURGERY FOR EARLY NON-SMALL-CELL LUNG CANCER (NSCLC)

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Background: Discussions about prognosis are an important part of a patient's consultation with their lung cancer clinician and many patients have a poor understanding of their prognosis. Good communication by cancer clinicians has been shown to have a measurable effect on patient outcomes. Currently there are only limited resources to assist clinicians in discussing prognosis in an understandable and comprehensive way in the adjuvant lung cancer setting.
Methods: We searched MEDLINE and the Cochrane Central Register of Controlled Trials for unconfounded randomised trials of cisplatin-based adjuvant chemotherapy published in English with overall survival (OS) curves. We digitized the OS curves with 'Un-Scan-It ®' and recorded the OS rates at 1, 2, 5, 7 and 10 years and the following percentiles (scenario): 90th (worst case), 75th (lower typical), median, 25th (upper typical) and 10th (best case).
Results: We analysed 38 OS curves from 19 trials (7042 patients). The median patients per arm was 106 (range 33 -935), median age was 61 and the median proportion male was 75%. With adjuvant chemotherapy the median OS rate (interquartile range, IQR) at 1y was 91% (85-95), 2y was 73% (69-88), 5y was 61% (45-65) and 7y was 49% (38-65). With observation only, the median OS rate (IQR) at 1y was 88% (83-92), 2y was 74% (65-82), 5y was 55% (42-58) and 7y was 40% (34-45). In both arms, survival rates at 1, 2, 5 and 7 years were well estimated by raising the 1 year survival rate to the power of 2, 5 and 7 respectively (83%, 62%, 49% in the adjuvant arm and 77%, 53%, 41% in the observation arm). Few trials reported survival rates at 10 years. The median OS time (IQR) for the worst

case scenario was 13 months (9-21), for the lower typical was 24 months (19-39) and for the median was 54 months (34-70). Median overall survival times could be predicted using simple multiples of the median: 0.25 x median estimated the 90th percentile, 0.5 x median estimated the 75th percentile. No trials reached 25th or 10th percentile.
Conclusion: Simple percentages and their powers provide a useful starting point for estimating and describing survival to patients considering adjuvant chemotherapy after surgery for NSCLC.
Keywords: Non-small cell lung cancer, survival, adjuvant, Chemotherapy

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P3.239 LONG-TERM RESULTS OF PERI-OPERATIVE CHEMOTHERAPY IN PATIENTS WITH COMPLETED RESECTED NON–SMALL-CELL LUNG CANCER

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Background: To evaluate the effect of cisplatin-based peri-operation chemotherapy (CT) on survival after completed resection of non-small cell lung cancer (NSCLC).
Methods: A randomized, multicenter study was conducted by Shanghai Lung Cancer Team since Feb 1995 to Feb 1996 for stage I-IIIA NSCLC with completed resection. Patients were randomly assigned to receive neoadjuvant chemotherapy (MMC/EPI/DDP, MMC/ADM/DDP) for 2 cycles or no neoadjuvant chemotherapy. Adjuvant chemotherapy was given for majority of the patients, except for partial stage I patients. Accumulated survival, log rank, MST, Cox uni-variance and multi-variance analyses, HR were used as statistics for evaluation.
Results: The trial included 337 patients with a follow-up of 15 years, 169 cases received neoadjuvant chemotherapy, and 168 cases didn't receive neoadjuvant chemotherapy. The 15 years survival rate of the neoadjuvant chemotherapy and no neoadjuvant chemotherapy group were 25% and 19%, MST were 37.4 months and 56.47 months, respectively. Results showed no beneficial effect of neoadjuvant chemotherapy on overall survival (HR, 1.245; 95% CI, 0.954 to 1.626; P =0.107) and on disease-free survival (HR, 1.281; 95% CI, 0.883 to 1.857; P =0.193). No difference on OS and DFS were seen in stage I to stage IIIA NSCLC
Conclusion: Neoadjuvant chemotherapy with second generation regimens can't improve overall survival and disease-free survival of NSCLC. The future of peri-operative treatment for NSCLC may lie in the outcome of trials investigating third generation regimens, molecularly targeted agents, anti-angiogenic agents, or multitargeted agents.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.240 FEASIBILITY STUDY OF S-1 ADJUVANT CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED NON-SMALL CELL LUNG CANCER

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Background: Adjuvant chemotherapy is important for preventing the recurrence in patients with completely resected non-small cell lung cancer (NSCLC). In stage II and IIIA NSCLC, Cisplatin-based combination chemotherapy is recommended for the adjuvant chemotherapy. In Japan, Tegafur/Uracil (UFT) is also used in patients given a diagnosis of stage IA (Tumor size ≥ 2 cm) or IB lung adenocarcinoma. However, the absolute benefit of the adjuvant chemotherapies is about 5% increase of survival at 5 years after surgery. Therefore, the novel therapeutic strategy is required in the postoperative patients. In the present study, we evaluated feasibility and efficacy of single-agent S-1, an oral fluorouracil agent, in patients with completely resected NSCLC.
Methods: We conducted the single-arm, multicenter phase II study of S-1 feasibility. Primary endpoint was the relative dose intensity (RDI), which was defined as the ratio of the actual dose to the planned

dose. Secondary endpoints were safety and 1-year disease free survival (1y-DFS). The present study had 90% power to demonstrate that the RDI was not fewer than 50% with a one-sided alpha 5% when the RDI was in fact over 80%. Eligibility criteria included; 1) stage IB to IIIA NSCLC, 2) patients who received the complete resection, 3) 20 to 75 years old. S-1 (80mg/m^2) was given for 4-week oral administration followed by 2-week rest, within 8 weeks after surgery.
Results: From May 2007 to Oct 2009, total 28 patients were enrolled from three hospitals in Hokkaido, Japan. The RDI was 63.1% (95% CI, 48.6% to 77.7%), and an average of courses of S-1 was 5.3. There was no grade 3 or worse hematological toxicity in the present study. Four patients (14.3%) had grade 3 non-hematological toxicities, and no one had grade 4 or worse non-hematological toxicities. Four patients had the recurrences and probability of 1-y DFS was 85.7% (95% CI, 72.8% to 98.6%). In the present study, the median RDI in patients over 65 years was less than that in patients 65 years or younger (P = 0.013, Mann-Whitney U test). In the over 65 years group, more patients experienced grade 2 or 3 non-hematological toxicities.
Conclusion: S-1 chemotherapy, in which S-1 is given for 4-week oral administration followed by 2-week rest, is not feasible as the standard regimen of administration for the adjuvant chemotherapy in patients with completely resected NSCLC. The modified S-1 regimen that consists of 2-week administration and 1-week rest would be recommended for adjuvant chemotherapy.
Keywords: Non-small cell lung cancer, Adjuvant chemotherapy, S-1

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P3.241 CAN MAXIMUM STANDARDIZED UPTAKE (SUVMAX) OF F-18 FDG BE AN INDICATOR OF PREDICTING THE ADJUVANT CHEMOTHERAPY IN EARLY STAGE NON-SMALL CELL LUNG CANCER?

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Background: The exact staging in non-small cell lung cancer (NSCLC) is the most important parameter in managing of the patients. There is still debate the need of the adjuvant chemotherapy in early stage NSCLC patients. In this study, we aimed to investigate a prediction value of SUVmax in primary tumor for the decision of the adjuvant chemotherapy and the correlation between SUVmax value and the histopathological parameters such as arteriovenous invasion, lymphatic invasion, perineural invasion, pleural invasion.
Methods: In a retrospective study, 33 NSCLC patients (31M, 2W) who were diagnosed as stage I and II (IA:8 patients, IB:15 patients, IIB: 10 patients) were included in this study . Primary tumors were resected by surgery. The marginal regions of all tumors were negative for all patients. A total of 20 patients received adjuvant chemotherapy (CT), 13 patients did not receive (Non-CT). The average follow-up duration was 11 months (± 0,7). All of the patients underwent F-18 FDG PET-CT imaging before surgery for staging. SUVmax values of the primary tumor were obtained. Mann-Whitney U, Pearson correlation test and Kaplan Meier analysis were performed for the evaluation.
Results: The average of SUVmax values were 9.44, 10.33 and 8.09 in all patients, CT group and Non-CT group respectively. There was no statistical difference in SUVmax values between CT group and Non-CT group (p=0,397). Disease free survival (DFS) was not statistically different between CT group and Non-CT group. DFS was shorter in patients with SUVmax>11 than in patients with SUVmax<11. (p:0.027). Although DFS was shorter in both CT and Non-CT group patients with SUVmax>11 than in patients with SUVmax<11, there was no statistically significant difference. This is probably due to limited number of patients. There is no statistically difference between SUVmax and artery invasion (p=0.557), venous invasion (p=0.271), lymphatic invasion (p=0.259), perineural invasion (p=0.302), visseral pleural invasion (p=0.285), parietal pleural invasion (p=0.826).

Table 1

	SUV>11	SUV<11	P
All patients(months)	9,7 (±0,7)	17,5 (±0,6)	0,027
CT group(months)	9,8 (±0,7)	16,3 (±2,2)	0,08
Non-CT group (months)	9,5 (±1)	15,6 (±0,8)	0,26

Conclusion: This preliminary study indicates that SUVmax: 11 might be a threshold value for predicting DFS for early stage NSCLC. The fact that no correlation was found between SUVmax and histopathological parameters, SUVmax may be an independent predictor of DFS. Adjuvant chemotherapy after surgery in early stage NSCLC patients with SUV>11 may be considered as an independent parameter. The further studies to examine this hypothesis are needed in larger groups of patients.

Keywords: SUVmax, early stage non-small cell lung cancer, F-18 FDG PET-CT

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P3.242 SAFETY AND TOLERABILITY OF DOCETAXEL-CARBOPLATIN IN THE ADJUVANT TREATMENT OF NON-SMALL CELL LUNG CANCER, A CHINA CLINICAL TRIALS CONSORTIUM STUDY

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Background: The combination of docetaxel and carboplatin is a well-established regimen in the treatment of late-stage non-small cell lung cancer (NSCLC). There are little data, however, regarding the safety and tolerability of this regimen in the post-operative setting for early stage patients, criteria which are critical to the successful application of an adequate course of adjuvant therapy intended to bolster the success of curative surgical resection. Previous studies of adjuvant chemotherapy for NSCLC have reported rates of treatment protocol completion as low as 60%.

Methods: A total of 133 patients with stage Ib-IIIa NSCLC were enrolled in an open-label, single arm study to assess the safety and tolerability of docetaxel (75 mg/kg) and carboplatin (AUC 5.5) administered for 3 cycles after attempt at curative resection (lobectomy, bilobectomy or pneumonectomy). A new cooperative research body, the China Clinical Trials Consortium (CCTC), comprised of leading centers of lung cancer treatment in four cities in China, was enlisted to accelerate accrual of the target sample. The primary endpoint of the study was safety, as reflected in the rate of febrile neutropenia believed to be associated with the treatment regimen, with a febrile neutropenia rate of less than 10% considered to be safe.

Results: Patient accrual was completed at 1 center in the US (2 patients) and 10 centers in China (131 patients) in less than six months. Surgeon preference resulted in 66 procedures (50%) being performed using a video-assisted thoracoscopic surgical (VATS) approach, including 62 of 118 lobectomies (53%). Successful completion of the entire three-course adjuvant regimen was achieved in 115 patients (86%) according to the study protocol; of those, 113 patients (98%) received greater than 66% of the target dose of carboplatin. VATS resection was associated with a higher rate of both delivery of 3 full cycles of chemotherapy (94% vs. 79%, P=0.01) and delivery of at least 90% of the target carboplatin dose (99% vs. 70%, P=0.001) compared to the open approach. Febrile neutropenia complicated treatment in 12 patients (9.0%), below the predetermined safety threshold of 14 patients. Serious adverse events (SAEs) were observed in 13 (9.8%) patients. There were no deaths attributable to the study regimen.

Conclusion: In this prospective study, docetaxel and carboplatin were well-tolerated in the adjuvant treatment of NSCLC. Very rapid patient accrual was

achieved at sites participating in the CCTC with protocol compliance that was high compared to that observed in similar adjuvant studies. Furthermore, this high compliance was achieved despite the pre-study perception among many Chinese investigators that these "Western" doses of the study drugs were too high to be tolerated by their Chinese patients. This new research body may therefore have the capability to substantially impact the clinical development of novel therapies for lung cancer, which has traditionally been hampered by slow patient accrual in definitive, large-scale studies.

Keywords: Adjuvant chemotherapy, Docetaxel, Carboplatin, China Clinical Trials Consortium

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P3.243 ORAL VINORELBINE IN COMBINATION WITH CARBOPLATIN IN ADJUVANT CHEMOTHERAPY OF NON-SMALL CELL LUNG CANCER: A PROSPECTIVE MULTICENTRE STUDY OF FEASIBILITY AND TOLERABILITY.

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Background: Adjuvant chemotherapy (ACT) has become a new standard in patients with stages IIA, IIB, and IIIA of non-small cell lung cancer (NSCLC) after radical resection. Results in stage IB are still not conclusive. Vinorelbine is a preferable associated drug in this indication and in advanced NSCLC , a randomized study proved the comparable effectiveness and tolerability of vinorelbine given both orally or intravenously (i.v.). Meanwhile oral vinorelbine gives better comfort to patients. Cisplatin is preferred to carboplatin in ACT combination, but compliance seems to be a problem in daily practice.

Methods: This prospective multicentre study evaluates the feasibility, toxicity and short time survival of adjuvant chemotherapy based on carboplatin- CBDCA (AUC 5) with vinorelbine 80mg/m2 D1 and D8 given orally (after a first cycle at 60 mg m,[2] with myelosensitivity control). After radical resection, ACT (4 cycles of 21 day regimen) was applied to outpatients with stage IB, II, and IIIA of NSCLC in 16 centres.

Results: ACT was applied to 104 eligible patients (72 men, 32 women, median of age 64 years). Out of them, 41 were smokers, 57 ex-smokers and 5 non smokers. Surgically determined stages were IB in 32 pts, II 36 pts and IIIA in 36 pts. Altogether 401 cycles were administered, 89.4% of patients finished four cycles of planned ACT. The reasons for 11 patients ending ACT prematurely were hematological toxicity in 8 pts and non-hematological toxicity in 3 pts. The most frequent WHO grade 3/4 of toxicity accounted on the cycle were neutropenia in 10.3%, leucopenia in 5.03%, thrombocytopenia in 1.01%, anemia in 0.76% , alopecia in 3.27%, nausea in 4.02%, neurotoxicity, diarrhoea and mucositis in 0.25%. During the follow-up period, median 0.98 year (11.7m), 11 (10.6%) pts died, 2 (1.9%) pts died because of the different reason than toxicity or progression. 91 (87.5%) pts lived, 13 (12.5%) pts of them survived with appearance of recurrence and 78 (75%) pts lived without progression of the disease.

Conclusion: ACT with carboplatin and vinorelbine given orally on day 1 and 8 appears to be a feasible and tolerable regimen in radically resected NSCLC. Present study is ongoing and the trends of overall survival, disease free interval and other survival parameters will be evaluated in the future.

Keywords: neoadjuvant chemotherapy, Vinorelbine, NSCLC, Carboplatin

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.244 EVALUATION OF RELATIONSHIP BETWEEN SERUM PROTEIN PROFILES AND LUNG CANCER BY SELDI-TOF-MS (SURFACE ENHANCED LASER DESABSORBTION IONIZATION TIME OF FLIGHT MASS SPECTROMETRY) METHOD

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Background: Advances in the proteomics study have introduced novel techniques for the diagnosing and screening of cancer biomarkers. The goal of this study was to establish proteomic patterns of tumor subsets in lung cancer patients with surface enhanced laser desabsorbtion ionization time of flight mass spectrometry (SELDI-TOF-MS) method.
Methods: 142 non-small cell lung cancer (NSCLC) and 27 small cell lung cancer (SCLC) totally 169 patients were included in this study. In non-small cell lung cancer group, there were 60 squamous cell carcinoma, 38 non-squamous cell carcinoma and 44 unclassified type of non-small cell lung cancer patients. Venous samples were taken from all cases. All of the serum samples were analyzed by SELDI-TOF-MS method for proteomics investigation.
Results: When the Mann–Whitney non-parametric test was used between NSCLC and SCLC groups, only 3 peaks were found to be discriminatory in serum SELDI profiles (Table 1). All of these 3 peaks showed higher intensity in patients with SCLC.

Proteomic feature (m/z)	p value	AUROC
9065	0.003	0.66
9175	0.017	0.63
9394	0.026	0.63

Table 1. Discriminatory peaks between NSCLC and SCLC cases. When analysis was performed between non-squamous and squamous cancer groups of NSCLC, 8 proteomic features were found to be discriminatory (Table 2). Among these peaks only 2 of them (5815 m/z, 5906 m/z) showed higher intensity in patients with non-squamous group.

Proteomic feature (m/z)	p value	AUROC
15879	0.0085	0.64
3145	0.0093	0.65
16051	0.0098	0.66
2855	0.0115	0.64
8683	0.0267	0.63
15172	0.0321	0.63
5815	0.0392	0.64
5906	0.0408	0.63

Table 2. Discriminatory peaks between non-squamous and squamous cancer groups.
Conclusion: Proteomic patterns could provide some valuable clues on the carcinogenetic mechanism of different types of lung cancer and may help us to discover some potential subtype-specific biomarkers of lung cancer by SELDI-TOF-MS method.
Keywords: proteomics, Lung cancer

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P3.245 HIGH RISK FEATURES IMPROVE PROGNOSTICATION IN RESECTED STAGE I NSCLC: A SINGLE INSTITUTION RETROSPECTIVE REVIEW.

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Background: In 2010 the seventh edition of the TNM staging for non-small cell lung cancer (NSCLC) was published. Like previous editions, the current system is an anatomical classification. However, the addition of various histological features to a tumour's stage may more accurately predict outcomes. In this vane, this study aims to evaluate the effect of certain histopathological features on the prognosis for resected NSCLC in light of the new staging system.
Methods: This is a retrospective review of 1513 patients (1005 M, 508 F) who underwent surgical resection for NSCLC from 1979 to 2009 at the Prince Charles Hospital (TPCH). Data extracted from the pathology reports include the presence of the following variables: vascular, lymphatic and perineural invasion. These variables are compared to clinical phenotypes including stage and overall survival by the univariate Kaplan-Meier method and multivariate Cox regression model.
Results: Of the 1513 patients, 56.5% were stage I and 22.4% were stage II. In the entire cohort of patients vascular, lymphatic and perineural invasion was present in 38.6%, 23.8% and 8.8% respectively.

Subjects with resected stage I NSCLC had a poorer prognosis if either vascular (HR 1.389, p = 0.001) or lymphatic invasion (HR 1.828, p <0.0001) were present, but not if perineural invasion (HR 1.235 p = 0.362) was present. In all subjects, preliminary multivariate analysis showed that vascular invasion remained a statistically significant prognostic variable independent of stage.

Conclusion: This is the largest single institution review of its kind and the final analysis is proceeding and will soon be ready to publish. However the preliminary analysis of our data suggests that in patients with resected stage I NSCLC the presence of vascular invasion portends a significantly worse prognosis. This study proposes that by considering vascular invasion in patients with resected Stage I NSCLC, a more precise prognosis can be determined so that adjuvant chemotherapy may be offered to those at higher risk with a better treatment benefit ratio.

Keywords: NSCLC, Lymphatic Invasion, Vascular Invasion, Perineural Invasion

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P3.246 ORAL VINORELBINE IN COMBINATION WITH CISPLATIN OR CARBOPLATIN IN ADJUVANT CHEMOTHERAPY OF NON-SMALL CELL LUNG CANCER: A PROSPECTIVE MULTICENTRE STUDY OF FEASIBILITY,TOLERABILITY AND 3-YEAR SURVIVAL.

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Background: Adjuvant cisplatinum-based chemotherapy is recommended for routine use in patients with stages IIA, IIB, and IIIA of non small-cell lung cancer (NSCLC) after radical resection. Results in stage IB were not conclusive. Vinorelbine is a preferable associated drug in this indication and a randomized study proved the comparable effectiveness and tolerability of vinorelbine given both orally or intravenously (i.v.) in advanced NSCLC, meanwhile oral vinorelbine gives better comfort to patients.

Methods: This prospective multicentre study evaluates the feasibility, toxicity and 3-year survival of adjuvant chemotherapy (ACT) based on cisplatin-CDDP (80mg/m^2) or carboplatin- CBDCA (AUC 5) with vinorelbine (25 mg/m^2 D1 i.v. and 60mg/m2 D8 given orally). After radical resection, ACT (4 cycles of 21 day regimen) was applied to patients with stage IB, II, and IIIA of NSCLC in 21 Czech and Slovak centres. Selection of CDDP or CBDCA was based on individual centre preference. Recruitment of patients started on the 12th of January 2005 and finished on the 5th of December 2008. Evaluation was closed on the 31st of January 2011.

Results: ACT was applied to 154 eligible patients (110 men, 44 women, median of age 63 years). Out of them, 89 were smokers, 49 ex-smokers and 16 non smokers. Surgically determined stages were IB in 46 pts, IIA in 18 pts, IIB in 38 pts and IIIA in 52 pts. CBDCA was given to 77 patients and CDDP to 77 patients, 4 of whom switched to CBDCA. All of them were treated as out-patients. Altogether 586 cycles (mean no 3.81, in CDDP 3.77, in CBDCA 3.84) were administered, 84% of patients finished four cycles of planned ACT. The reasons for 25 patients ending ACT prematurely were hematological toxicity in 8 pts, non-hematological toxicity in 9 pts and other reasons in 8 pts. The most frequent WHO grade 3/4 of toxicity were neutropenia in 10.3%, leucopenia in 4%, anemia in 4.5%, thrombocytopenia in 1.9%, alopecia in 2.9%, nausea in 5.8%, neurotoxicity, diarrhoea and mucositis in 0.7%. There was significantly higher incidence of neutropenia (p 0.034) and slightly higher incidence of vomiting (p 0.055) in CDDP regimen, and non significantly higher incidence of anemia (p 0.054) in CBDCA regimen. Median of follow-up was 31 month, 3-year survival during this period was 69,8%. After evaluation closing 98 pts has lived, 31.2 % (48 pts) died because of NSCLC , 5,2 % (8 pts) died because of the different reasons than toxicity or progression (7 pts died without progression, 1 patient died during the cancer recurrence but progression was not the reason of the death). Out of all alive patients, 18 survived with appearance of the recurrence and 80 pts lived without progression of the disease. Disease free interval was 43 months.

Conclusion: ACT with vinorelbine given orally on day 8 appears to be a feasible and tolerable regimen

in radically resected NSCLC. Short time survival results are optimistic. Present study is ongoing and the trends of overall survival, disease free interval and other survival parameters will be evaluated in longer follow-up period.

Keywords: oral vinorelbine, Adjuvant chemotherapy, short time survival, NSCLC

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P3.247 A WINDOW STUDY EVALUATING THE ACTIVITY OF SINGLE AGENT BEVACIZUMAB PRIOR TO INDUCTION CHEMOTHERAPY FOR OPERABLE NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Neoadjuvant and adjuvant chemotherapy are integral components of treatment for resectable NSCLC. The 5 year survival for stage IB-IIIA NSCLC, however, remains disappointing. Incorporating new agents into preoperative treatment allows for an in vivo evaluation of treatment effect and pathologic correlation at resection. Bevacizumab added to chemotherapy benefits patients with advanced NSCLC. Its single agent activity is not well characterized, however. We hypothesized that the addition of bevacizumab prior to neoadjuvant chemotherapy would be an effective preoperative approach. Our specific objectives were to determine: 1) response to single agent bevacizumab, and 2) subsequent rate of downstaging compared to historical controls treated without bevacizumab. We report the results of this correlative radiologic study herein.

Methods: Patients with resectable stage IB-IIIA adenocarcinoma and large-cell carcinoma without a history of hemoptysis received preoperative bevacizumab (15mg/m^2) alone followed by a repeat CT scan 2 weeks later. Thereafter, patients received 4 cycles of docetaxel and cisplatin and 2 additional cycles of bevacizumab. Correlation between downstaging and response to bevacizumab was assessed by Wilcoxon rank test.

Results: Thirty nine patients evaluable for response were- Stage IB: N=6 (15%); Stage II: N=6 (15%); Stage IIIA: N=27 (69%). KRAS mutations: 10/34 (29%); EGFR mutations: 4/34 (12%). Two weeks after bevacizumab, 37/39 patients (95%) had a reduction in bidimensional measurement (Figure 1). Six of 39 (15%) had a >25% response at 2 weeks. 9/34 patients (26%) developed new tumor cavitation at 2 weeks following single agent bevacizumab. TTP in patients with and without cavitation was not reached versus 17 months. 15/35 evaluable patients (43%) were downstaged. 11/23 stage IIIA patients (48%) achieved nodal downstaging. There was no correlation between response to bevacizumab at 2 weeks and downstaging (p=0.17). 6/34 (18%) patients had >90% tumor necrosis in the resection specimen. With a median follow-up of 18 months, all patients with >90% tumor necrosis were alive and disease-free. Of note, 4/6 patients with >90% tumor necrosis were those who developed new cavitation at 2 weeks following 1 dose of bevacizumab.

Conclusion: Nearly all patients had a reduction in bidimensional measurement at 2 weeks following single-agent bevacizumab. The magnitude of response did not, however, correlate with downstaging. Cavitation following single-agent bevacizumab may predict for marked pathologic treatment effect and may be associated with improved TTP.

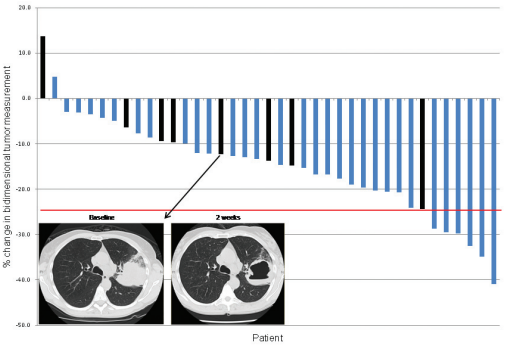

Figure 1. Waterfall plot of bidimensional response 2 weeks after single-agent bevacizumab. Black bars denote cavitation. Inset image: Example of cavitation 2 weeks after single-agent bevacizumab.

Keywords: bevacizumab, Non small cell lung cancer, neoadjuvant

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P3.248 ONCOLOGISTS, PHYSICIANS AND SURGEONS OPINIONS ON THE PERCEIVED VALUE AND APPROPRIATENESS OF THE SPECIALITY TO INFORM PATIENTS ON ADJUVANT CHEMOTHERAPY AFTER RADICAL SURGERY FOR NON-SMALL CELL LUNG CANCER

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Background: The benefit of adjuvant chemotherapy after radical surgery for non-small cell lung cancer is established, but the roles and responsibilities of discussing adjuvant chemotherapy are not well established. Whilst the risks are relatively straight forward to convey, the difficulties in conveying the benefit results from published hazard ratios in the literature as the benefit varies with stage and therefore needs to be calculated individually and conveyed in a language that is understood by the patient.

Methods: From 2010 to 2011, a survey was conducted by email to cancer physicians, oncologists and surgeons in the United Kingdom. Clinicians were asked to rank who they felt were the most appropriate to discuss adjuvant chemotherapy with patients, to calculate expected survival with adjuvant chemotherapy given baseline survival probability of 80% and a hazard ratio of benefit of 0.80, and then surveyed for the additional expected gain in survival in cohorts with a 5 year survival probability of 40%, 60% and 80% respectively before they would recommending adjuvant chemotherapy

Results: A total of 202 responses were received from 27 surgeons, 77 physicians, 87 oncologists (11 were others or unstated). The majority of 56% of surgeons, 79% of physicians and 61% of oncologists felt an oncologist as the most appropriate initial clinician to discuss adjuvant chemotherapy with patients after surgery. In total 33% of surgeons, 53% of physicians and 73% of oncologists were able to correctly calculate the expected survival of patients. When asked about the perceived value before considering recommending adjuvant chemotherapy with a 5 year survival probability of 40%, 60% and 80% respectively, clinicians reported an expected a mean gain (SE) of 20.8% (2.7), 15.6% (2.4) and 13.2% (2.1) against an expected of 12%, 8% and 4% respectively with a hazard ratio of 0.80.

Conclusion: Our survey suggest oncologists as the clinicians best able to calculate the individual benefit of adjuvant chemotherapy and the majority of specialities polled agreed oncologists as the more appropriate initial person to discuss adjuvant chemotherapy with patients after radical surgery for lung cancer. The perceived value prior to recommending adjuvant chemotherapy in clinicians greatly exceeds current published results.

Keywords: Non-small cell lung cancer, Surgery, Adjuvant chemotherapy

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P3.249 NON-SMALL CELL LUNG CANCER PATIENTS WITH VERY GOOD PROGNOSIS: INTRODUCTION OF A NOVEL 'TRIPLE-NEGATIVE' ENTITY.

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Background: Staging is of paramount importance in treatment planning, recommendation of best treatment modality and survival predilection.Despite the multinational, multiinstitutional basis of the database which has been used for construction of 7th staging system, data regarding lymph node staging and histopathologic markers remained suboptimal and it prones to selection-bias. We aimed to evaluate the prognostic importance of lymphatic and perineural invasion in patients with N0 disease and try to define a new triple-negative group of patients.

Methods: Two hundred sixtyeight patients (221 men, 47 women)who had undergone complete surgical resection for non-small cell lung cancer between January 2005 and December 2010 were investigated.. Mean age was 59.8 (ranging from 20 to 82) years. Mean follow-up time was 23

months (ranging from 1 to 111 months). Kaplan Meier analysis along with log-rank test and Cox multivariate analysis were used.
Results: The 5-year survival of in our series was 61.5%, median survival time was 59±5 months (95% CI:52-70 months). Statistically significantly different stage stratifications according to new T staging were observed (p=0.03). Mediastinal nodal tumor involvement was found to be a prognostic factor (p=0.02).Perineural involvement and Among patients without mediastinal lymph node metastasis, perin lymphatic invasion independently indicated worse survival (p=0.02 and p=0.04 respectively). N0 patients without lymphatic and perineural invasion (triple negative patients) had the best survival (mean survival time was 75±7 months (95% CI: 62 -88 months). The survival rate of triple negative patients was statistically better that that of N0 patients(p=0.0351)
Conclusion: : Perineural invasion and lymphatic invasion seemed to be good prognosticators. Patients with triple negative tumors (N0, lymphatic invasion-perineural invasion-) had the best survival.
Keywords: Perineural Invasion, early stage lung cancer, Lymphatic Invasion, triple negative tumor

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P3.250 COMPUTED TOMOGRAPHY LYMPHOGRAPHY BY TRANSBRONCHIAL INJECTION OF A WATER-SOLUBLE EXTRACELLULAR CT CONTRAST AGENT TO IDENTIFY THE SENTINEL LYMPH NODES IN PREOPERATIVE NSCLC PATIENTS

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Background: Segmentectomy for clinical stage IA peripheral non-small lung cancer (NSCLC) patients should be converted to lobectomy when intraoperative frozen section reveals metastasic hilar or mediastinal lymph nodes. It is important to identify a lymph node which receives first lymphatic flow from the regional segment containing a lung tumor (ie, sentinel lymph node; SN). We have developed computed tomography lymphography (CTLG) by transbronchial injection of a water-soluble extracellular CT contrast agent of iopamidol to identify the SNs in preoperative NSCLC patients. This study was conducted to evaluate feasibility of safety of this method.
Methods: Eleven patients with clinical stage I NSCLC were enrolled in the study. They included 3 males and 8 females and their mean age was 65.1 (range; 47 - 76). Mean tumor size was 20.5 mm (range; 14 - 35). The histologic types were adenocarcinoma in 10 patients and squamous cell carcinoma in 1 patient. Tumor locations were as follow; right upper lobe in 6, right lower lobe in 2, left upper lobe in 2, and left lower lobe in 1. Virtual bronchoscopic navigation images which aid bronchoscopists in guiding the bronchoscope to a targeted location were reconstructed using 1 mm thickness CT scan data prior to the CTLG. An ultra-thin bronchoscope was inserted to the targeted peripheral bronchus under a guidance of the navigation images. A sheath was inserted through a channel of the bronchoscope and 3ml of iopamidol was injected. CT images (1 mm thickness) of the chest were obtained at 30 seconds and 5 minutes after injection. The respective CTLG and contrast enhanced CT images were checked simultaneously on a workstation. Max CT number of every pulmonary, hilar and mediastinal lymph node was measured. SNs were identified when the lymph nodes were enhanced clearly in the postcontrast CT images, or max CT number of the lymph nodes in the postcontrast CT images (30 seconds after injection) increased by more than 30 Hounsfield unit (HU) higher compared to the precontrast ones. Patients underwent lobectomy with standard lymph node dissection. All lymph nodes include the SNs were histopathologically examined by hematoxylin and eosin staining.
Results: The ultrathin bronchoscope could access targeted bronchus and iopamidol was delivered into peritumoral area in all patients without any complication. CTLG was usually performed after transbronchial tumor biopsy (10/11), and it took about 10 minutes to complete the CTLG method itself. SNs were identified in all patients and the average number of SNs was 1.54 (range: 1-2). SNs were identified at pulmonary or hilar station in all patients and at mediastinal station in 4 patients. CT

images at 30 seconds were suitable to identify SNs visually. Max CT number of the SNs of precontrast, postcontrast at 30 seconds and 5 minutes after injection were 107 ± 31 HU, 243 ± 217 HU, and 179 ± 108 HU, respectively. Pathologic examination revealed n2 in one patient. This metastatic lymph node was included in the SNs.
Conclusion: CTLG by transbronchial injection of iopamidol was safe and useful method to identify the SNs in NSCLC patients.
Keywords: lymphography, segmentectomy, Sentinel lymph node, computed tomography

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P3.251 ACCRUAL TO ADJUVANT TARGETED CLINICAL TRIALS IN RESECTED NON-SMALL CELL LUNG CANCER: MORE HOLES IN THE "LEAKY PIPE."

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Background: Accrual to clinical trials is the primary approach for developing novel and improved treatment strategies for patients with cancer. A clinical trials design strategy to improve the therapeutic index for novel targeted therapies is to select individuals with specific tumor molecular characteristics. Overall, accrual to therapeutic clinical trials has been a concern and reported analogous to a "leaky pipe." Now with the addition of molecular patient selection accrual may further be impeded. For this report, we evaluated the accrual to 2 international adjuvant targeted treatment trials for patients with resected non-small cell lung cancer (NSCLC) at our institution.
Methods: From our cancer tumor registry, we identified retrospectively patients with resected NSCLC from 2007 to 2009. Patients from the tumor registry were excluded with diagnosis other than NSCLC, wedge resection, incomplete nodal staging and R1 resection as major ineligibility requirements of these adjuvant trials. We then compared the results from the cancer registry analysis with the number of patients approached in the clinic to participate in 1 of 2 adjuvant placebo-controlled targeted therapy trials with either EGFR tyrosine kinase inhibitor (RADIANT) or the melanoma antigen vaccine MAGE-A3 (MAGRIT). Participants initially consented to have their resected tumor tissue evaluated for targets either EGFR or MAGE. If the target was identified, participants would then consent to enroll in the treatment portion of these clinical trials. In both clinical trials, patients were permitted to receive standard adjuvant chemotherapy.
Results: From our tumor registry, we identified 135 patients with resected stage I to IIIA NSCLC who were potential candidates to participate in these adjuvant treatment trials, RADIANT or MAGRIT. From these 135 patients, only 43 (32%) pre-screened patients consented to have their tumor tissue evaluated for either EGFR (16 patients) or MAGE (27 patients). Twenty-two (22) participants of the 43 consented patients (51%) had a positive tissue target identified for participation in the treatment portion of either the RADIANT (15 of 16 patients, 94%) or MAGRIT (7 of 27 patients, 26%). Of these 22 participants, only 6 patients (27%) enrolled in the treatment portion of these clinical trials; RADIANT (4 patients, 27%) or MAGRIT (2 patients, 28%). Overall, from the 135 patients identified retrospectively in our tumor registry only 4% enrolled in these 2 trials. The reasons for non-participation were 1) ineligibility at initial pre-screening, 2) treatment at another institution, 3) unacceptable frequency of follow-up visits and 4) declining any further therapy after adjuvant chemotherapy. Inability to comply with the protocol and the placebo-controlled study design were less common reasons for non-participation.
Conclusion: Accrual to adjuvant targeted cancer clinical trials is further impeded by the need for molecular selection of participants. Broader eligibility requirements not related to molecular selection, integrated treatment strategy of conventional and investigational therapies, reduction in the frequency of follow-up evaluations, and improved clinical trials education for investigators

and participants may lead to enhanced participation in adjuvant targeted clinical trials in NSCLC.
Keywords: clinical trials accrual, Adjuvant targeted therapies

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P3.252 PROSPECTIVE STUDY OF PROGNOSTIC FACTORS IN SMALL PERIPHERAL LUNG CARCINOMAS

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Background: Some cases of peripheral lung carcinoma with the largest nodule diameter ≤ 3 cm have poor outcomes after early post-operative recurrence. We prospectively collected data on peripheral lung carcinoma cases with the largest nodule diameter ≤ 3 cm confirmed by thin-section computed tomography (TSCT) to find statistical differences in prognosis between the cases with air-containing type lesion and those with solid density type lesion. Further, we aimed to clarify other prognostic factors that may contribute to early post-operative recurrence of peripheral lung carcinoma.
Methods: 50 patients with peripheral lung carcinoma confirmed at our hospital between January and October 2009 were enrolled. In all cases, the largest nodule diameter was ≤ 3 cm in TSCT images and carcinoma was histopathologically confirmed. A written agreement [Informed consent] for participation in the study was obtained from each patient. Investigated prognostic factors are age, gender, smoking history, and classification of the tumors (air-containing type lesion or solid density type lesion) by TSCT.
Results: The study enrolled 23 male and 27 female patients, median age 69 years (range: 40 - 86). There were 23 smokers and 27 non-smokers in the group. The number of air-containing type lesion was 19 and that of solid density type lesion was 31, based on the findings of the TSCT images. Histological breakdown: 40 cases of adenocarcinoma, 7 cases of squamous carcinoma, 1 case each of atypical carcinoid, large cell neuroendocrine carcinoma, and mucoepidermoid carcinoma. Pathological stage breakdown: 47 cases of Stage I, 2 of Stage II, and 1 of Stage III. During a mean observation period of 514 days (283 - 608), 4 recurrences were confirmed in the solid group.
Conclusion: No statistical difference was found between the aerated and solid groups (Log-rank test, p=0.1089) due to the small sample number of 50. We continue our observation for future re-analysis on survival and recurrence.
Keywords: Thin-section CT, recurrence, small-size lung cancer, Lung cancer
A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.253 PROGNOSTIC VALUE OF PREOPERATIVE FDG-PET IN STAGE IA LUNG ADENOCARCINOMA

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Background: Maximum standardized uptake value (SUVmax) of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been found to have prognostic value. We previously reported the correlation between SUVmax and pathological invasive area, and determined a SUVmax cut-off value of 2.15 for predicting the recurrence potential of an invasive area of diameter 5 mm. Here, we evaluate the validity of FDG-PET for prediction of recurrence in pathological stage IA lung adenocarcinoma.
Methods: From February 2006 to May 2008, 100 patients with pathological stage IA lung adenocarcinoma underwent complete resection at our hospital. Tumors were classified as air-type or solid-type based on thin-section computed tomography (TS-CT) findings and the influence of TS-CT classification, SUVmax, and clinicopathologic features in terms of the incidence of recurrence were evaluated.

Results: Unlike air-type adenocarcinomas, recurrent disease was detected in 8 of 62 solid-type adenocarcinomas. SUVmax and diameter of invasive area were significantly correlated with recurrence and a shorter time to recurrence. All 8 recurrent cases had pathological invasive area > 5 mm. All except one case of recurrence showed solid-type adenocarcinomas with SUVmax >= 2.15. Three-year disease-free survival rates were 100% in air-type adenocarcinomas, 97.3% in solid-type adenocarcinomas with SUVmax < 2.15, and 74.1% in solid-type adenocarcinoma with SUVmax >= 2.15.
Conclusion: Combined evaluation of TS-CT classification and SUVmax had significant value in predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decision-making regarding the choice of surgical procedure and treatment after surgery.
Keywords: FDG-PET, Thin-section CT, Adenocarcinoma

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P3.254 ASSESSMENT FOR UNDERLYING ETIOLOGY OF BRONCHIOLOALVEOLAR CARCINOMA (BAC). IMPACTS OF SMOKING HABIT AND EGFR MUTATION.

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Background: Bronchioloalveolar carcinoma (BAC, or adenocarcinoma in situ) is a non-invasive variant of lung adenocarcinoma which is expected to have 100% cause-specific survival after complete removal. This tumor is generally recognized to be more frequent in female than in male, more in non-smokers than in smokers, but the fact is not fully examined. In this study, we investigated clinical backgrounds and pathological characteristics of the 119 BACs to improve our understanding of this tumor and, especially, to focus on the underlying etiology of male patients with BAC.
Methods: Among 2087 patients who underwent surgery for primary lung cancer in our institute from 1995 to 2010, 1549 patients had lung adenocarcinoma and 119 (7.8%) of them were BAC. As comparison groups, we used invasive adenocarcinomas (n=1430, Group 1) and NSCLCs other than adenocarcinoma (excluding bronchial gland carcinoma and carcinoid) (n=438, Group 2). We studied the gender distribution and smoking habit of BAC patients in comparison with other Groups. Pathological findings of these BACs such as size, presence of mucin, multiplicity and coexistence of other tumors were also examined. Thirty of 34 male patients and 27 of 85 female patients, whose samples were available, were also analyzed for EGFR mutations.
Results: There were 34 males and 85 females. The rates of males among the BAC patients, Group 1 and Group 2 were 29, 50 and 87 (%). The smoker rates were 26, 48 and 92 (%) (68, 79 and 95 (%) for male, and 9, 18 and 71 (%) for female, respectively). The mean age was 61±10, 64±10, 67±9.0, which showed no gender difference. The mean size was 16±10 mm. Histologically, 9 of 119 (8%) were mucinous BAC, 21 (18%) were multiple, 13 (11%) were presented with advanced lung cancer (12 with adenocarcinoma and 1 with squamous cell carcinoma) and 21 (18%) were presented with AAH in the same resected specimen. None of these histological characteristics showed gender difference. Among male patients with BAC, EGFR mutations were identified in 47% (14 of 30) while there were 67% (18 of 27) in female patients.
Conclusion: There was a gender difference among BAC patients, 2.6 times more in female than male, and younger patients were affected compared to other Groups of lung cancer. All these data were comparable with former reports. The rate of smokers among BAC was lower (26%) than those of the other Groups as was also expected, although this was much evident when only female patients are considered (9%) and was not so low in male (68%). EGFR mutation rate was quite high both in male and female (47% and 67%, respectively), while it was equal between smoker and non-smoker (56% and 57%), suggesting that smoking habit is not a causative factor for BAC (the mutation data is not yet attained in all the cases, though.) Although it seems that BAC has least effects of smoking for its

carcinogenesis, we will still elucidated whether or not BAC of smokers and that of non-smokers are really similar from viewpoints of pathology and signaling pathway.
Keywords: EGFR mutation, Smoking, lung adenocarcinoma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.255 DISCOVERY AND VALIDATION OF A PLASMA PROTEIN BIOMARKER PANEL FOR EARLY DETECTION OF NON SMALL CELL LUNG CANCER

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Background: Successful treatment of lung cancer suffers from the lack of tools for early diagnosis. Here, we describe the discovery and a panel of biomarkers to detect stage I non small cell lung cancer (NSCLC).
Methods: We produced complex nascent monoclonal antibody libraries (> 1200 mABs) directed against the natural protein antigens present in the plasma of patients. Unbiased mAB profiling of plasma proteomes of lung cancer patients and controls (301 patients and 235 controls) from independent clinical cohorts, identified thirteen cancer specific ($p<0.05$) mABs, recognizing five plasma proteins. Using quantitative sandwich ELISA for each protein we have developed a five biomarker classifier for early detection of NSCLC.
Results: The majority of the mABs detect antigens present in the cancer tissue in-situ. The panel had a diagnostics performance of 77% sensitivity and 87% specificity (all stages). Combination of the new panel with a well established marker, results in a performance of 83 % sensitivity at 95 % specificity for stage I NSCLC.
Conclusion: The new composite panel may have important utility for early detection and routine diagnosis of NSCLC in combination with imaging technologies.
Keywords: NSCLC, Early Detection, mAB proteomics, blood biomarkers

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.256 PROGNOSTIC SIGNIFICANCE OF FDG-PET IN SURGICALLY TREATED PATHOLOGICAL STAGE I LUNG ADENOCARCINOMA

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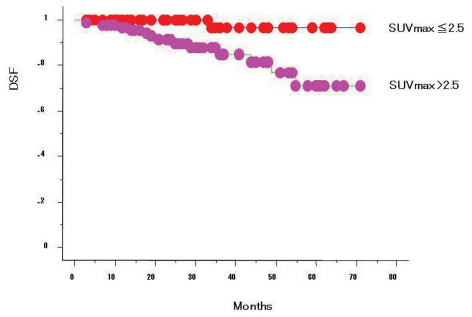
Background: We often experience recurrent disease after surgery in adenocarcinoma even in the early staged patients. In general, pathological (p-) stage IB to III cases are considered to be good candidates for adjuvant chemotherapy, and furthermore p-stage IA cases over 2 cm in size are also regarded to be candidates of adjuvant uracil-tegafur in Japan. We have conducted this retrospective study to evaluate whether we could determine the indication of adjuvant chemotherapy by using maximum standardized uptake value (SUVmax) on FDG-PET in p-stage I adenocarcinoma patients.
Methods: We analyzed consecutive 157 patients who underwent curative surgical resection for lung adenocarcinoma and diagnosed as p-stage IA or IB between April 2004 and October 2010 who have also examined preoperative FDG-PET imaging. We analyzed the association between disease free survival (DFS) and clinicopathological factors. DFS was calculated by means of Kaplan-Meier analysis and statistical significance between the groups was analyzed by using log-rank tests. Cox proportional hazard regression was used to ascertain independent predictors of recurrence.
Results: The median follow-up time was 30.7 months. 5-year DFS was 80.8%. There were 14

patients (8.9%) with recurrence after surgery. We divided patient population into two groups according to SUVmax of 2.5. The 5-year DFS of the group with SUVmax of less than 2.5 was significantly better compared with the group with SUVmax more than 2.5 (96.4% and 71.0%, respectively, p=0.0119). These groups were subdivided by using tumor diameter of 2.0cm. The 5-year DFS for patients with both SUVmax less than 2.5 and tumor diameter less than 2cm was 100%, for those with SUVmax less than 2.5 and tumor diameter more than 2cm, it was 88.9%, for those with SUVmax more than 2.5 and tumor diameter less than 2cm, it was 68.1%, for those with SUVmax more than 2.5 and tumor diameter more than 2cm, it was 73.8%, respectively.



Conclusion: The results of this study suggested that we could decide the indication of adjuvant chemotherapy by means of SUVmax regardless of tumor size in p-stage I adenocarcinoma.

Keywords: pathological stage I adenocarcinoma, recurrent disease, FDG-PET, Adjuvant chemotherapy

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P3.257 HYPERFRACTIONATED RADIOTHERAPY AND PROPHYLACTIC CRANIAL IRRADIATION IN THE ROUTINE TREATMENT OF PATIENTS WITH LIMITED-DISEASE SMALL-CELL LUNG CANCER

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Background: The results of several randomized clinical studies and meta-analyses demonstrated that the addition of thoracic irradiation to chemotherapy significantly improved overall survival in limited-disease small-cell lung cancer (LD-SCLC). However, the choice of optimal fractionation schedule and the timing of thoracic radiation is still controversial. The phase III trial (Turrissi et al., 1999) reported improved overall survival rates with accelerated hyperfractionated (45 Gy radiation therapy, 1.5 Gy twice daily) compared to once daily conventional radiotherapy. A limitation of the study was, however, that total radiation dose in control arm was low according to present-day standards. Ongoing CONVERT study compares twice daily thoracic radiotherapy (45Gy in 30 fractions) to a higher dose of conventional radiation (66 Gy w 33 fractions).

The aim of the present study is to compare the effectiveness of hyperfractionated, conventional and split-course hypofractionated radiotherapy in a large series of patients with LD-SCLC treated in a single institution. The effect of prophylactic cranial irradiation is also addressed.

Methods: Between 1994 and 2009 505 patients with LD-SCLC were treated in Center of Oncology Maria Sklodowska-Curie Memorial Institute, Gliwice, Poland. All patients received platinum based chemotherapy and thoracic radiotherapy: 77 patients received accelerated hyperfractionated radiotherapy (45Gy in 30 fractions, 1,5 Gy per fraction given twice a day), 364 patients received conventional radiotherapy (50,4-60 Gy in 1,8 to 2.0 Gy per fraction) and 64 patients received hypofractionated split-course radiotherapy (40-51 Gy in 3,0 to 4,0 Gy per fraction). The characteristics of the groups was comparable with respect to gender, age and use of chemotherapy. 170 patients received prophylactic cranial irradiation. Kaplan-Meier method was used to plot survival curves, the curves were compared using Mantel procedure and chi-square statistics.

Results: The 2-years overall survival rate was 23% for accelerated hyperfractionated radiotherapy, 16% for conventional radiotherapy and 10% for hypofractionated radiotherapy, (p=0,007). Use of prophylactic cranial irradiation significantly improved overall survival (2-years overall survival rate was 22% and 13% respectively, in the group with and without cranial irradiation, p<0,001). The

best 2-years overall survival (25%) was observed in a group of patients with hyperfractionated thoracic radiotherapy and prophylactic cranial irradiation.
Conclusion: This study shows that routine use of hyperfractionated thoracic radiotherapy with cranial irradiation in LD-SCLC patients allows to achieve results that are comparable to those attained in published clinical trials. Hypofractionated split-course thoracic radiotherapy and lack of prophylactic cranial irradiation does not allow to achieve similar results and has, thus, only historical value.
Keywords: SCLC, Hyperfractionated radiotherapy, prophylactic cranial irradiation

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.258 SUVMAX MEASUREMENT BY PET SCANNING IN SMALL CELL LUNG CANCER.

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Background: Small cell lung cancer (SCLC) is an aggressive tumor with poor prognosis. Limited results of the prognostic and predictive value of the maximum standard uptake values (SUVmax) in SCLC are available.
Methods: An observational study in 75 chemonaive patients diagnosed with SCLC who underwent a positron emission tomography (PET) scan was performed. SUVmax was defined as maximum tumor concentration of FDG divided by the injected dose, corrected for the body weight of the patients: (SUVmax = maximum activity concentration/ [injected dose/body weight]). The SUVmax was the peak SUV in one pixel with the highest counts within the region of interest. The region of interest was only the primary tumor. With use of the CT scan, primary tumor was localized by the radiologist. Patients were subdivided into high and low SUVmax according to median SUVmax level. SUVmax values were related to overall survival (OS) and progression free survival (PFS). Data were evaluated using a two-tailed Student's t-test and adjusted for age, gender and performance. Survival time was estimated by the Kaplan-Meier method and the survival difference between groups was assessed by the log-rank test.
Results: 75 patients, 29 women and 46 men, with a mean age of 66 years (range 49 - 81) were included between 2007 and 2009. Follow up was at least 12 months. Patients diagnosed with limited disease (LD) were treated with surgery (n=4) or chemo/radiotherapy (n= 26). Patients with extended disease (ED) with chemotherapy alone (n=28) or, due to bad performance, no treatment (n=10) Significant lower SUVmax values of the primary tumor were observed in patients with LD (9.6) compared to ED (11.9) (p-value= 0.02). For overall survival, SUVmax was not discriminatory comparing the whole group of patients, LD and ED, treatment and no treatment. In a subgroup analysis it was found that in patients, staged as ED and treated with chemotherapy, significant differences in OS and PFS were found between the low and high SUVmax. Patients with ED and a high SUVmax value had a significant better OS (8.7 months) compared to the patients with ED and a low SUVmax (4.5 months) (p-value 0.008). Also longer PFS, 5.9 versus 3.2 months, between high and low SUVmax in patients with ED were observed (p-value 0.002).
Conclusion: In patients with SCLC, SUVmax was higher in ED compared to LD. Although data are still limited due to low patient numbers, a high SUVmax showed to be a factor for prolonged PFS and OS.
Keywords: PET scan, Small cell lung cancer, SUVmax

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P3.259 INCIDENCE AND IMPACT SYNDROME OF INAPPROPRIATE ANTI-DIURETIC HORMONE HYPERSECRETION (SIADH) IN SMALL CELL LUNG CANCER (SCLC).

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Background: Small cell lung cancer (SCLC) is a common cause of Syndrome of Inappropriate Anti-

Diuretic Hormone hypersecretion (SIADH). This study was performed to investigate the incidence and prognostic impact of SIADH in SCLC.
Methods: A retrospective review was performed after IRB approval on data abstracted from consecutive SCLC patients at the Medical College of Wisconsin (MCW) and its affiliate Veterans Affairs Medical Center (VAMC) from 2003 to 2010. Patients with hyponatremia were classified to have SIADH if they had normal renal function, were euvolemic and had urine osmolality over 100mOsm/kg.
Results: A total of 197 patients with small cell lung cancer were included. Patient demographics were: median age 65.9 years (41-87 years), male 153 (78%); race - Caucasian 171 (86%), African American 26 (13%); stage – limited stage 67 (34%), extensive stage 130 (66%); treating site - VAMC 117 (59%), MCW 80 (41%). Out of the 197 patients, 23 patients (12%) had SIADH with a median sodium level of 119 mmol/L (112-133mmol/L). Fourteen patients (61%) had extensive stage disease and 9 (39%) had limited stage disease. Symptomatic hyponatremia was observed in 15 patients (65%). These patients had a median sodium level of 116 mmol/L (112-132 mmol/L) compared to 121 mmol/L (112-133 mmol/L) in the 8 (35%) asymptomatic patients (p=0.12). The most common presenting symptoms were weakness (47%), confusion (33%), refractory nausea (13%) and seizures (7%). Out of the 23 patients with SIADH, 2 patients did not receive treatment for SCLC. Following chemotherapy, 15 out of 21 patients (71%) had normalization of sodium levels. Median overall survival in limited stage SCLC patients with and without SIADH were 12.5 and 15.8 months (log-rank p=0.425), respectively. Median overall survival in extensive stage SCLC patients with and without SIADH were 7.2 and 6.8 months (log-rank p=0.808), respectively.
Conclusion: SIADH occurs in approximately 12% of patients with SCLC but does not appear to impact overall survival in SCLC.
Keywords: Small cell lung cancer, Syndrome of Inappropriate Anti-Diuretic Hormone hypersecretion, Hyponatremia

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P3.260 PHASE II STUDY OF IRINOTECAN AND CISPLATIN WITH CONCURRENT SPLIT-COURSE RADIOTHERAPY IN LIMITED-DISEASE SMALL-CELL LUNG CANCER

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Background: Irinotecan and cisplatin is a standard treatment in patients with extensive-stage small cell lung cancer. To determine the efficacy and toxicity of irinotecan and cisplatin with concurrent split-course thoracic radiotherapy in limited-disease small-cell lung cancer, we conducted a phase II study.
Methods: Thirty-five patients fulfilling the following eligibility criteria were enrolled: chemotherapy-naïve, good performance status (PS 0-1), age < 75, limited-disease, and adequate organ function. Based on the phase I study (Eur J Cancer 38:1998, 2002), the patients received irinotecan 40 mg/m2 i.v. on days 1,8 and 15, and cisplatin 60 mg/m2 i.v. on day 1. Four cycles of chemotherapy were repeated every 4 weeks. Split-course thoracic radiotherapy of 2 Gy/day commenced on day 2 of each chemotherapy cycle, with 26 and 24 Gy administered in the first and second cycles, respectively.
Results: Thirty-five patients were eligible and 34 patients were assessable for response, toxicity and survival. Patients' characteristics were as follows: male/female=29/5; PS 0/1=18/16; median age(range)=67(50-73); stage IB/IIA/IIB/IIIA/IIIB=2/2/3/16/11. The overall response was 100% (CR 7, PR 27). Grade 4 leukopenia, neutropenia, grade 3-5 pneumonitis, diarrhea and esophagitis occurred in 22%, 39%, 6%, 3%, and 0%, respectively. There were 2 treatment-related deaths from pneumonitis. The median overall survival time, and the 2- and 5-year survival rates were 28.9 months, 58.6% and 34.4%, respectively.
Conclusion: Irinotecan and cisplatin with concurrent split-course thoracic radiotherapy was effective in untreated limited-disease small cell lung cancer.

Keywords: irinotecan, chemoradiotherapy, Clinical trial, Small-cell lung cancer

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P3.261 EXTENSIVE STAGE SMALL CELL LUNG CANCER: METASTATIC PRESENTATION, PROGRESSION, AND IMPLICATIONS FOR OLIGOMETASTATIC TREATMENT

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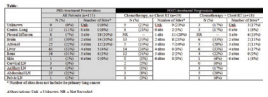
Background: Treatment of oligometastatic cancer with definitive radiation therapy (RT) is emerging as an option for patients once considered incurable. Extensive Stage Small Cell Lung Cancer (ES-SCLC) is considered a widely metastatic cancer, however its sites of metastatic presentation and progression are not well characterized. The purpose of this study is to explore if ES-SCLC is appropriate for this paradigm.
Methods: From 2003-2010, 115 pts with ES-SCLC were treated at 2 hospitals affiliated with the Medical College of Wisconsin. The median age was 68 yrs (range 47-87) and 82% were male. Only 57 pts received 2 or more cycles of chemotherapy and had a median follow-up 8.5 months (range 2.3-43.8). Of these, 39 pts were treated with primary chemotherapy (+/- palliative RT) and 18 pts received chemotherapy + consolidative chest RT (median 45 Gy, range 34-62). In these two cohorts, prophylactic cranial irradiation (PCI) was administered in 1 and 7 pts, respectively.
Results: At initial presentation, the most common sites of metastases were to the liver (53%), bone (31%), and brain (30%); 90% were limited to 1-3 sites [Table]. For pts treated with primary chemotherapy, metastatic progression was most common in the liver (36%), brain (33%), and bone (31%); 72% progressed in 1-3 sites. For patients treated with chemotherapy + consolidative chest RT, metastatic progression was most common in the liver (33%), brain (33%), and adrenal glands (28%); 61% progressed in 1-3 sites. Patients with consolidative chest RT had improved 1 yr chest failure free survival (FFS) (17% vs. 5%, p=0.0132) and overall survival (OS) (33% vs. 21%, p=0.0459) over those who did not. Patients with PCI (n=8) or whole brain RT for metastases (n=2) had improved 1 yr brain metastasis FFS (60% vs. 13%, p=0.0003) and OS (60% vs. 18%, p=0.0013) over those with no cranial RT.



Conclusion: In our series, 90% of ES-SCLC pts present with disease confined to 1-3 metastatic sites. Even after primary chemotherapy or chemotherapy + consolidative chest RT, the majority of failures continued to be limited to 1-3 sites. Local RT to both the chest and brain improved site specific FFS and OS, thus local treatment to limited metastatic sites may similarly improve survival. This is currently being tested in RTOG 0937.
Keywords: Oligometastasis, Patterns of failure, Radiation Therapy, Small cell lung cancer

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P3.262 PHASE I/IIA STUDY OF CHEMOTHERAPY WITH BENDAMUSTINE AND IRINOTECAN (BI) FOLLOWED BY ETOPOSIDE/CARBOPLATIN (EC) IN UNTREATED PATIENTS (PTS) WITH EXTENSIVE SMALL CELL LUNG CANCER (E-SCLC)

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Background: The results of first-line therapy (EC) for E-SCLC remain poor with progression-free survival and overall survival of approximately 4 months and 9 months, respectively. The goal of this study is to evaluate the safety and early efficacy of a novel combination of BI followed by EC. Bendamustine, an alkylating agent with a purine-like benzimidazole ring, and irinotecan have single-agent

activity in SCLC with a tolerable safety profile.
Methods: This is an ongoing phase I/IIa study in untreated pts with E-SCLC with performance status of 0-2 and adequate organ function. Three dose levels (DL) of B (80 mg/m^2, 100 mg/m^2, 120 mg/m^2 - days 1, 2) in combination with I (150 mg/m^2 - day 1) every 3 weeks [Regimen A] for 3 cycles, followed by 3 cycles of E (100 mg/m^2 - day 1-3), and C (AUC 6, day1) [Regimen B] are evaluated in the phase I portion of this study. Dose limiting toxicity (DLT) and maximum tolerable dose (MTD) of Regimen A are evaluated in cycle 1 in 3-6 pts in each dose level. Toxicity (CTCAE) is evaluated with CBC (weekly) and chemistry (every 3 weeks), and response (RECIST) with imaging studies at the end of Regimen A and B. Exploratory correlations of tumor expression of ERCC1 and topoisomerases with efficacy parameters are evaluated
Results: Fourteen pts (DL 1-3, DL 2-6, and DL 3-5) have been enrolled in the phase I portion of the study. Baseline characteristics include: median age, 65 years; male, 69%; increased LDH, 54%; low albumin, 31%; and 1 pt with brain metastases. There was 1 DLT in DL2) grade [gr] 3 diarrhea) and 1 DLT in DL3 (gr 3 nausea/vomiting/diarrhea). Worst toxicities during each regimen included: Regimen A - 3/14 gr 3 diarrhea; 2/14 gr 3 nausea/vomiting; and 5/14 gr 3-4 neutropenia. Regimen B - 1/13 gr 3 anemia; 1/13 gr 3 neutropenia; and 1/13 gr 4 thrombocytopenia. Dose reduction was required in 2 and 3 pts in Regimen A and B, respectively. The objective response after Regimen A was 67% (PR-8) with 2 pts with progressive disease and 2 pts too early for evaluation.
Conclusion: Bendamustine/Irinotecan combination chemotherapy appears to be a generally well tolerated and active regimen in E-SCLC; and assessment of DL-3 (B - 120 mg/m^2) is ongoing for MTD and phase II dose recommendation.
Keywords: Extensive small cell lung cancer, Bendamustine-based chemotherapy, Phase I/II clinical trial

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P3.263 A STEREOTACTIC BODY RADIOTHERAPY-BASED TREATMENT MODEL FOR STAGE I MEDICALLY INOPERABLE SMALL CELL LUNG CANCER.

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Background: Purpose: Stage I Small Cell Lung Cancer (SCLC) is a rare disease presentation which generally includes resection for primary tumor management. We now wish to report on outcomes for a series of medically inoperable early stage SCLC patients for whom Stereotactic Body Radiotherapy (SBRT) was employed to manage the primary.
Methods: Review of the Cleveland Clinic IRB-approved SBRT registry revealed 6 cases of stage I SCLC out of 430 patients treated over the period 2004-2010. All patients had biopsy proven disease and had been deemed medically inoperable by a thoracic surgeon. Staging consisted of PET/ CT and MRI brain scans. The treatment model consisted of SBRT to the primary tumor followed by platinum/etoposide chemotherapy (CHT) and then prophylactic cranial irradiation (PCI). SBRT was delivered employing a Novalis/BrainLAB platform and Exactrac for image-guidance.
Results: Patient characteristics revealed: median KPS was 80 (range 50-90), median age was 68 years (range 57-73), 66.7% of patients were female, median BMI was 27.55 (range 20.1-31.9), 17% of were smoking at treatment, and impaired pulmonary function was the reason for inoperability in 50% of cases. Tumor characteristics revealed: median tumor size was 2.6 cm (range 1.4-3.6), with 4 T1a and 2 T1b cases, 1 (17%) tumor was “central” (per RTOG 0236 criteria), median PET-SUVmax was 9 (range 2.8-21.1). One patient had a mediastinoscopy, one had CHT before SBRT, one died after SBRT of a brain aneurysm and never received CHT or PCI and was one of 2 patients who died before receiving PCI. SBRT was 60 Gy/3 fractions (50%), 50 Gy/5 fractions (33%), 30 Gy/1 fraction (17%). Median follow up was 11.9 months. There was no grade 3 or higher toxicity and only one grade 2 toxicity (chest wall). Three patients were alive at analysis and 3 had died of non-cancer causes, although one did have distant disease. At one year, local control was 100%, there was no regional nodal failure and one (17%) distant failure (liver). Overall and disease-free survival at 1 year were 63% and 75%, respectively.
Conclusion: 1. SBRT for stage I medically inoperable SCLC is feasible, with excellent local control. 2. Disease-specific survival is encouraging. 3. The absence of regional nodal failure lends support to PET for mediastinal staging. 4. Platinum-

based CHT is feasible in this vulnerable population.
Keywords: Small cell lung cancer, Stage I, stereotactic body radiotherapy, outcomes

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P3.264 RETROSPECITIVE ANALYSIS OF THE TREATMENT FOR RELAPSED SMALL-CELL LUNG CANCER IN A UNIVERSITY-AFFILIATED HOSPITAL IN JAPAN.

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Background: The limited impact of survival benefit of topotecan (TPT) monotherapy for patients with relapsed small-cell lung cancer (SCLC) warrants the need for more effective treatments. Amrubicin (AMR) was approved by Japanese Ministry of Health, Labor and Welfare for patients with SCLC in 2002 and several clinical trials of AMR have been conducted, demonstrating promising efficacy. The objective of this study was to describe the clinical outcome of second-, third-, and fourth-line chemotherapy for the treatment of relapsed SCLC.
Methods: We retrospectively evaluated consecutive patients with relapsed SCLC who received first-line chemotherapy between January 2003 and December 2009 at our institution.
Results: Seventy-nine patients were evaluable. Patient characteristics were as follows: median age; 66 years (range 45-86), male/female; 60/19 (cases), ECOG performance status 0/1/2/3; 9/54/12/4 (cases), limited disease/extensive disease; 27/52 (cases), sensitive relapse/refractory relapse; 33/46 (cases). Overall, 61(77%), 43(54%), and 27(34%) of the patients with relapsed SCLC received second-line to fourth-line chemotherapy, respectively. The mean number of chemotherapy regimens was 2.8±1.3. Patients with sensitive relapse received more chemotherapy regimens than those with refractory relapse (3.5±1.1 vs. 2.3±1.3, p<.0001). For all relapsed patients, the median survival times (95% confidence interval) from the start of first-line, second-line, third-line, and fourth-line chemotherapy were 18.9 (14.8 – 22.9), 11.3 (8.7 – 15.7), 9.2 (4.8 – 11.7), and 7.0 (3.1 – 8.7) months, respectively. Platinum-based chemotherapy was conducted for all patients as the first-line treatment. Among the several agents, AMR were the most used regimens for second- and third-line chemotherapy (44% and 51%, respectively) and the second most used regimen for the fourth-line.
Conclusion: A substantial proportion of relapsed SCLC patients received second- to fourth-line chemotherapy including AMR in a university-affiliated hospital in Japan.
Keywords: Small-cell lung cancer, amrubicin, second-line chemotherapy, third-line chemotherapy

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P3.265 A PHASE I STUDY OF EVEROLIMUS PLUS PACLITAXEL IN PATIENTS WITH SMALL CELL LUNG CANCER

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Background: Paclitaxel (P) was proved to have clinical effects in small cell lung cancer (SCLC). Everolimus (E) has previously shown preclinical activity in SCLC cell lines but has limited single-agent antitumor activity in patients with pretreated SCLC. The synergism between P and E was suggested in a preclinical study. We conducted a phase 1, dose-escalation study of E in combination with P in patients with SCLC who failed standard chemotherapy.
Methods: Eligibility included SCLC with disease progression after at least 2 prior chemotherapy regimens, ECOG performance status (PS) 0-2, and adequate organ function. We excluded patients with poorly controlled diabetes mellitus (fasting blood glucose > 165 mg/dl) or hypercholesterolemia (grade 3 or 4). In this phase Ib using classic 3+3 dose escalation study, patients were treated with E 2.5mg/d (level 1), 5mg/d (level 2), or 10mg/d (level 3) in combination with P (175mg/m^2 every 3 weeks). Tumor measurements performed every 2 cycles or at the appropriate time.
Results: Fifteen pts were enrolled: 13 males/2 females; median age 60 years (44-72); PS 1/2: 10/5 pts; sensitive/refractory relapse (sensitive relapse: > 60 days from completion of second-line chemotherapy): 6 pts/9 pts. Four pts experienced end-of-cycle 1 dose-limiting toxicities (DLTs). After identifying no end-of-cycle 1 DTL in the first 6 pts at the levels of 1 and 2, three pts were further treated

at the level of 3 where two pts experienced end-of-cycle 1 DLTs (one febrile neutropenia and one grade 3 hyperglycemia). Two end-of-cycle 1 DLTs were also detected among three additional pts at the level of 2 (one grade 4 thrombocytopenia and one febrile neutropenia; 2 events among total 6 pts). We regarded level 1 (2.5mg/d) as the recommended dose after assuring there was no event in additional three pts at the level 1; no event among total 6 pts). On the basis of observed DLTs, 2.5mg/d was determined as the recommended dose for future trials. The common treatment-related toxicities (all grades) were anemia (n=13), neutropenia (n=12), hyperglycemia (n=12), thrombocytopenia (n=9), hypercholesterolemia (n=7), peripheral neuropathy (n=7), and stomatitis (n=7). The median progression-free survival was 11.4 weeks (95% CI: 7.1-15.8 weeks). Among 13 pts who could be evaluated, objective response rate was 31% (4/13: one at the each levels of 1 and 2, and two at the level of 3).

	Dosage by Grade						All (n=15)
	2.5mg Daily (n=6)		5mg Daily (n=6)		10mg Daily (n=3)		
Adverse Event	1/2	3/4	1/2	3/4	1/2	3/4	Any Grade
<Hematologic disorder>							
Anemia	5	0	5	0	3	0	13
neutropenia	3	1	0	5	1	2	12
Thrombocytopenia	2	0	3	1	2		

Conclusion: The combination of E with P has shown promising antitumor activity in pts with heavily pretreated SCLC and warrants further investigation.
Keywords: everolimus, paclitaxel, phase 1, Small cell lung cancer

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P3.266 COMPARATIVE ANALYSIS IN PATIENTS WITH SMALL-CELL LUNG CANCER (SCLC) DETECTED BY CHEST COMPUTED TOMOGRAPHY (CT) AND X-RAY MASS-SCREENINGS

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Background: Recently, a randomized clinical trial revealed 20 percent fewer lung cancer deaths seen among those who were screened with chest CT than with chest X-ray. Patients with small-cell lung cancer (SCLC) usually presents more rapid progress than non-small cell lung cancer (NSCLC) and are found from some symptoms, but rarely detected by such chest CT and X-ray mass-screenings.
Methods: We retrospectively analyzed the clinical courses of SCLC patients found from chest CT and X-ray mass-screenings 1998 to 2010, and compared them.
Results: We found 8 SCLC patients from CT screenings (clinical stage IA, 3 (37.5%) patients; IB, 1 (12.5%) patient; 2 (25.0%) patients; B, 1 (12.5%) patient; 1 (12.5%) patient) and 14 patients from X-ray screenings (clinical stage B, 3 (21.4%) patients; A, 6 (42.9%) patients; B, 4 (28.5%) patients; 1 (7.1%) patient) during 1998 and 2006. Surgical resections were performed 6 (75.0%) patients in CT group and 1 (7.1%) patient in X-ray group. There were no significant difference in the survival of CT group and that of X-ray group.
Conclusion: Chest CT mass-screenings detected earlier stage SCLC and could lead more patients to surgical resections than chest X-ray mass-screenings, but survival of CT screening group were not different from that of X-ray screening group in this study.
Keywords: Small-cell lung cancer, chest CT mass-screening

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P3.267 PROGNOSTIC FACTORS IN SET OF LIMITED DISEASE SMALL-CELL LUNG CANCER PATIENTS TREATED WITH CHEMORADIOTHERAPY

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Background: Combined chemoradiotherapy is the standard treatment for patients with limited disease small cell lung cancer (LD SCLC). Prophylactic cranial irradiation (PCI) is recommended in case of complete remission (CR) since late 90´ and for partial remissions last few years. Early concurrent radiation (RT) has been found as slightly beneficial at cost of higher toxicity. Use of granulocyte colony-stimulating factor (G-CSF) for prophylaxis of febrile neutropenia is controversial in SCLC. We

analyzed patients and treatment related variables for prognostic significance in long term follow-up of regional treatment protocol since 2000 in VFN, University Hospital Prague.
Methods: The planned treatment consisted of 4 to 6 courses of platinum/etoposide chemotherapy (CT) and thoracic irradiation of 45 to 66 grays with one daily fraction. Patients with CR or later with PR were assigned to PCI (30Gy in 15 fractions) at the end of treatment. Sequential strategy was preferred due to age over 70 or worse performance status. In some patients G-CSF prophylaxis was used. Influence of factors as sex, age, timing and dose of RT, dose and regimen of CT, G-CSF delivery, treatment response and PCI yes or not, were tested for survival impact.
Results: Eighty consecutive patients were treated between Jan-2000 and Sep-2010, 49 men, 31 women, median age 62 years (range 49 – 80). CT in median dose of 5 cycles was predominantly cisplatin based, RT in median dose of 57.6 Gy was given concurrently in 56% and sequentially in 33% of patients. Thoracic RT was omitted in 9 patients, for poor performance status or progressive disease in 6 and due to radical surgery in 3 subjects. Esophagitis grade 3-4 occurred in 42%, significantly more often in concurrent RT (60% vs. 19%, $p< 0.01$). Response rate (RR) 90% and CR 62% in concurrent group did not differ significantly from sequential one (RR 88%, CR 52%). The median survival was 19.5 months and 3- and 5-year survival was 27% in all the patients. Survival differences in groups according to sex, age, stage, carbo or cisplatin and partial versus complete treatment response did not differ significantly. Significantly longer survival was observed in groups with PCI, with concurrent radiation or in patients treated with G-CSFs. Median time to progression was 14 months for the whole group. Significantly longer time to progression was in CR patients, concurrent RT, PCI patients and G-CSF delivery.
Conclusion: Concurrent early chemoradiotherapy, PCI delivery and G-CSF treatment have shown significant impact on time to progression and overall survival in our group of LD SCLC patients.
Keywords: Small cell lung cancer, limited disease, chemoradiotherapy, prognostic factors

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P3.268 WEEKLY SEQUENTIAL DOXORUBICIN, CYCLOPHOSPHAMIDE, CARBOPLATIN, VINCRISTIN AND ETOPOSIDE (ACOCEV) FOR ELDERLY/ POOR PERFORMANCE STATUS (PS) SMALL CELL LUNG CANCER (SCLC) PATIENTS (PTS): AN OBSERVATIONAL STUDY

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Background: SCLC is characterized by rapid kinetics, early metastatic involvement and frequent development of drug resistance. A dose-intense (i.e.weekly) sequential use of active drugs with non-overlapping toxicities, may play a role for a better disease control owing to a non cross-resistent mechanism of action in elderly or poor PS pts.
Methods: Sequential ACOCEV (Doxorubicin 30 mg/m2, Cyclophosphamide 400 mg/m2 on day 1 of every first week, Vincristin 1,4 mg/m2 on day 1 of every second and fourth week, Carboplatin AUC 4 and VP16 60 mg/m2 on day 1 of every third week, every 28 days for 3 to 4 cycles) were administered to 24 pts enrolled from March 2005 to July 2010; median age was 71.5 years (range 54-84). To determine the toxicity and the response rate of the treatment we evaluated patients who completed almost 2 cycles of chemotherapy (18 patients). 11 patients (61%) had a PS (ECOG) 2 and 4 patients had a PS 3; 15 patients (84%) had Extensive Disease (ED) at diagnosis and 6 patients (33,3%) were previously pretreated.
Results: We observed a 72% overall response rate (only partial response). Stable disease (SD) was observed in one patient, progression of disease (PD) in 4 patients (22%). Median time to progression (TTP) was 5,5 months. Hematologic toxicity includes 22% G3-G4 neutropenia without neutropenic febrile episodes and 5% G3-G4 piastrinopenia. We observed moreover 22% G2 neurotoxicities (paresthesia); 2 and 3 patients presented constipation and alopecia respectively.
Conclusion: ACOCEV has comparable efficacy to conventional chemotherapy schedules with a more

favourable toxicity profile and significant clinical benefit; also it is feasible in patients with a poor PS or elderly. Further investigations on a larger patient population are needed.

Keywords: SCLC, weekly chemotherapy

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P3.269 CORRELATION OF DOSIMETRIC FACTORS IN THE DEVELOPMENT OF ESOPHAGITIS AND RADIATION PNEUMONITS IN PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CARCINOMA

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Background: Esophagitis and radiation pneumonitis (RP) are significant sources of morbidity and mortality in patients receiving curative intent chemo-radiotherapy for limited stage small cell lung carcinoma (LS-SCLC). The purpose of this study was to correlate dosimetric factors with the development of esophagitis and RP in patients with LS-SCLC.

Methods: Between December 2004 and July 2009 93 patients were treated with curative intent chemo-radiotherapy for LS-SCLC and had electronically archived radiation treatment plans available for analysis. All patients were CT simulated and planned in Pinnacle treatment planning system with doses corrected for tissue heterogeneity. The medical charts were reviewed retrospectively to determine demographic information, chemotherapy details, toxicity (graded per CTCAE v3.0) and vital status. Each patient's original treatment plan was reviewed, dose delivered confirmed and critical structure delineation reviewed/corrected for lungs, heart and esophagus. Treatment planning data were exported from the treatment planning system and analyzed using CERR (Computational Environment for Radiotherapy Research). Overall survival (OS) was determined using the Kaplan-Meier Method. Patients lost to follow-up were censored. The cumulative incidence of RP and esophagitis were calculated and compared using Gray's test. Dosimetric parameters were correlated to the risk of toxicity using Spearman's rank correlation (rs) and logistic regression.

Results: Of the 93 patients 56 (60%) were male and the median age was 67 years (range 45 to 83). The median follow-up time was 19 months (range 2 to 104). Seventy patients (75%) received 40Gy in 15 fractions and 23 patients (25%) received 45Gy in 30 fractions BiD. Seventy-six patients (82%) received concurrent chemotherapy of which 66 (87%) received early (cycle 1-3) concurrent chemotherapy. Sixty (65%) patients were former smokers and 33 (35%) patients were current smokers. The median survival was 22 months. Nine patients developed RP: 5 G2, 1 G3 and 3 G5 events. The median time from radiation to the first incidence of G3+ RP was 5 months (range 2 to 8 months). The cumulative incidence rate of RP was 8% at 1 year for the 40/15 group and 18% at 1 year for the 45/30 group (p=0.15) . Fifty-eight patients developed esophagitis: 49 G2 and 9 G3 events. The median time from radiation to the first incidence of G3 esophagitis was 21 days (range 1 day to 1.5 months). The cumulative incidence rate of G3 esophagitis was 9% at 3 months for the 40/15 group and 13% at 3 months for the 45/30 group (p=0.52). G3+ pneumonitis was correlated with V20 (rs = 0.19, p = 0.03) and mean lung dose (rs = 0.19, p = 0.03). G3+ esophagitis was correlated with mean esophagus dose (rs = 0.22, p = 0.02).

Conclusion: Toxicity was not significantly different in patients who received 40/15 or 45/30. Mean dose and V20 were correlated with radiation pneumonitis and mean dose was correlated with esophagitis in our population.

Keywords: small cell, pneumonitis, esophagitis

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P3.270 NGR-HTNF PLUS DOXORUBICIN IN RELAPSED SMALL CELL LUNG CANCER (SCLC)

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Background: NGR-hTNF consists of human tumor necrosis factor fused with the peptide NGR, which specifically binds to a CD13 overexpressed on tumor blood vessels. Preclinically, NGR-hTNF is able to improve the intratumoral doxorubicin uptake by selectively damaging tumor vasculature and decreasing tumor interstitial fluid pressure. A phase I trial previously selected NGR-hTNF 0.8 μg/m^2 plus doxorubicin 75 mg/m^2 for further phase II testing.
Methods: SCLC patients relapsing after a platinum-based regimen received every 3 weeks NGR-hTNF until progression (PD), while the maximum lifetime dose of doxorubicin was capped at 550 mg/m^2. Progression-free survival (PFS) was the primary study aim. The trial had two-stage design with 16 and a total of 27 patients to be accrued.
Results: Twenty-eight patients with a median age of 63 years (range 41-76) were recruited. Baseline characteristics were: men/women 19/9; PS 0/1-2 13/15; brain metastases (yes/no) 9/21. The baseline serum neutrophil-to-lymphocyte ratio (NLR), an index of the systemic host immune response to tumor, was lower or higher the median value of 4 in 18 and 10 patients, respectively. Prior treatment lines ranged from 1 to 3 (median 1) and eight patients (29%) were pretreated with two or more regimens. The median treatment-free interval from last chemotherapy line was 2.8 months (95% CI, 1.0-3.9). (57%) presented with platinum-refractory or resistant disease (platinum-R; PD ≤ 3 months) and 12 patients (43%) with platinum sensitive disease (platinum-S; PD > 3 months). A total of 114 cycles were delivered (median 3; range 1-10) and 7 platinum-R patients (44%) and 6 platinum-S patients (50%) received ≥ 4 cycles. NGR-hTNF did not increase doxorubicin-related toxicity. No grade 3 to 4 toxicities related to NGR-hTNF were noted, while common grade 1 to 2 related events were transient chills (61%). Six patients had partial response (PR; 22%) and nine stable diseases (SD; 33%), yielding an overall disease control rate of 55% (95% CI 35-74). The median PFS was 3.2 months (95% CI 2.6-3.8). The patients who achieved PR had a median PFS of 6.3 months, and those with SD had a median PFS of 4.1 months. With median follow-up time of 19.3 months, the 6-month and 1-year overall survival (OS) rates were 49% and 34%, respectively. By subset analyses, response rates were 19% and 27% (p=0.66), median PFS were 2.7 and 4.1 months (p=0.07), and 1-year OS rates were 27% and 42% (p=0.81) in platinum-R and platinum-S patients, respectively. Median PFS and 1-year OS were 3.3 months and 27% in patients with brain metastases, and 4.1 months and 44% in patients pretreated with 2 or more regimens, respectively. By Cox analyses, either PFS or OS did not correlate with age, gender, PS and platinum sensitivity, while only NLR resulted associated with OS (HR=0.30). The 1-year OS rates in patients with NLR lower or higher than the median value were 48% and 10%, respectively (p=0.01).
Conclusion: Further development of NGR-hTNF plus doxorubicin in platinum resistant or sensitive SCLC is of interest.
Keywords: NGR-hTNF, SCLC, Doxorubicin

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.271 THE SEROLOGICAL FEATURES OF HIGH-GRADE NON-SMALL CELL NEUROENDOCRINE CARCINOMA

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Background: Pro-gastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) are specific neuroendocrineserological markers of small cell lung cancer (SCLC), the carcinoembryonic antigen (CEA) is not as specific marker for SCLC. Some of non-small cell lung cancer (NSCLC) raises serum neuroendocrine markers
level. The aim of this study is to assess the feature of serological markers between with SCLC and high-grade non-small cell neuroendocrine carcinoma (HNSCNEC) proposed by us, which likely includes most pulmonary large cell neuroendocrine carcinoma (LCNEC) except for combined types.
Methods: Newly diagnosed patients with SCLC and HNSCNEC at our institution between September 2002 and June 2010, we retrospectively reviewed 163 patients with SCLC and 35 patients with unresectable HNSCNEC, which was defined using biopsy specimens.
Results: Sixty-three (38.6%) pts had limited stage disease (LD) and 100 (61.3%) pts had extensive stage

disease (ED) in SCLC. The serum ProGRP levels were elevated (>46 pg/ml) in 130 SCLC patients(81.2%, median levels: 407pg/ml) and in 14 HNSCNEC patients (40.0%, median levels: 27.4pg/ml) (p<0.0001), NSE levels were elevated(>10ng/ml) in 145 SCLC patients (90%, median levels: 32ng/ml) and in 29 HNSCNEC patients (82.8%, median levels: 25.0ng/ml) (p=0.09), CEA levels were elevated(>5nf/ml) in 85 SCLC patients (54%, median levels: 5.7ng/ml) and in 24 HNSCNEC patients (68.5%, median levels: 12.3ng/ml) (p=0.01),respectively. Comparing the area under curve (AUC) of receiver operating characteristics (ROC) analysis of the ratio of ProGRP to CEA (AUC: 0.80) with that of NSE to CEA (AUC: 0.66), the ratio of ProGRP to CEA wasa favorable ratio to distinguish between SCLC and HNSCNEC.
Conclusion: In this series, significantly low serum ProGRP levels and high serum CEA levels compared with SCLC patients
represent clinical features of serological marker in HNSCNEC, while NSE is high positive rate in both SCLC and HNSCNEC.
Keywords: Small-cell lung cancer, Neuroendocrine, tumor marker, Non small-cell lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.272 A RANDOMIZED PHASE II STUDY OF CARBOPLATIN AND ABRAXANE WITH TWO DIFFERENT SCHEDULES, IN PATIENTS WITH EXTENSIVE STAGE SMALL CELL LUNG CANCER (ES-SCLC)

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Background: In the United States, standard cisplatin and etoposide chemotherapy for SCLC has remained unchanged since the 1980s. It is hypothesized that abraxane, the nanoparticle albumin-bound formulation of paclitaxel with superior toxicity and efficacy profile compared with standard paclitaxel, given weekly or every 3 weeks together with carboplatin may provide improved toxicity with acceptable efficacy. The primary objective was overall response rate; secondary objectives included progression free survival (PFS), overall survival (OS) and assess the toxicity profile.
Methods: Patients with ES-SCLC, ECOG PS 0-2, and no prior chemotherapy were randomized in a 1:1 ratio to Arm A (carboplatin AUC=6 IV on day 1, abraxane 300mg/m^2 IV day 1; q21 days) or Arm B (carboplatin AUC=6 IV on day 1, abraxane 100 mg/m^2 IV days 1, 8, 15; q21 days) for 4-6 cycles. Response was assessed every 2 cycles.
Results: Baseline characteristics were similar between arms. Exposure to chemotherapy in each arm was similar. Due to excessive toxicities and dose delays, an unplanned interim analysis was performed after the first 10 patients in each arm; abraxane doses were reduced to 240mg/m^2 and 80 mg/m^2 respectively for Arms A and B. Median follow-up times are 18.6 and 16.1 months, respectively. Results are reported in the table by Arm for all evaluable patients. Four patients were evaluable for toxicity (3 in arm A; 2 in arm B) but died during treatment. Response rate is reported by intention to treat. Table: Results by arm

		Cbp+Abraxane (q3wks) Arm A (N=14)	Cbp+Abraxane (weekly) Arm B (N=13)
BASELINE DEMOGRAPHICS			
	Gender (male)	10	8
	Race (Caucasian)	13	11
	ECOG PS		
	0	5	2
	1	8	11
	2	1	0
	Age, median (range)	60 (45-80)	67 (52-72)
EFFICACY			
	Partial Response	11 (79%)	11 (85%)
	Median PFS, (mo)	5.8	5.2
	Median Survival (mo)	8.6	11.6
	Overall Survival (1 year)	36%	42%
SAFETY (All ≥ Grade 3/4)			
	Neutrophils	8 (57%)	5 (38%)
	Hemoglobin	4 (29%)	4 (31%)
	Platelets	3 (21%)	3 (23%)
	Neuropathy:sensory	3 (21%)	0
	Pain	4 (29%)	0
	Fatigue	0	1 (8%)
	Nausea	0	3 (23%)
	Vomiting	0	2(15%)
	Diarrhe	1 (7%)	(8%)

Conclusion: Carboplatin and abraxane (given weekly or every 3 weeks) appear to have activity with encouraging RR in both arms; Arm B appears somewhat better tolerated. The majority of toxicities are hematologic in both arms.
Keywords: Small cell lung cancer, Abraxane, Carboplatin, Chemotherapy

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P3.273 HOW DOES INFLUENCE CHANGES IN STANDARD TREATMENT IN OUTCOME RESULTS FOR LIMITED STAGE SMALL-CELL LUNG CANCER PATIENTS IN A RADIATION ONCOLOGY DEPARTMENT?

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Background: The purpose of this study is to evaluate the treatment outcome of standard chemoradiotherapy (CTRT) for patients with limited stage small cell-lung cancer in the daily clinical practice. Secondarily, we analyze the effect in survival produced by the evolution of the treatment in the last years.
Methods: We review the treatment in our Radiation Oncology Department, for patients diagnosed of limited stage small-cell lung cancer. At the beginning, patients were submitted after induction chemotherapy and received sequential radiotherapy. Since 2001 concurrent CTRT was administered to nearly all patients and radiotherapy volumes were significantly reduced to the visible lesions by CT and affected regional lymphatic areas. Finally, logistics permitted in 2006 the systematic use of hyperfractionated radiotherapy. Two hundred and sixty-six patients (236 males and 30 females) were treated between May 1994 and December 2010. The mean age was 62.97 years (range 36-85). All patients except 5 received chemotherapy. At least one cycle of previous chemotherapy was administered to 257 patients but only 141 patients received concomitant CTRT. Conventional daily radiotherapy was used in 211 patients at 1.8-2 Gy per fraction and mean total dose of 46.49 Gy (range 16-66). Fifty-five patients were treated with hyperfractionated radiotherapy, 45 Gy in 30 fractions of 1.5 Gy BID (mean total dose of 44.64 Gy, range 36-45). Prophylactic cranial irradiation was performed in 146 patients, at a mean total dose of 31.47 Gy (range 4-40) in daily fractions of 1.8-2.5 Gy. One patient rejected the treatment after the second fraction and was analyzed as intention-to-treat.
Results: Overall survival (OS) is 23.4% at 5 years and median overall survival is 20.7 months. Three-year OS for patients receiving hyperfractionated radiotherapy and conventional daily radiotherapy were 45.6% and 30.1%, with median survival of 33.4 and 19.7 months, respectively (NS). We have found a clear benefit (p=0.03) for patients receiving prophylactic cranial irradiation, with median OS of 24.5 months, while those who were not treated obtain a median OS of 18.4 months. Patients receiving systemic concurrent chemotherapy achieve a median OS of 26.9 months and a 5-year OS of 28.9% while patients with sequential treatment have a median OS of 18.1 months and a 5-year OS of 16.8% (p=0.007).
Conclusion: Our results confirm that survival in limited stage small-cell lung cancer is significantly improved by concurrent CTRT and prophylactic cranial irradiation. Nowadays, is early for us to demonstrate the benefit of the use of hyperfractionated radiotherapy that still have not obtained better results than conventional treatment.
Keywords: prophylactic cranial irradiation, concurrent chemoradiotherapy, Limited stage small-cell lung cancer, Hyperfractionated radiotherapy

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P3.274 SURVIVAL OUTCOMES OF SMALL CELL LUNG CANCER PATIENTS (SCLC) TREATED WITH CISPLATIN-ETOPOSIDE (EP) VS. CARBOPLATIN-ETOPOSIDE (EC) IN BRITISH COLUMBIA (BC)

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Background: Lung cancer is the leading cause of cancer deaths with SCLC representing approximately 13% of all cases. Although a previous randomized study did not demonstrate an advantage for EP over

EC, cisplatin-based therapy remains the standard in North America. The purpose of this study was to compare survival outcomes between EP and EC at a population level.
Methods: A retrospective review was performed that included all SCLC patients in the BC Cancer Agency database diagnosed from January 2006 to December 2008, and treated with EP or EC. All patients were categorized as having limited (LD) or extensive disease (ED) according to treatment intent. Demographic comparisons were made using Fisher's exact test for discrete variables and the Mann-Whitney non-parametric test for continuous variables. Overall Survival (OS) was determined from the date of diagnosis and survival curves were calculated using the Kaplan-Meier method. Median follow-up time was calculated using the reverse Kaplan-Meier estimator.
Results: 351 patients with SCLC were included in the review. Of the 168 with LD disease, 98 received EP and 70 received EC. For the 183 with ED disease, 99 received EP and 84 received EC. In both groups, EC patients were significantly older (median age 74 vs. 62 with LD and 71 vs. 61 with ED, $p<0.0001$). Median follow up was at least 21.4 months in all subgroups. There was no statistically significant difference in the median OS between the EP and EC subgroups with LD (21.5 vs. 22.1 months respectively, $p=0.633$) or ED (10.8 vs. 11.1 months respectively, $p=0.584$). The two year survival rates were also similar in both LD (EP-41%, EC-47%) and ED (EP-11%, EC-12%).
Conclusion: Despite the preferential use of EC in an older population, the median survival time and two-year survival rates were similar to patients treated with EP. We plan on examining local control rates of patients receiving EP vs. EC and the effects of concurrent thoracic radiation.
Keywords: survival, Small cell lung cancer, Cisplatin Etoposide, Carboplatin Etoposide

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.275 MULTIMODALITY TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: The aim of our research is to increase the efficiency of the treatment of malignant pleural mesothelioma.
Methods: Materials and **Methods:** the randomized research from 2006 to 2011 includes 22 patients with biopsy-proven and immunohistochemical confirmed malignant pleural mesothelioma.
The patients were randomized into two groups: 1) extrapleural pneumonectomy and 4 courses adjuvant chemotherapy (cysplatin 90 mg/m^2 in 1st day+vinorelbine 30 mg/m^2 in 1st and 8th days) – 11 patients: 2 women and 9 men from 38 to 65 years old (mean 53,5) (combined treatment); 2) intrapleural perfusion thermochemotherapy (ThermoChem HT-1000, regimen 42D¾C in an hour, cysplatin 120 mg/m^2 + vinorelbine 30 mg/m^2), extrapleural pneumonectomy and 4 courses adjuvant chemotherapy (cysplatin 90 mg/m^2 in 1st day+vinorelbine 30 mg/m^2 in 1st and 8th days) – 11 patients: 6 women and 5 men from 30 to 65 years old (mean 51,4) (multimodality treatment).
Results: The III stage of malignant pleural mesothelioma was diagnosed at all patients in the group of combined treatment. In the group of multimodality treatment there was only 1 patient with II stage of the disease and 9 with III stage. After intrapleural thermochemotherapy 2 patients (18%) had complications: 1 patient had pleural empyema and 1 patient – renal and hepatic failure, there was no cases of lethality. Postoperative complications were registered at 5 patients (45,5%) in the group of combined therapy: pleural empyema (n=2), heart rate failure (n=1), thromboembolism of pulmonary artery (n=1), intrapleural bleeding (n=1). Mortality was 18,2% in this group (n=2 – thromboembolism, bleeding). In the group of multimodality treatment complications after extrapleural pneumonectomy were observed at 3 patients (27%): intrapleural bleeding (n=1), heart failure (n=1), acute respiratory distress syndrome (n=1). Mortality was 18% in this group (n=2 – heart failure, acute respiratory distress syndrome). In the first group local recurrence was registered at 1 patient, at 4 patients were observed recurrence in peritoneum, 2 patients had distant metastasis. In the second group local recurrence was not registered, 4 patients had distant metastasis. 2-years survival is 12,5±11,7% in the group with combined treatment and 71,4±17,1% in the group with multimodality treatment (p=0,1).
Conclusion: Multimodality treatment does not increase the frequency of complications and the rate of mortality in comparison with the combined

therapy. Intrapleural perfusion thermochemotherapy increases the efficiency of the treatment of malignant pleural mesothelioma.

Keywords: Multimodality treatment, malignant pleural mesothelioma, intrapleural thermochemotherapy, Extrapleural pneumonectomy

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.276 RESPONSE EVALUATION AND PROGNOSIS WITH COMBINED 18F-FDG PET-CT SCAN IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) TREATED WITH PLATINUM AND PEMETREXED DOUBLET CHEMOTHERAPY.

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Background: Malignant pleural mesothelioma (MPM) represents a very aggressive and rare tumor where platinum-based chemotherapy may improve survival. Monitoring therapeutic evaluation represents a challenge in this setting. The aim of this study was to evaluate the impact of standard uptake value (SUV) max and SUVmean of [^{18}F]Fluorodeoxyglucose (FDG) measured by photon emission tomography (PET) integrated with Computed Tomography (CT) imaging in the assessment of chemotherapic response and the relationship with prognosis.

Methods: Patients with histologically proven MPM performed chemotherapy with platinum-based (Carboplatin or Cisplatin) regimen combined to Pemetrexed were eligible for this study. All patients were evaluated by PET/CT-scan at baseline and after three-four courses of chemotherapy: they fasted and received a 5,18 MBq FDG per kilogram of FDG dose. Whole-body emission studies were acquired, followed by whole-body transmission scans with iterative reconstruction. Metabolic response (MR) was evaluated according to EORTC-criteria [1], whereas radiological response (RR) from CT-scan was determined according to RECIST-modified criteria [2].

Results: From January 2004 to December 2010, 15 patients with a median age of 66 years (range: 54 – 77) and with biopsy proven MPM (14 epithelial, 1 biphasic) were assessable for metabolic and radiologic response with ^{18}F-FDG PET-CT scan. On average 3.5 courses (range: 3 – 4) of chemotherapy were administrated between the two exams. An average of 25 days (range 3 - 42) elapsed between ^{18}F-FDG PET/CT scan staging and the first course of chemotherapy and 26 days (range 6 - 48) elapsed from the last cycle of chemotherapy to the re-staging ^{18}F-FDG PET/CT scan. There were respectively one (6.7%) RR, 6 (40%) and 4 (26.7%) MR at the SUVmax and SUVmean analyses. As far as concordance between metabolic and radiological response is concerned, overlapping of the two evaluations was more frequent for the SUVmean (10/15, 67%) than for the SUVmax analysis (2/15, 13%). No advantage in survival was seen for patients with responsive disease over those with stable or progressive disease at SUVmax analysis (75%, 95% CI 33 - 100, vs. 37%, 95% CI 4 -71) and SUVmean analysis (50%, 95% CI 1 - 99, vs. 48%, 95% CI 11 - 85) or at the radiological evaluation (100% vs. 47%, 95% CI 17 - 78 all performed at 24 months).

Conclusion: In our experience MR expressed by SUVmax and SUVmean analysis and RR are not predictive for survival in patients with MPM treated with platinum and pemetrexed; this may be due to the limited number of patients analyzed.

References: 1. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 1999;35:1773-1782. 2. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004;15:257-260.

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Keyword: Pemetrexed doublet chemotherapy

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Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.277 FDG PET/CT RESPONSE EVALUATION IN MALIGNANT PLEURAL MESOTHELIOMA PATIENTS TREATED WITH TALC PLEURODESIS AND CHEMOTHERAPY

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Background: Talc pleurodesis (TP) is worldwide employed for the management of persistent pneumothorax or pleural effusion, particularly if malignant origin. In this setting, the concomitant presence of a procedure like TP and a disease such as malignant pleural mesothelioma (MPM), may interfere in metabolic assessment and in chemotherapeutic tumor response evaluation. The aim of this retrospective MPM case series was to report the concordance rate between radiologic and metabolic response, expressed by SUVmean and SUVmax, after TP and chemotherapy.
Methods: Patients with histologically proven MPM underwent to TP and following to integrated PET/CT-scan of staging and restaging after three-four courses of Pemetrexed-based chemotherapy. All patients fasted and received a 5,18 MBq FDG per kilogram of FDG dose. Whole-body emission studies were acquired, followed by whole-body transmission scans with iterative reconstruction.
Results: From January 2004 to March 2010, 8 patients with a median age of 65 years (range: 54 – 77) and with biopsy proven MPM (7 epithelial, 1 biphasic). Overall 5 (63%) MPM were located on the left side and 3 (37%) MPM on the right side with 7 (88%) patients at stage I and 1 (12%) patient at stage II disease. Three patients received Pemetrexed combined with Carboplatin, 4 patients Pemetrexed combined with Cisplatin and finally one patient Pemetrexed alone. The mean number of chemotherapic courses received before restaging was 3.5 (range: 3 - 4). On average there were 14 days (range: 9 – 22) and 125 days (range: 76 – 162) between TP and respectively staging and restaging PET/CT-scan. According to modified EORTC [1] and RECIST [2] criteria, after a median follow-up of 30 months (range: 7 – 44) there was a concordance between the radiologic and metabolic SUVmean and SUVmax responses in 6 (75%) and 3 (37.5%) patients, respectively.
Conclusion: In our series, MPM patients treated with TP and chemotherapy, metabolic response to chemotherapy expressed with SUVmean seems to be in better agreement with radiological response than the SUVmax, thereby SUVmean index may be helpful to distinguish sensitive or resistant disease to chemotherapy. References: 1. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 1999;35:1773-1782. 2. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol 2004;15:257-260.
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Keyword: talc pleurodesis

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Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.278 PHASE II STUDY OF CARBOPLATIN AND VINORELBINE 1ST LINE TREATMENT IN ADVANCED MALIGNANT PLEURAL MESOTHELIOMA

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Background: Platinum-based combination chemotherapy improve survival and quality of life in Malignant Pleural Mesothelioma (MPM). Vinorelbine (VNB) is also among the most active drugs. Thus, the combination of Carboplatin with VNB was explored.
Methods: Chemotherapy naïve inoperable MPM patients (pts) in performance status (PS) 0-2, normal

renal function, no major comorbidity, and no upper age limit received Carboplatin AUC 5 and VNB 25 mg/m2 i.v. day 1 and VNB 80mg/m2 p.o. day 8 q. 3 weeks for 4-6 courses. CT-scans were done initially and for every 2 courses. Modified recist criteria were used for response assessment. The study was approved by the National Health Authorities and the regional ethical committees. Pts gave written informed consent.
Results: Median age among 47 pts included was 66 years (range 42-79), there were 89% males, 59% had epithelial subtype while 11% and 30% had sarcomateous or biphasic subtypes, respectively. 55% had IMIG stage stage IV, and PS 1 and 2 occurred in 66% and 11%, respectively. Median no. of courses were 4 (range 1-6) and median time on treatment was 15 weeks. Toxicity was modest, only grade 4 toxicity encountered was leucopenia (8.5 % of pts). There were 3 episodes of febrile leucopenia (7%), no bleeding episodes and no toxic deaths. Dose reductions were done in 13 pts (39%). Partial remission occurred in 13 pts (28%) and Complete remission in one patient (2%). Medians of Progression Free Survival was 7.2 months (range 1.4-49.4+ months), Overall Survival was 14.6 months (range 1.4-57.1+ months), and 1- and 2-years survival rates 53% and 19%, respectively.
Conclusion: Carboplatin with VNB was safe among MPM pts including poor prognostic and frail pts in PS2, sarcomateous and biphasic subtypes, and age >70 years. The overall survival is among the longest reported for any chemotherapy regimen in MPM and the activity is comparable to that of other regimens combining platinum with drugs such as Pemetrexed, Raltitrexed, Gemcitabine, or Epirubicin in this patient population.
Keywords: mesothelioma, Chemotherapy, Vinorelbine, phase II trial

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.279 PROGNOSTIC VALUE OF STANDARD UPTAKE VALUE (SUV) OF 18F-FDG ASSESSED BY POSITRON EMISSION TOMOGRAPHY (PET) INTEGRATED WITH COMPUTED TOMOGRAPHY (CT) SCAN IN STAGING OF MALIGNANT PLEURAL MESOTHELIOMA (MPM).

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Background: Malignant pleural mesothelioma (MPM) is a rare and aggressive tumour with disappointed results in terms of survival. However this disease may have a variable clinical course, with occasional long-term survivors. Standard uptake value (SUV) of ^{18}F-Fluorodeoxyglucose ([^{18}F]FDG) evaluated by photon emission tomography (PET) is now widely accepted as an important prognostic indicator in several malignancies. The aim of this study is to verify if SUVmax and SUVmean is inversely correlated to prognosis and if there is a correlation between grading and stage disease with SUV value.
Methods: Patients with histologically proven MPM underwent integrated PET and computed tomography (CT) scanning. Patients fasted and received a 5,18 MBq [^{18}F]FDG per kilogram of weight. Studies were acquired from the upper thighs to the head, followed by CT transmission scan with iterative reconstruction. Receiver operating characteristics (ROC) curve analysis was used to calculate SUVmax and SUVmean value. On the basis of the maximal Chi-Square method, a SUVmax of 4.21 and a SUVmean of 2.78 were chosen as threshold to classify patients as good or poor prognosis. Survival probabilities for both SUV groups were estimated by the Kaplan-Meier method.
Results: From January 2004 to December 2010, 27 patients with a median age of 65 years (range: 54 – 77) and with biopsy proven MPM (23 epithelial, 4 biphasic) were analyzed. Histological exam revealed an epitheliod subtype in 23 (85%) patients and a biphasic subtype in 4 (15%) patients. Regarding the histological grading lesions, we recognized: well differentiated disease in five patients, moderately differentiated disease in thirteen patients, poorly differentiated disease in seven patients and finally very poor differentiated disease in two patients. The disease localization was left in 16 (59%) patients and right in 11 (41%) patients with: 15 (55%) stage I, 4 (15%) stage II and 8 (30%) stage III disease. The median follow-up was 23 months (range: 1 - 52), there is no difference in term of median survival

neither with high or low SUVmax [26 months (95% CI: 11 – not reach) versus 19 (95% CI: 12 – not reach); p=0.811] nor with high or low SUVmean [26 months (95% CI: 8 – not reach) versus 19 (95% CI: 11 – not reach); p=0.831]. High SUVmax (p=0.018) is statistically related to high stage disease whereas there is no correlation with high SUVmean (p=0.203). Regarding the relationship between high histological grade disease and SUVmax or SUVmean value, no statistical significant correlations were found (respectively: p=0.268 and p=0.083).
Conclusion: In our series there is correlation between high SUVmax value and high stage disease and only a trend in the correlation between high SUVmean value and high grade histological disease.
Supported by GIPO.
Keyword: malignant pleural mesothelioma

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Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.280 HISTONE DEACETYLASE ACTIVITY IN PERIPHERAL BLOOD OF PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA.

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Background: Histone deacetylase (HDAC) is currently the focus of new target for cancer therapy, because of its role in cell cycling, apoptosis and differentiation There is an increasing amount of preclinical data on the effectiveness of HDAC inhibition in mesothelioma cell lines and mouse xenograft models. One of issues in the treatment of malignant pleural mesothelioma (MPM) with HDAC inhibitor is to determine the most appropriate surrogate marker for predicting and monitoring the molecular effect of this agent.
Methods: We evaluated pre-treatment HDAC activity in the peripheral blood mononuclear cells (1×10^5) of patients with MPM (n=42) and healthy volunteers without asbestos exposure (n=25) using HDAC fluorometric assay.
Results: The level of HDAC activity in patients with MPM was significantly higher than that in normal subjects (p<0.01). The median HDAC activity in epithelioid subtype (n=29) was higher than that in non-epithelioid subtype (n=13), which was not statistically significant. MPM with early clinical stage (IMIG T1 stage, n=4) showed an increase in HDAC activity, and there was no significant difference among the IMIG clinical stages.
Conclusion: MPM patients had a markedly increased level of pretreatment HDAC activity in peripheral blood mononuclear cells. This finding suggests that HDAC activity can be surrogate marker in the treatment of MPM with HDAC inhibitor.
Keywords: surrogate marker, malignant pleural mesothelioma, histone deacetylase activity

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P3.281 TREATMENT AND PROGNOSIS OF RECURRENT THYMOMA

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Background: The treatment of recurrent thymoma and its result are not well known. This study was designed to evaluate the results of treatment and to analyze the prognosis of recurrent thymoma.
Methods: Between 1987 and 2009, Forty-one patients out of 305 patients who underwent resection for thymoma had recurrence. We reviewed these patients retrospectively.
Results: Median time to recurrence was 52 months (range, 6 to 234 months). Median follow up time after recurrence was 25 months (range, 2 to 134 months). 12 patients had local recurrence, 28 had regional recurrence, 10 had distant recurrence, and 7 had overlapped recurrence. 15 patients underwent re-resection for recurrent tumors. The mediastinal mass resections were in 2 cases, pleural or pericardial metastasectomes in 10, both mediastinal mass resection and pleural metastasectomy in 1, pulmonary metastasectomy in

1, and all mediastinal mass, pleural metastasectomy and pulmonary metastasectomy in 1. 13 patients underwent complete resection of the recurrent tumor and 2 incomplete resection. 11 patients received chemotherapy for recurrent thymoma and 5 chemoradiotherpy, 9 patients did not receive any treatment and one received other treatment. Overall five-year and 10-year survival rate after recurrence were 59.7% and 33.2%, respectively. Survival rate after initial thymoma resection was not different between patients without recurrence and patients who underwent re-resection for recurrent thymoma (five year survival, 90.7% vs 91.7%, p=0.618). Patients who did not underwent re-resection or underwent incomplete re-resection had poor survival compared to patients without recurrence (90.7% vs 77.7% p<0.0001). Survival after recurrence was significantly different between complete re-resection group and others(90.9% vs 44.7%, p=0.014). According to the pattern of recurrence, WHO histologic classification, Masaoka stage of initial thymoma and time to recurrence, survival difference after recurrence was not significant.

Conclusion: Patients who underwent complete re-resection for recurrent thymoma had comparable survival to patients without recurrence. In addition, patients who did not undergo complete re-resection had poor prognosis. Lifetime surveillance is essential to increase the chance of the complete re-resection of the recurrent thymoma.

Keywords: treatment, Prognosis, recurrent thymoma

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P3.282 THE IMPACT OF SURGERY AS PART OF MULTIMODAL TREATMENT APPROACHES IN MALIGNANT PLEURAL MESOTHELIOMA PATIENTS - A SINGLE CENTER EXPERIENCE

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Background: Malignant Pleural Mesothelioma (MPM) is a rare but aggressive disease. However with advances in neoadjuvant therapy, a higher number of patients become potential candidates for surgery. Aim of this study was to evaluate the impact of surgery alone or as part of multimodal therapy approaches on patients' outcome.

Methods: We performed a retrospective analysis of all consecutive MPM patients referred to our institution for surgical curative therapy from 01/1994 to 10/2010. Overall survival was the primary endpoint. Patients were also analyzed with regard to hospital and ICU stay.

Results: 66 patients were identified in our database with mean age 61 ± 9 years. (14 female, 52 male). Histopathology was epithelial, nonepithelial, and unclassified in 42, 20 and 4 patients, respectively. 13 patients were in stage I, 16 patients in stage II, 31 patients in stage III and 6 patients in stage IV. All patients underwent surgical treatment, either alone (n=28) or in multimodality treatment protocols (n=38). Among the multimodality treatment group, patients received additionally to surgery: neoadjuvant chemotherapy (n=28), adjuvant chemo- and radiotherapy (n=5), adjuvant radiotherapy (n=12), and adjuvant chemotherapy (n=11). Surgical treatment was extrapleural pneumonectomy in 58, pleurectomy/decortication in 5 and other surgical procedures in 3 cases. Mean overall survival of all patients was 447 ± 461 days (range: 8 to 2325 days, 30 days survival: 90%, 1 year survival 47%, 3 years survival 17%). Patients undergoing multimodal therapy had a significant (Log Rank: p= 0.000) longer mean overall survival (598 days) than patients undergoing surgery alone (318 days). Histological and lymph node status had a significant influence on overall survival. Perioperative complications did not differentiate significantly between both treatment groups (multimodal treatment: n= 13; surgery alone: n= 15). There was no significant difference between both treatment groups with regard to hospital and ICU stay.

Conclusion: Surgery as part of multimodal treatment protocols had a significant impact on patients overall survival. Perioperative complication rate or length of hospital and ICU stay were not enhanced in these patients compared to patients treated with surgery alone.

Keywords: pleural mesothelioma, Extrapleural pneumonectomy, multimodality treatment

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.283 NET OF THE LUNG , FROM A SINGLE INSTITUTION TO THE CREATION OF AN ITALIAN REGISTRY

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Background: Pulmonary NETS are typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNC), and SCLC. Purpose: to evalue prognosis of pulmonary well differentiated NET and establish an Italian registry.
Methods: From 1996 to 2007 our lung cancer working group followed 51 pulmonary NETs. 2/51 were metastatic at the diagnosis. 44/51 underwent radical surgical resection with adenectomy. 2/51 TC had definitive endobronchial laser, 3/51 had disostructive laser (2/3 followed by bilobectomy). 37/51 (72%) are TC. 11/51 (21%) are AC, 2/51 (4%) undetermined.
Results: Follow-up at dec 07: 3/51 were lost. 1 AC dead 7 yrs after diagnosis for progressive disease (liver metastasis, high CgA, and 3 yrs of octreotide). 1 undeterminated histology dead 1 yr after diagnosis (high CgA, octreotide therapy). 7 had preoperating CgA: 2 high (1 developed hepatic metastasis, in 1 normalized and 48 mths DFS). 3 TC had progressive disease. 1 TC (IA,high pre-lobectomy CgA), had persistent high CgA and hepatic lesion octreoscan+, 4 mths later: PR after 18 mths of octreotide. 1 TC (IB) with normal pre-lobectomy CgA had carcinoid syndrome with high CgA and octreoscan positivity, 4 mths later: negative restaging at 34 mths with 1 yr of octreotide. A sixteen girl - TC IB - with high CgA (normal after pneumonectomy) developed octreoscan + thoracic lesions, 18 mths later. PR after 56 mths with radiometabolic therapy.
Conclusion: NETS are heterogeneous lung cancers. AC radically resected had good prognosis (1/11 metastasis), sometimes TC gave metastasis (2/37). Octreotide- and radiometabolic therapy can control metastatic disease. CgA is not indicative of relapse but correlates with the extension of metastatic disease. High CgA values are not predictive of carcinoid syndrome. It is important to evalue CgA before and 2-3 mths after surgery. From this experience, we have created an Italian registry; since January 08 - an Italian registry of Net of the lung (all histologies), with the collaboration of many Italian centers. The purpose is to have more data about incidence, prognosis and treatment of this rare disease. At January 11, 23 centers have given their adhesion and 120 cases are reported. We think that is useful the effort of all Italian centers to have more data and increase the knowledge of the disease. The next question: is useful an European registry?

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P3.284 DIFFERENTIATION OF MALIGNANT PLEURAL MESOTHELIOMA FROM BENIGN ASBESTOS-RELATED PLEURAL DISEASE WITH MICRORNA AND GENE EXPRESSION PROFILING

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor which remains a worldwide problem because of its poor prognosis and increasing incidence. The major risk factor for this cancer is exposure to asbestos. The diagnosis of MPM is based on immunohistochemical stain of the pleural tissue obtained by biopsy. Differentiating between MPM and benign pleural disease (BAP) on pleural biopsy may be difficult in some cases. Although MPM has poor clinical outcomes overall and is frequently untreatable, recent series show that overall survival of this disease with aggressive treatment strategies is much longer than previously thought when it is diagnosed at an early stage. One of the most recent advances in cancer molecular biology is the identification of a role for microRNAs (miR) in regulating gene expression at the posttranscriptional level. In this study, we investigated the expression of miRs and their target mRNAs in both MPM and BAP.
Methods: All of the patients provided written

informed consent for genetic analysis on their pleural specimens. Biopsy specimens from 18 MPM and 6 BAP patients who were diagnosed and followed up at the Eskisehir Osmangazi University Hospital in Turkey were enrolled in this study. Specimens were obtained by medical thoracoscopy, CT-guided Abrams needle, or thoracotomy. All biopsy samples underwent review in Turkey by a single pathologist and these were confirmed by a lung pathologist at Mayo Clinic. None of the patients had received chemotherapy or radiotherapy prior to diagnosis. Clinical data including age, sex, asbestos exposure history, smoking history, Karnofsky performance status, histology, stage, treatment history, and survival characteristics were collected from all mesothelioma patients, while age, sex, asbestos exposure history and survival data were collected from the BAP patients. Follow-up was for 3 years or death. Gene expression profiling of mRNA was performed using the Affymetrix GeneChip® Human Genome U133 Plus 2.0 array in the Mayo Clinic Advanced Genomic Technology Center Microarray Shared Resource. Profiling of microRNA expression was performed using the TaqMan® Human MicroRNA Array Card A on the 7900HT fast Real-Time PCR System. Expression data were normalized in standard fashion and both MPM and BAP microRNA data were normalized separately to a miR mammalian U6 endogenous control gene.
Results: We discovered differential expression of miR and mRNA between the MPM and BAP samples. The most significant miRs included Hsa-let-7c-4373167, Hsa-miR-24-437-3072, Hsa-miR-29a-4395223, Hsa-miR-92a-4395169, Hsa-miR-191-4395410, Hsa-miR-193b-4395478, Hsa-miR-197-4373102, Hsa-miR-320-4395388, Hsa-miR-155-4395459, Hsa-let-7b-4395446, Hsa-miR-484-4381032, Hsa-miR-532-3p-4395466, and Hsa-miR-574-3p-4395460. Within the MPM samples, unique differences in miR levels were found for stage and prognosis, which included the following: Hsa-miR-193b-4395478, Hsa-miR-320-4395388, Hsa-miR-494-4395476 and Hsa-miR-532-3p-4395466.
Conclusion: We have identified specific miRs as potential diagnostic and prognostic utility for patients with MPM or BAP.
Keywords: malignant pleural mesothelioma, microRNA, gene expression, asbestos

P3.285 LOW-DOSE GEMCITABINE IN PROLONGED INFUSION AND CISPLATIN FOR THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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Background: After favorable experience with gemcitabine in low dose (130-250 mg/m2) in 6-hours infusion in combination with cisplatin for the treatment of advanced non-small cell lung cancer, we conducted a phase II trial of the same chemotherapy regimen in patients with malignant pleural mesothelioma (MPM).
Methods: Eligible patients had biopsy-proven medically inoperable MPM, were chemo-naïve, were in fair general condition (Eastern Oncology Cooperative Oncology Group performance status 0-2), had normal hematopoietic, liver and renal function and gave informed consent. Treatment consisted of gemcitabine 250 mg/m2 in 6-hour infusion on days 1 and 8 and cisplatin at 75 mg/m2 on day 2 of a 3-week cycle for 4 cycles, followed by 2 additional cycles without cisplatin.
Results: Between December 2002 and May 2008, 78 patients (58 male, 20 female; age 33 to 82 years, median 61.5) were included in the trial. Histologic subtype analysis revealed epitheloid in 56 (71.8%); sarcomatoid in 4 (5.1%); mixed in 15 (19.2%), and "not otherwise specified" mesothelioma in 3 (3.8%) of cases. Median number of treatment cycles was 6 (1-6). Grade III/IV toxicities were anemia in 2 (2,6%), leucopenia in 4 (5,1%), neutropenia in 18 (23,1%) patients and nausea/vomiting in 1 (1,2%) patient. Alopecia was seen in 60 (76.9%) patients; 53 patients (67.9%) had thrombocytosis with platelets over 500 x 10^9 /L. Four (5.1%) patients had complete response and 35(44.9%) had partial response; additional 36(46.2%) patients had minimal response with symptomatic improvement or stable disease. Four (5.1%) patients had disease progression during treatment. Median progression free survival was 8.0 months (C.I. 7.0-9.0) and median overall survival was 16.0 months (C.I. 13.6-18.3). One, two, three and five year survival were 67.2%, 30.3%, 14.5%, and 8.5%, respectively.
Conclusion: Due to the acceptable toxicity, remarkable efficacy and reasonable cost, this

treatment should be further explored.
Keywords: Cisplatin, malignant pleural mesothelioma, Chemotherapy, gemcitabine

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P3.286 CLINICAL ANALYSIS AND TREATMENT OUTCOME OF PRIMARY MALIGNANT GERM CELL TUMOR IN MEDIASTINUM - A 30-YEAR SINGLE INSTITUTION EXPERIENCE.

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Background: The treatment of primary mediastinal germ cell tumors (GCT) with cisplatin-based chemotherapy, followed by surgical resection of residual disease, has been established. We reviewed our institution's 30-year experience in the treatment outcome in patients with primary mediastinal malignant GCTs.
Methods: We identified 16 patients (15 males and 1 females), with a mean age of 27 years (range, 19 to 43 year) in our insitutde from 1982-2011. There were 11 patients with nonseminomatous GCTs and 5 seminoma. One patient had a hepatic metastasis, but other had located diseases.
Results: Cisplatin-based chemotherapy with VAB-6, PE and BEP was performed in three, five and seven cases, respectively. After 2-8 cycles of the chemotherapy, 14 cases underwent thoracic salvage resection. Two patients died 13 and 19.5 months after initiation of therapy, respectively, who was treated with VAB-6 and viable malignant cells were observed in the resected specimens. Other patients are currently disease free with a median survival period of 108 months (range 7-324 months).
Conclusion: Our institutional experience indicated that an improved survival advantage was ensured with preoperative chemotherapy in patients with primary mediastinal GCTs.
Keyword: Germ cell tumor

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P3.287 PEMETREXED IN THE FIRST LINE CHEMOTHERAPY OF MALIGNANT PLEURAL MESOTELIOMA. A MULTICENTRE PROSPECTIVE STUDY.

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Background: Malignant pleural mesothelioma (MPM) is a tumour with extremely unfavourable prognosis. Early diagnostic is rarely possible and chemotherapy has only a limited value in prolongation of survival. During the last years pemetrexed became the standard 1st line chemotherapy.
Methods: Results of MPM treatment with pemetrexed and platinum in the 1st line were evaluated in 9 centres. Data about consecutive patients were prospectively collected from January 2008 till December 2010. Demographics, tolerance of therapy and prognostic factors were discussed.
Results: The series consisted of 85 patients (pts) 60 men and 25 women, mean age 61 years (26 -84), 29 were nonsmokers, 32 exsmokers, 24 smokers. PS was 0 in 16 pts, 1 in 58 pts, 2 in 11 pts. TNM was I in 6 pts, II in 18 pts, III in 27 and IV in 31 pts. The professional exposition was found in 21 pts (median of exposition was 15 years), nonprofessional exposition was known in 14 pts. Side effects of treatment (Gr 3, 4) appeared in 22 pts, leucopenia in 11, neutropenia in 10, nausea/vomiting in 9, fatigue in 7, trombocytopenia in 7, anaemia in 6 pts. Therapeutical response: PR in 27, SD 38, PD in 22 pts, overall therapeutical response was 71.8%. Median of progression free survival (PFS) was 8.2 months, it was 8.1 m in men and 9.9 m in women (p 0.444). The median of overall survival (MOS) was 13.4 m, it was 13.4 m in men and 15.2 m in women

(p 0.921). PFS according TNM staging: 16.6 m in stage I, 13.4 m in stage II, 4.9 m in stage III (p 0.001). MOS according TNM staging: NA in stage I, 13.4 m in stage II, 9.7 m in strage III (p 0.063). PFS according PS: 16.6 m in PS 0, 9.9 m in PS 1, 2.6 m in PS 2 (p 0,008). MOS according PS: NA in PS 0, 11.9 m in PS 1, 3.3 m in PS 2 (p 0.001).
Conclusion: Pemetrexed is an effective and well tolerable drug in routine MPM treatment. PS and TNM staging influenced the prognosis, albeit sex, age and type of asbestos exposure had no prognostic impact in this study.
Keywords: malignant pleural mesotelioma, Pemetrexed, first line chemotherapy, survival

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.288 TREATMENT WITH 177LU-DOTA-OCTREOTATE IN PATIENTS WITH BRONCHIAL CARCINOIDS

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Background: Metastatic bronchial carcinoids are rare tumors, where efforts of medical treatment thus far have been disappointing. A previous study has reported favourable results of treatment with 177Lu-DOTA-Octreotate in these patients.
Methods: Twelve patients with metastatic bronchial carcinoid have so far been treated with 177Lu-DOTA-Octreotate at our center between 2006 and 2011. Five tumors were classified as atypical and 3 as typical carcinoids, whereas 4 tumors could not be classified. One patient had ectopic ACTH production, resulting in Cushing's syndrome. Seven patients had previously received chemotherapy. Somatostatin analogues had been given to 5 patients prior to start of Lutetium, and was given to 4 additional patients during the Lutetium therapy. Median follow-up was 22 months from start of Lutetium and 109 months from initial diagnosis.
Results: There were no complete responses. A partial response was seen in 6 patients (50%), stable disease in 5 (42%) and progressive disease in 1 patient (8%). Three patients with stable disease and one with partial response have later progressed. Three patients have died and the remaining 9 are alive, median 28 months from start of Lutetium and median 115 months from initial diagnosis. Bone marrow toxicity was mild.
Conclusion: Treatment with 177Lu-DOTA-Octreotate is active and well tolerated in patients with metastatic bronchial carcinoids, and should be considered as first-line therapy in this patient group.
Keywords: PRRT, Bronchial carcinoids, 177Lutetium-octreotate

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P3.289 ANALYSIS OF SOLUBLE MESOTHELIN-RELATED PEPTIDES AS DIAGNOSTIC MARKERS OF MALIGNANT PLEURAL MESOTHELIOMA EFFUSIONS

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Background: It has been reported that the serum levels of soluble mesothelin-related peptides (SMRP) are higher in patients with malignant

pleural mesothelioma (MPM) than in other patients. Therefore, serum SMRP was proposed as a marker for mesothelioma diagnosis. However, few studies have shown the potential value of SMRP for the differential diagnosis of pleural effusions (PE). In the present study we assessed the PE levels of SMPR from a large panel of patients and investigated their possible utility in routine clinical practice.
Methods: We evaluated SMRP in a total of 211 PE (38 from MPM, 71 from non-MPM pleural metastasis (PM), 102 from benign PE) by means of the MesoMark enzyme-linked immunosorbent assay kit (Fujirebio Diagnostic, Malvern, PA). Mesothelin dignostic performance parameters were estimated through the receiver operating characteristic (ROC) analysis. In particular, the area under the ROC curves (AUC) was used as an index of pure accuracy, namely the overall proportion of correctly classified patients. Youden's index was applied to obtain the biomarker's cut off level of maximum discrimination between patient groups. For each cut off, empirical accuracy (Ac), positive (PPV) and negative (NPV) predictive values, along with sensitivity (Se) and specificity (Sp), were calculated. Finally, the degree of correlation between SMRP levels and patients' disease stutus was estimated using the Diagnostic Odds Ratio (DOR). For each index 95% confidence limits (95% CLs) were also computed and, wherever appropriate, chi-square test was performed to assess the statistical significance (P) of the study comparisons.
Results: The Mean PE SMRP level was higher in MPM (41.7±49.4 nM/L) than in patients with PM (8.8±14.1 nM/L) or benign PE (4.8±8.4 nM/L). We found a statistically significant difference between SMR levels in MPM vs benign PE (DOR=30.8, P<0.001), vs PM (DOR=11.8, P<0.001) and vs all other PE (DOR=15.7, P< 0.001). The AUC for SMRP-differentiating MPM PE and benign PE was 79.8 (cut off=10.8 nM/L, Se=65.8%, SP=94.1%, Ac=86.4%, PPV=80.6% and NPV=88.1%), the AUC for SMRP-differentiating MPM PE and PM PE was 75.6 (cut off=11.8 nM/L, Se=63.2%, SP=87.3%, Ac=78.9%, PPV=72.7%, NPV=81.6%). Finally, the AUC for SMRP-differentiating MPM PE and all other disease PE was 78.1 (cut off=10.9 nM/L, Se=63.2%, SP=90.2%, Ac=85.3%, PPV=58.5%, NPV=91.8%). At the cut off of 10.9 we found higher SMPR values in 25/38 (66%) MPM PE, 13/71 (18%) of PM PE and 8/102 (8%) of benign diseases PE.
Conclusion: Our findings show that SMPR level in PE, as reported in serum, is a promising diagnostic marker to distinguish MPM PE from benign and PM PE.
Keyword: malignant pleural mesothelioma, Soluble mesothelin-related peptides, pleural effusion

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P3.290 THE DIAGNOSTIC ROLE OF F-18 FDG PET/CT IN PATIENTS WITH PLEURAL THICKENING AND PLEURAL EFFüSION

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Background: AIM:To investigate the diagnostic role of F-18 FDG PET/CT in patients with pleural thickening and pleural effusion.
Methods: The mean age of the patients were 61.9±12.7 (26 patients; 21 male, 5 female) in this retrospective study. Three patients had only pleural effusion (PE), 4 patients had both pleural effusion and pleural thickening (PT), the rest of the patients had pleural nodules (PN) and (PT). All patients were fasted for at least 12 h (blood glucose level <200 mg/dL) before FDG PET/CT examinations. A low-dose CT was performed prior to the PET images (1.5 min/bed position) and obtained 60 min after F-18 FDG injection. The final diagnosis was reached by histopathological examination or by clinical follow-up. The SUVmax values were calculated and the highest values for the patients were used for statistical analyses. Mann Whitney U test was performed for statistical analysis.
Results: All the lesions were benign in PE patients. The final diagnosis revealed a malignant lesion in 2, and a benign lesion in the the other 2 referred with both PE and PT. In PN and PT group 12 were diagnosed to have malignant lesions and the rest were benign. The mean SUVmax value of the benign PE was 2.6 ± 0.9. One of the two patients with both PE and PT was diagnosed to have fibrous pleuritis (SUVmax: 6.5) and the second with tuberculosis (no increased uptake, SUVmax: 1.0). The rest of two patients were diagnosed as metastatic pleural involvement; the one with a

metastatic lesion due to a prostate cancer was F-18 FDG negative (SUVmax: 1.0), the other with nonsmall cell lung cancer had a SUVmax of 12.9. In 19 patients with PT and PN were diagnosed as benign pleural changes (7 patients), malignant mesothelioma (6 patients) and metastatic pleural involvement (6 patients). The mean SUVmax were 2.43±2.15, 10.13±3.0, and 9.05±6.0 for benign lesions, malignant mesothelioma and metastatic involvement, respectively. The SUVmax values ranged between 1.0-6.80 and 1.0-21.5 in benign and malignant lesions respectively. There was significant difference of SUVmax values between benign and all malignant lesions ($p<0.0001$). There was also a significant difference between benign and malignant mesothelioma lesions (p: 0.001). There was not a difference of SUVmax values between malignant mesothelioma and metastatic lesions (p: 0.25). In malignant mesothelioma patients, PET/CT demonstrated two nodular lesions which were located in paracaval (SUVmax: 5.0) and paracardiac (SUVmax: 10.0) regions that were not reported by diagnostic CT study. A high F-18 FDG uptake was also demonstrated on femoral diaphysis.
Conclusion: PET/CT may be valuable diagnostic tool in evaluating patients with pleural lesions. It should be taken into consideration that benign lesions could demonstrate reasonably increased FDG uptake. The crucial diagnostic role of PET/CT may be the demonstration of extrapleural dissemination and the determination of small lesions that were not reported on CT.
Keywords: FDG PET/CT, Pleural effusion and thickening, mesothelioma

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P3.291 PRIMARY SARCOMA OF THE LUNG: A SURGICAL SERIES

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Background: Primary pulmonary sarcomas (PPS) are rare mesenchymal tumors, accounting for 0.013% to 0.4% of all lung malignancies. Their prognosis remains poor, despite the entire therapeutic arsenal that is available for the treatment of non-small-cell lung cancer (NSCLC). The aim of this study is to investigate clinical, histological characteristics and survival after resection of these tumors.
Methods: On a series of 1582 patients operated on for lung cancer, 43 patients were retrospectively identified as having been treated surgically for primary pulmonary sarcoma. The records of all patients were reviewed.
Results: There were 33 males and 10 females with a mean age of 55 (range 12-75). Clinical findings were dominated by thoracic symptoms. Imaging findings showed a peripheral mass in the majority of cases (n=29). The mean tumor's size was 5.2 cm (range, 1 - 17.5cm). Careful investigation failed to discover a primary lesion elsewhere. The preoperative histological diagnosis was a NSCLC in 19 patients. Seven patients received induction therapy for wall involvement. Lobectomy or bilobectomy was performed in 30 patients and pneumonectomy in 11 patients. One patient underwent exploratory thoracotomy and one underwent a resection of a nodule. Of the resected patients, 3 had a positive resection margin. The histologic diagnoses were: pleomorphic carcinoma (n=28), carcinosarcoma (n=5), angiosarcoma (n=3), leiomyosarcoma (n=1), rhabdomyosarcoma (n=2), blastoma (n=3), and primitive neuroectodermal tumor (n=1). Different stages were: Ia (n=2), Ib (n=13), IIb (n=14), IIIa (n=5), IIIb (n=6) and IV (n=7). There were no operative deaths. Two died within 1 month of surgical complications and 5 died of disease within 17 months. Adjuvant therapy was performed in 8

patients. Recurrence happened in 4 patients within 12 months after operation. Median survival for all patients was 8 months.
Conclusion: Resection of primary pulmonary sarcomas is associated with an acceptable survival rate if the resection is complete. The particularity of our study is that, despite the large size of the tumor, an acceptable survival can be obtained. Nevertheless, these patients require carefully follow-up to evaluate local recurrence, and metastases.
Keywords: Lung cancer, Pulmonary sarcomas, Surgery

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P3.292 ACUTE TOXICITIES OBSERVED WITH NEOADJUVANT SHORT ACCELERATED HEMITHORACIC RADIOTHERAPY (RT) FOLLOWED BY EXTRA-PLEURAL PNEUMONECTOMY (EPP) FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM): PRELIMINARY RESULTS

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Background: MPM is a rare, aggressive tumour with poor outcomes. We have routinely treated suitable patients with neoadjuvant chemotherapy (currently cisplatin and pemetrexed/raltitrexed), followed by EPP, followed by adjuvant high dose hemithoracic radiation over the past 10 years. Many patients develop distant disease in the peritoneum or contralateral lung, suggesting incidentally seeding at time of EPP to these areas. We are, therefore, conducting a study where MPM patients are treated with short accelerated neoadjuvant hemithoracic RT followed by EPP and present the acute treatment toxicities seen.
Methods: We are conducting an REB approved prospective study evaluating the feasibility of neoadjuvant short accelerated hemothoracic RT followed by EPP within 1 week for clinically resectable early stage MPM followed by adjuvant chemotherapy if mediastinal nodes are involved. The dose prescribed is 25 Gy/5 daily fractions over 1 week to the entire hemithorax. Acute treatment related toxicities are presented (defined as any toxicity seen within 3 month of treatment completion). Toxicities are graded according the CTCAE v3.0 criteria.
Results: Nine patients (6 males) of an intended 12 have been accrued to this feasibility study. Mean age is 63 years (range: 46-72 years). All patients were ECOG ≤ 1. Median follow-up is 8 months from time of EPP. All patients were clinically staged cT1-3 N0 M0. After EPP, the pathological stages were: ypT3 N0 M0 (1); ypT4 N0 M0 (2); ypT3 N2 M0 (1); ypT4 N2 M0 (4); and ypT4 N3 M0 (1). No fatal or life threatening toxicities (G4+) were observed during treatment. Four patients developed severe (G3) toxicities, seen during the peri-operative period (thromboembolism requiring anticoagulation; hemothorax requiring operative correction, atrial fibrillation, infection). Two patients have recurred (both distantly).
Conclusion: These results are preliminary and should be interpreted cautiously. Short accelerated neoadjuvant hemithoracic RT followed by EPP appears feasible. More mature follow-up is needed to evaluate outcomes and late toxicities.
Keywords: mesothelioma, Radiotherapy, Extrapleural pneumonectomy, combined therapy

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P3.293 SECOND-LINE THERAPY IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA. FRENCH RETROSPECTIVE STUDY 2005-2006

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Background: The role of second-line chemotherapy (SLC) is not yet established in malignant pleural mesothelioma (MPM) but SLC is being used increasingly in our experience because many patients are still fit at the time of disease progression.
Methods: In this retrospective study, we reviewed our experience of SLC in pemetrexed-pretreated patients with MPM at two French thoracic oncology

units (Institut Gustave Roussy, Villejuif ; Hôpital Percy, Clamart).
Results: Between January 2005 and December 2006, 84 consecutive patients with MPM who progressed after pemetrexed-chemotherapy were enrolled. Forty-four patients (52,3%) received a SLC. There were 30 men and 14 women. The median age was 58 years (range, 34-76). Most patients had a PS ≤ 1 (82%) and an epithelial histologic subtype (91%). The median time to progression (TTP) after first-line chemotherapy was 6,1 months. The SLC was a pemetrexed therapy in 21 patients (with a relapse more than 3 months), and a new regime in 20 patients (gemcitabine alone or with oxaliplatin). The other 3 patients were enrolled in a phase I study. According to RECIST criteria, a partial response was observed in 7 patients and 9 patients had stable disease after SLC. The median TTP after SLC was 3,8 months. The median survival was 12,2 months (range: 2 to 72 months). Four of these 44 patients then received third-line (4,8%) and two received fourth-line therapy (2,4%).
Conclusion: Our experience suggests the feasibility of giving SLC to patients with MPM who are healthy at the time of disease progression. The optimal treatment has not been defined to date and prospective trials are needed in this setting.
Keywords: pleural mesothelioma, Chemotherapy, second-line therapy

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P3.294 PLEURECTOMY FOR THE TREATMENT OF MASAOKA STAGE IVA THYMOMA

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Background: The surgical approach to Masaoka stage IVa thymoma is not standardized but challenging. Pleuropneumonectomy for Masaoka stage IVa thymoma is associated with high morbidity and mortality. We investigated the outcome of pleurectomy in locally advanced Masaoka stage IVa thymoma.
Methods: Eleven patients (56 women, age 50.3 ± 14.4 years) were diagnosed with thymoma at Masaoka stage IVa between January 2000 and December 2010 at a single institution and were included in the present study. Preoperative imaging studies included computed tomography and magnetic resonance imaging of the chest. All patients underwent needle biopsy for histological classification. World Health Organization classification were Type AB (n=2), Type B3 (n=3) and Type C (n=6), respectively.
Results: After 6 cycles of platinum-based induction chemotherapy, 3 patients were inoperable at the time of surgery and proceeded to chemoradiation therapy due to infiltration of the arcus aortae (n=2) and conus pulmonalis (n=1), respectively. Complete mediastinal tumor resection and pleurectomy were performed in 8 patients. Complete pleurectomy was performed in 2 patients. Two patients underwent 4 cycles of platinum-based induction chemotherapy. Six patients without induction therapy proceeded to adjuvant chemoradiation (n=3) or adjuvant radiation (n=3), respectively. Morbidity occured in 2 patients (25%) including chylothorax and the necessity of mechanical ventilation because of myasthenic crisis. No mortality occurred. No patient was lost to follow-up and mean follow-up was 40.3 ± 22.4 months. Pleurectomy resulted in prolonged survival (66.1 ± 3.6 months) compared to unresectable patients who underwent chemoradiation (22.4 ± 9.2 months, p=0.017).
Conclusion: Locally advanced Masaoka stage IVa thymoma can be treated by pleurectomy with low morbidity and mortality. Exploratory thoracotomies might occur because of possible gray zones in distinguishing between tumor invasion and attachments despite imaging studies. Long-term survival can be achieved in highly selected patients. The time of application chemotherapy and radiotherapy (neoadjuvant vs. adjuvant setting) remains unanswered.
Keywords: pleurectomy, Thymoma, locally advanced, Surgery

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P3.295 EXPERIENCE OF THE TREATMENT OF MALIGNANT MESOTHELIOMA AT A UK CANCER CENTRE

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Background: An audit was conducted to describe the demographics, treatment modalities utilized and survival of patients with malignant mesothelioma in Leicester.
Methods: Retrospective audit was undertaken including all mesothelioma patients referred to Leicester Lung Cancer MDT from 01/01/2006 to 31/12/2009.
Results: There were 108 patients discussed at the MDT, mean age 71yrs (39-89 yrs) (88% male). 106 cases of pleural and 2 cases of peritoneal mesothelioma were diagnosed. Histological diagnosis was obtained in the majority (n=99), with the remainder cytological (n=7), radiological (n=1) and at post mortem (n=1). The epithelioid subtype was the most common (n=67). Other subtypes included sarcomatoid (n=20), biphasic (n=15) and malignant mesothelioma not otherwise specified (NOS) (n=5). 66.6% had a definite recall of exposure to asbestos. At presentation 65.7% of patients had a performance status (PS) 0 or 1. 15.7% had no PS recorded. The main presenting symptoms were breathlessness (n=87), chest pain (n=45), cough (n=38) and weight loss (n=32). A third of patients received a surgical treatment (EPP, decortication or pleurectomy) and 75.9% were referred for oncological assessment. 39.8% of all patients had first line chemotherapy and 41.7% had radiotherapy to the biopsy/scar site (n= 26) or for symptom management (n=26). 4 patients were enrolled into a clinical trial. 13% and 2.7% received second and third line chemotherapy respectively. Main reasons for not receiving first line chemotherapy were poor performance status (n=49), patient refusal (n=6). 4 patients underwent a watch and wait policy but deteriorated before treatment. Of 43 patients that received first line chemotherapy, majority had doublet (n=42) containing either cisplatin (n=25) or carboplatin (n=17) alongside pemetrexed (n=28) or vinorelbine (n=14). Cisplatin switched to carboplatin in 5 patients due to falling GFR (n=3) or other toxicities (n=2). Vinorelbine doublet switched to gemcitabine doublet in 2 patients (abnormal LFT's). Due to deteriorating PS, cisplatin/pemetrexed was switched to pemetrexed single agent in one patient. Mean number of cycles 3.4 (range 1-6). 19 discontinued due to toxicity (n=9), progressive disease (n=7) and other (n=3). Radiological assessment included stable disease (n=15), partial response (n=9), progressive disease (n=6). Main reasons for no radiological assessment included chemotherapy given in the adjuvant setting (n=5) and toxicity/progressive disease (n=5). Second line chemotherapy administered included gemcitabine (n=2), vinorelbine (n=4) or pemetrexed (n=4) as single agents. Doublet regimes included gemcitabine/vinorelbine (n=1) or platinum/pemetrexed (n=2). Mean survival was 266 days (8.9 months). Survival was longer in those able to receive chemotherapy (402 versus 219 days p 0.001).
Conclusion: This is a comprehensive audit of mesothelioma patients diagnosed in Leicester. A histopathological diagnosis was obtained in the vast majority of patients. A third of patients underwent a surgical treatment and of those assessed in oncology over half received chemotherapy. Very few patients were enrolled into a clinical trial.
Keywords: mesothelioma, Audit

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P3.296 HIGH RESPONSE OF SECOND-LINE CHEMOTHERAPY WITH PEMETREXED COMBINED WITH CARBOPLATIN IN PATIENTS WITH UNRESECTABLE MALIGNANT MESOTHELIOMA EXPERIENCING PROGRESSION AFTER THREE MONTHS OF CONCLUDING PLATINUM-BASED CHEMOTHERAPY

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Background: Malignant Pleural Mesothelioma (MPM) is in most cases a lethal neoplasm; few patients are candidates for surgical treatment. Chemotherapy remains a challenging issue in this entity. Platinum analogues, doxorubicin and some antimetabolites such as pemetrexed have a modest activity against malignant mesothelioma when used in first line as single agents with response rates ranging from 10 to 40 percent. The combination of antimetabolite with a platin like pemetrexed/cisplatin has shown an improvement in survival, lung function and symptom control when compared

to single drug cisplatin. There is no standard second line chemotherapy for treatment of malignant mesotheliomaMPM. Second-line therapies are being increasingly used in the clinical practice since patients frequently have a good performance status at the time of disease progression. However, the role of these treatments in MPM is unproven; and the optimal regimens still remain to be defined. We reporte our experience with the combination of carboplatin and pemetrexed as second-line treatment for patients with MPM.

Methods: Patients with histologically proven MPM experiencing progression 3 months after conclusion of chemotherapy (doxorrubicin-cisplatin or gemcitabine-cisplatin) received pemetrexed-carboplatin as second line treatment. Patients were age 18 or older, had a good performance status (ECOG 0 to 2), measurable disease and written informed consent. Life expectancy of at least 3 months.Pemetrexed was administered at 500 mg per square meter in a 10 minute-infusion and Carboplatin at AUC of 5 on day 1 in 21-days cycles. Response was evaluated using the RECIST criteria after every two treatment cycles. The study protocol was approved by both the Institutional Boards.

Results: A total of 30 patients with unresectable MPM were included. Previous chemotherapy regimens included: gemcitabine-cisplatin (6 patients) or doxorrubicine-cisplatin (24 patients). Twenty-three patients were males and 7 were females. 25 patients had stage III disease, the remaining 5 had stage IV disease. The mean age was of 60 ± 13 years. Five patients had a good EORTC while 25 had a bad prognosis. Histological subtypes were: 21 epithelioid mesotheliomas, 2 sarcomatoid mesotheliomas and 7 mixed mesotheliomas. Partial response was seen in 9 patients, 11 patients had stable disease and 7 progressive disease. Response was not evaluable in 3 patients. Progression free survival was of 7 ± 3 months. Overall Survival was of 21.9 ± 8.7 months. Nine patients had a three month interval between end of chemotherapy and progression. 6 out of nine (66%) patients had over 6 months with partial response. 3 out of 21 patients had a partial response duration of less than three months. Pemetrexed-carboplatin has a high response rate in patientes with a period of more than three months between the end of chemotherapy and progression.

Conclusion: The use of the pemetrexed-carboplatin combination as second-line chemotherapy seems to have a place in the management of patients with unresectable MPM, especially those with an interval time to progression greater than 3 months. Response rates with this second-line treatment correlate with progression free survival in previously platinum-treated patients. Further studies need to be carried out.

Keywords: second line chemotherapy, Malignant mesothelioma, Pemetrexed-cisplatin

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P3.297 PEMETREXED/ CARBOPLATIN(AC) OR PEMETREXED/ CISPLATIN (AP) AS FIRST LINE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA (MPM): TOLERABILITY AND RESPONSE RATE IN OPERABLE PATIENTS.

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Background: Trimodality treatment based on preoperative chemotherapy, surgery and adjuvant radiotherapy can be considered an effective therapeutic option for MPM selected patients. The objective of this study is to evaluate the tolerability and activity of pemetrexed/carboplatin (AC) or pemetrexed/cisplatin (AP) as neoadjuvant chemotherapy.

Methods: Patients with histologically confirmed MPM, stage I-III, ECOG PS=0-1, received three cycles of pemetrexed 500mg/m2 plus carboplatin AUC5 or cisplatin 75mg/m2 on day 1 every 21, with standard premedication. From January 2005 to December 2009 first-line chemotherapy was based on pemetrexed plus carboplatin, the standard regimen we used in this setting. From June 2005 to December 2007 patients were included in a clinical trial ongoing at our centre, and they were treated with pemetrexed plus cisplatin. Baseline staging and preoperative restaging were assessed with CT-scan and PET-CT. Patients without disease progression underwent surgery followed by radiotherapy.

Results: Since 2005, 54 patients were included in the study, 30 treated with AC, 24 with AP.

Haematological toxicity by patient in the intent to treat (ITT) population showed grade-3 leucopenia (7%), neutropenia (13%), thrombocytopenia (7%) and anaemia (3%) in AC-treated patients and leucopenia (8%), neutropenia (17%), anaemia (8%) in the AP group. No grade 4 haematological toxicities were shown in the two groups. Grade-3 non-haematological toxicities were diarrhoea (3%) and asthenia (4%) in AC and AP cohorts respectively. Cumulative grade 2-3 asthenia at the last cycle of chemotherapy was commoner with AP (21%) than with AC (7%); worsening of PS was shown in 29% and 17% of patients in the two groups respectively. 2(8%) AP-treated patients had dose reduction because of hypercreatininemia and infection, and 1(4%) died within 30 days from surgery for endocarditis. Response to AC and AP were: complete 3% vs 0%, partial 30% vs 17%, stable disease 64% vs 79%, progressive disease 3% vs 4% (DCR 97% vs 96%; RR 33% vs 17%). Patients in AC and AP groups showed: resection rate 87% vs 79%; median overall survival (OS) in patients treated with carboplatin and cisplatin was 118 vs 66 weeks respectively (p=0.03); progression free survival was 76 and 57 weeks (p= 0.07) in the two groups. Multivariate analysis showed the histologic subtype (p

Conclusion: AC and AP are active and feasible neoadjuvant regimens without major toxicities. AC apparently gave higher response rate and OS, but resection rate and progression free survival were similar. Cumulative non-haematological toxicities and PS worsening were commoner in AP-treated patients, and this could impair the clinical conditions of patients undergoing surgery.

Keywords: Malignant mesothelioma, Chemotherapy, Carboplatin, Cisplatin

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.298 MALIGNANT MESOTHELIOMA (MM) – 11 YEARS IN REVIEW

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Background: The MM is a tumor originating from the mesothelial surface surface of the pleural cavity. It has an insidious onset and generally affects individuals between 50-70 years. MM is a highly malignant tumor and has a poor prognosis with median survival between 6 and 18 months. Portugal is a country of low incidence of MM in which the peak has not yet been reached.

Methods: Retrospective analysis of patients with MM diagnosed between April 1998 and April 2009. The parameters evaluated included age, gender, job, occupational history, smoking habits, assessment of performance status (Zubrod score) and symptoms at presentation, TNM staging, diagnostic methods, histology, therapy and median survival.

Results: A total of 27 patients were studied, 19 (70.4%) males and eight (29.6%) females. Mean age at diagnosis was 62.8 ± 10.33 yrs. Four (14.8%) patients had a history of direct asbestos exposure and 10 (37.0%) of them had a high-risk occupation. Most (55.6%) were non-smokers, 5 (18.5%) were ex-smokers and 4 (14.8%) current smokers. Twenty-two patients (81.5%) were Zubrod 1 and 3 (11.1%) Zubrod 2. Most common symptoms at presentation were dyspnea (48.1%), chest pain (37.0%), asthenia (33.3%) and weight loss (29.6%). TNM staging: 19 (70.4%) were in stage III, 7 (25.9%) in stage IV and 1 (3.7%) in stage I. The most common methods used for definitive diagnosis were thoracoscopy (52.2%) and transthoracic biopsy (21.7%). The most common histological type was epithelial mesothelioma. First-line chemotherapy regimens used were cisplatin/ pemetrexed (45.0%) and cisplatin/ gemcitabine (45.0%). As second-line therapy, 11 (40.7%) received pemetrexed or gemcitabine. Three (11.1%) were enrolled in a clinical trial. All patients performed prophylatic radiotherapy directed to the site of puncture or diagnostic thoracoscopy. One patient underwent surgery.

Fourteen (51.9%) died, 8 (29.6%) were lost to follow-up and 5 (18.5%) are still alive.

Conclusion: Similarly to international data, MM was diagnosed in advanced stages in most patients. Moreover, median overall survival (18 months) is consistent with results from the best international series. Our study showed that in most cases, it was possible to identify an occupational source, which confirms the importance of exposure in the development of MM. In our country, given the paucity of references in relation to survival of MM, this might be a modest contribution in understanding the behavior of the disease in Portugal.

Keywords: Malignant mesothelioma, review

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.299 THE EFFECT OF 24 VERSUS 48 HOUR DRUG LIGHT INTERVAL ON THE TOXICITY OF HPPH-MEDIATED PDT IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA UNDERGOING RADICAL PLEURECTOMY

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Background: For patients with pleural dissemination of malignancy, the current standard of care is palliative chemotherapy. We have previously demonstrated that multi-modality therapy including surgical resection with intraoperative porfimer sodium-mediated photodynamic therapy (PDT) can be effective in the treatment of patients with malignant pleural mesothelioma (MPM) or pleural dissemination of non-small cell lung cancer (NSCLC) or recurrent thymoma. HPPH is a novel second-generation photosensitizer with superior photophysical properties and significantly decreased duration of skin photosensitivity as compared to porfimer sodium.
Methods: In this study, we have evaluated the toxicity of HPPH-mediated PDT delivered to the entire pleural surface when combined with lung sparing surgical resection in patients with pleural dissemination of malignancy. The PDT dose was increased by either shortening the drug light interval or increasing the light dose from 15-45 J/cm2 of 661nm light. Dose limiting toxicity (DLT) was defined as grade 3 non-hematologic or grade 4 hematologic toxicity that was possibly, probably or definitely related to PDT. We have also evaluated the efficacy of HPPH-mediated PDT with a 24h vs 48h drug light interval in an ectopic murine model of MPM.
Results: To date 12 patients with pleural dissemination of malignancy limited to one hemithorax (9 MPM, 3 carcinoma metastatic to pleura) have been treated at 5 dose levels. In all patients, a lung sparing, macroscopically complete tumor resection was achieved. In 11 patients treated with a 48h drug light interval, there were no DLT with 3 patients treated at 15, 22.5 or 30 J/cm^2 and 2 patients treated at 45J/cm2 light dose. One patient treated at a 24h drug light interval and 15 J/cm^2 light dose experienced edema-related complications including abdominal compartment syndrome and ARDS that were definitely related to PDT. In preliminary studies of PDT efficacy using ectopic murine AB12 mesothelioma tumors, a similar level of cure rate could be achieved in mice by a 2.5 fold increase in light dose with 48h as compared to 24h drug light interval. Interestingly, at these light doses, the animals treated with 48h drug light interval experienced decreased edema at the treatment site.
Conclusion: In humans, HPPH-mediated PDT can be safely combined with surgical resection with a 48h drug light interval. However, while increased light dose can compensate for increased drug light interval in animal studies, both humans and animals experienced markedly more severe edema-related toxicities at 24h versus 48h drug light interval.
Keywords: malignant pleural mesothelioma, radical pleurectomy, Thymoma, intraoperative therapy

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P3.300 USEFUL IMMUNOHISTOCHEMICAL AND FUNCTIONAL MARKERS IN DISTINGUISHING THYMIC CARCINOMAS FROM THYMOMAS AND/OR SQAUAMOUS CELL CARCINOMAS

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Background: Thymic carcinomas are rare epithelial neoplasms of anterior mediastinum with higly malignant nature and thought to be derived from epithelial cells of thymic origin. Although some thymic carcinomas are morphologically indistinguishable from typical forms of tissue-common carcinomas, such as squamous cell carcinoma (SCC), adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma, in the vast majority of thymic carcinomas tumor cells exhibit uniformly solid microscopic appearance without forming any particular architecture. It is, however, not infrequently difficult to distinguish thymic carcinomas from type B3 thymoma and SCC. In this study, we attempted to find reliable immunohistochemical markers to distinguish thymic carcinomas from type B3 thymomas and/or SCC.
Methods: Formalin-fixed, paraffin-embedded tissue-sections of thymic carcinomas (17 cases), type B3 thymomas (11 cases), and SCC (lung cancers; 13 cases) were examined immunohistochemically. Monoclonal antibodies against cytokeratin AE1/AE3 (CK), c-kit, MIB-1, synaptophisin, claudin-1 (CLDN-1), fascin, HLA-DR, CD68, CD99, and CD205 were used. Single immunoperoxidase method was performed.
Results: In all cases of thymic carcinomas examined, tumors were composed of solid sheets of polygonal CK^+ tumor cells without squamous or glandular differentiation and abundant hyalinized fibrous stroma. In these cases, cellular atypia of tumor cells were manifest and mitosis and tumor necrotis were frequently observed. In 15 out of 17 cases of thymic carcinoma, tumor cells were positive for c-kit. The immunoreactions for c-kit were detected intensely at cell-membrane and in cytoplasm of tumor cells. In 3 out of 13 cases of SCC, tumor cells were positive for c-kit. However, the immunoreactions for c-kit were detected in cytoplasm but scarcely at cell-membrane. Although c-kit was detected in 3 out of 11 cases of B3 thymoma, membrane immunoreactions to c-kit was detected in only one case. CLDN-1 was detected at cell-membrane in all cases of thymic carcinomas and SCC, while this antigen was detected in only 2 cases of type B3 thymoma. Average of MIB-1 index of thymic carcinomas were not significantly different from that of SCC, but it was significantly higher than that of B3 thymoma ($p<0.05$). None of thymus-specific cells, such as thymic cortical dendritic macrophages (TCDM), and $CD99^+$ thymocytes (THY) were detected in any cases of thymic carcinoma or SCC, while these cells were detected in type B3 thymomas in varied numbers.
Conclusion: Both c-kit and CLDN-1 are useful markers for distinguish thymic carcinoma from SCC and type B3 thymoma, although they are not specific for thymic carcinomas. Especially, membrane-immunostaining, but not cytoplasmic immunostaining, of c-kit is highly specific for thymic carcinoma, and may be one of the most reliable markers of thymic carcinoma. The presences of TCDM and/or THY are useful functional markers to distinguish thymomas including B3-thymomas from thymic carcinomas.

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P3.301 THE BURDEN OF MESOTHELIOMA MORTALITY: ESTIMATION AS THE FIRST STEP TO PREVENTION.

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Background: Mesothelioma is a rare cancer that principally affects the pleura and is almost always caused by asbestos exposure. The disease is rapidly fatal; most of those affected dying within a year of diagnosis. There is a long latent period between first exposure to asbestos and diagnosis of mesothelioma that is seldom less than 15 years and often exceeds 60 years. Mesothelioma incidence has increased in South East England of which East Kent is a major part, particularly for men aged over 70 years, reflecting areas of asbestos use in shipbuilding and industry in the past.
Methods: Work-related cancers are largely preventable. The aim of the study is to estimate the current burden of cancer in the area of East Kent in the UK attributable to occupational factors, and identify carcinogenic agents, industries and occupations for targeting risk prevention. Data of all cases diagnosed at East Kent Hospitals NHS Trust were collected retrospectively from April 2009 to March 2010.
Results: There were a total of 15 cases in East Kent Hospital NHS trust, UK over the period of one year which is a significantly high number as compared to previous years,the current population being 614,576. All of them were male. Median age was 74 years and median survival from diagnosis was 8.9

months. All of them had histological or cytological confirmation and 85% had documented evidence of definite or probable exposure to asbestos. There were seven cases that were treated with chemotherapy and 6 patients had advanced malignancy and received radiotherapy and 2 patients with advanced malignancy had palliative treatment only. No patient had radical surgery and there was minimal difference in relative survival between men with localised and non-localised disease stage.

Conclusion: In Great Britain, where asbestos use continued later than many other countries, the peak is anticipated to occur later between 2011 and 2115. Between 1981 and 2000, North East England and South East England were the areas with the highest standardised mortality ratios. Cancer networks, especially those with primary care trusts with high incidence, need to be aware of this disease and ensure that risk reduction strategies and services are in place to assist these patients. More research is needed to understand the interrelationships of prognostic factors, treatment choices and survival, and to determine the best care and support for these patients and their families.

Keyword: mesothelioma

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P3.302 PEMETREXED-CARBOPLATIN DOUBLETS SHOWED BETTER MEDIAN SURVIVAL THAN PEMETREXED-CISPLATIN IN THE TREATMENT OF TURKISH MALIGNANT PLEURAL MESOTHELIOMA PATIENTS

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive tumour and commonly presents at an advanced stage. Antifolate-platinum doublets are commonly used chemotherapy regimens with a shown survival advantage. In this study we assess our treatment results with pemetrexed+cisplatin or pemetrexed+carboplatin combinations in patients with MPM.

Methods: Fifty-four chemo naïve patients who were treated between 1999 and 2010 were retrospectively evaluated. Chemotherapy consisted of pemetrexed 500 mg/m2 in combination with either cisplatin 75 mg/m2 or carboplatin AUC= 5 mg/mL/min , once every 21 days. All patients received folic acid and vitamin B12 supplementation.

Results: Patients were 34 males and 20 females with a median age of 33 years old (range, 53-80). The most commonly seen histopathology was epitheliod type (83%) and 80% of the patients had prior environmental mineral fibre exposure (tremolite asbestos or fibrous zeolite). Twenty patients received pemetrexed+cisplatin and 34 patients received pemetrexed+carboplatin doublets of median 6 cycles (range, 1-8). Twenty-nine patients (54%) received radiotherapy (6 preventive, 11 palliative, and 12 curative intent). Twenty-two patients had debulking surgery (9 pleurectomy+decortication-P/D- and 13 extrapleural pneumonectomy-EPP-). Median overall survival for the whole group was 16 months (range, 1-69). Patients with epithelioid type of histopathology have better prognosis. The median overall survival and time to relapse values for pemetrexed+cisplatin and pemetrexed+carboplatin groups were 15 months vs. 20 months (p=0.0097) and 9 months vs. 10 months (p=0.95) respectively. Overall objective response rate (complete and partial response) to chemotherapy was 59%. There was no difference in response to the two chemotherapy regimens (p=0.087). The type of surgery effects the time to relapse. Patients who had EPP and P/D have longer time to relapse (12 months vs. 9 months, p=0.047). Fifteen patients who received median 4 cycles of (range,2-13) maintenance single agent pemetrexed showed increase in median survival (30 months vs. 16 months, p=0.03). Both doublets were well tolerated. There was no difference in terms of adverse haematological toxicity between the two chemotherapy groups. Non haematological toxicities were negligible.

Conclusion: Our results showed highly encouraging long term median survival outcome in patients treated with pemetrexed+carboplatin. This combination seems to be a well tolerated and a valid option as a first line treatment in MPM.

Keywords: malignant pleural mesothelioma, pemetrexed-platinum doublets

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P3.303 CLINICO-PATHOLOGICAL CHARACTERISTICS OF IRANIAN PATIENTS WITH THYMOMA REFERRED TO NATIONAL RESEARCH INSTITUTE OF TUBERCULOSIS AND LUNG DISEASE: A SINGLE INSTITUTE STUDY FROM IRAN

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Background: Thymoma is a neoplasm originating from the Thymus. This tumor is usually benign, and frequently encapsulated; but it could be invasive or rarely metastatic in malignant forms. Thymoma is an uncommon tumor, best known for its association with some paraneoplastic syndromes including myasthenia gravis. In this study we retrospectively reviewed Iranian patients, referred to our thoracic surgery and/or oncology departments.
Methods: Retrospectively, the demographic and clinico-pathological data of 55 patients with definite diagnosis of Thymoma were retrieved from their files and subsequently their pathology were reviewed again. All these patients were referred to our institute from different parts of Iran.
Results: In 55 patients, male to female ratio was 1.25(32/21) with mean age 43.13±13.9 years (range 17-75). Most Common presenting symptoms included cough (43.4%), dyspnea (39.6%), myasthenia gravis (20.8%). The other symptoms were weight loss, fever, diaphoresis, chest pain and aplastic anemia. Eighty three percent of tumors were in anterior mediastinum. The majority of patients were regionally invasion or metastasis at the time of diagnosis (stage I: 27.1%, stage IIa: 6.2%, stage IIb: 14.6%, stage III: 29.2%, stage IVa: 20.8, stage IVb: 2.1%). The most common pathologic subtypes were: type A: 11.3%, type B1: 26.9%, type B2: 11.3%, type AB: 17%, type C: 20.8%, type B3: 26.9%, missing data:11.3%. Surgery, radiotherapy and chemotherapy were performed in 55.1%, 39.5% and 30.1% of patients, respectively. Median follow up was 2.86 years. Progression Free Survival (PFS) was 5.75±2.45 years. Log-rank test showed no difference in PFS (P=.394) between invasive and non invasive groups.
Conclusion: We speculate that the most Iranian patients referred to our institute were diagnosed in advanced stages and it could probably translate higher recurrence rate and poorer 5-year survival compare to other reports.
Keyword: Thymoma

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P3.304 EXTRAPLEURAL PNEUMONECTOMY (EPP) FOR MALIGNANT PLEURAL MESOTHELIOMA: WHAT IS THE QUALITY OF LIFE OF SURVIVORS?

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Background: The outcomes of treatment and prognostic factors of our first 70 extrapleural pneumonectomy patients have been reported by Yan et.al 2009. We are now reporting the quality of life of survivors of this group of patients as well those who have since had EPP and are living with or without disease. The study was approved by our local Ethics Review Committee and comprises of a quantitative component followed by a qualitative component.
Methods: The quantitative component consisted of inviting patients to complete quality of life (QOL) questionnaires. The two questionnaires have been proven to be reliable and valid in assessing cancer related QOL. They were The European Organization of Research and Treatment of Cancer (EORTC) QLQ-C30 and LC13and the McGill Quality of Life Questionnaire. The qualitative component consisted of in-depth interviews of patients and carers. A phenomenological methodology was used to transcribe the interviews into text. The text is then interpreted in order to explore the lived experience of recovery following surgery. 21 patients who had surgery between 2003 and December 2009 were invited to participate, however only 14 completed the questionnaires. This data was analyzed in July 2010. Another round of questionnaires was mailed to the same patients in February of 2011 and to a new group of 8 patients who had surgery during 2010 and 2011. The complete data will be analyzed using SPSS Graduate Pack 13.0 in accordance with the

scoring manuals from EORTC and McGill Quality of Life Questionnaire. Taped interviews are taking place. Each interview will be transcribed into text and scrutinized for key concepts from which a number of thematic statements will be derived.
Results: The results of the initial 14 quantitative QOL questionnaires showed that the quality of life of those survivors was comparable to or in some categories better than three other patient groups. One group was living with Mesothelioma without treatment, one group were receiving chemotherapy for Mesothelioma, and the third group were pre-operative patients who were having potentially curative surgery for primary non small cell lung cancer.
Conclusion: This study will enable the voices of patients and carers who are survivors after EPP to be heard. It will provide real patient experiential information, and it is our intention to make this available to new patients who are considering the option of radical surgery to prolong their life.
Keywords: Quality of Life, survivors, Extrapleural pneumonectomy, mesothelioma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.305 TEMOZOLOMIDE IN PATIENTS WITH METASTATIC BRONCHIAL CARCINOIDS

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Background: Malignant bronchial carcinoids are rare neoplasms. Treatment of patients with metastatic disease have thus far been disappointing. A previous study from our center has however indicated that temozolomide as monotherapy might be of value.
Methods: All patients with metastatic bronchial carcinoid treated with temozolomide as monotherapy at our center between 2004 and 2010 (n=34) were included. Ten tumors were typical carcinoids and 14 were atypical carcinoids, whereas 10 tumors could not be classified. Seventeen patients had previously received other chemotherapy combinations. Temozolomide was given on five consecutive days every four weeks. The daily dose for the first cycle was 150 mg/sqm which was increased to 200 mg/sqm during subsequent cyles if well tolerated. Toxicity was evaluable in 29 of 34 patients, and 23 patients had CT scans evaluable by RECIST.
Results: There were no complete responses. A partial response was seen in 4 patients (17%), stable disease in 11 (48%) and progressive disease in 8 patients (35%). Median progression-free survival was 5.5 months and median overall survival was 34.2 months from start of temozolomide and 80.1 months from diagnosis. Bone marrow toxicity was moderate.
Conclusion: Temozolomide as monotherapy shows activity in patients with metastatic bronchial carcinoids. Bone marrow toxicity was moderate. Combinations of temozolomide with other agents (e.g. capecitabine and/or bevacizumab, everolimus) should be further studied in these patients.
Keywords: Temozolomide, Bronchial carcinoid, Chemotherapy

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P3.306 TYPE AB THYMOMA IS NOT A MIXED TUMOR OF TYPE A AND TYPE B THYMOMAS BUT A DISTINCTIVE TYPE OF TYMOMA

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Background: Type AB thymoma is generally regarded as a mixed tumor of type A and type B thymomas in WHO classification. However, the nature of type AB thymoma remains obscure. On the other hand, we previously reported the presence of thymic cortex-specific macrophages named "thymic cortical dendritic macrophages" (TCDM) as scavengers for apoptotic thymocytes in the human thymus. (Immunobiology 213:837, 2008) We recently found that TCDM, as well as thymocytes, are useful micro environmental markers for thymic cortex in studying thymomas. We also found that mature dendritic cells (mDC) are also useful micro environmental markers for thymic medulla. Using

these cells as thymic micro environmantal markers, we investigated the nature of type AB thymoma.
Methods: Formalin-fixed, paraffin-embedded tissues of type A (4 cases), AB (12 cases), and B1 (6 cases), and B2 (5 cases) thymomas were examined by immunohistochemical methods. Monoclonal antibodies against pancytokeratin (CK:AE1/AE3), claudin-1 (CLDN-1), vimentin, epithelial membrane antigen (EMA), CD99, fascin, and HLA-DR were used. TCDM were defined as fascin^{+} HLA-DR^{-} dendriform cells, mDC as fascin^{hi} HLA-DR^{hi} dendriform cells, and thymocytes as CD99^{+} lymphocytes.
Results: In all cases of type A thymoma examined, tumor cells were composed solely of CK^{+} vimentin^{-} EMA^{-} CLDN-1^{+} short spindle cells. TCDM, thymocytes, and mDC were almost completely absent. Type AB thymoma was mixture of type A-like areas, where long spindle cells formed bundles, and type B-like areas, where numerous lymphocytes were densely distributed. In all cases examined, long spindle cells in type A-like areas were CK^{-} vimentin^{+} EMA^{+} CLDN-1^{-} fibroblast-like cells. Type B-like areas were composed of wide cortical areas, where small nondendriform fascin^{dim} TCDM were scattered among numerous thymocytes, and narrow indistinct medullary areas, where several mDC and mature T-cells were compactly distributed. CK^{+} epithelial cells were detected exclusively in type B-like areas, where they were identified as irregularly shaped epithelial cells randomly extending numerous long cytoplasmic projections, and were morphologically different from normal thymic cortial epithel cells (cTEC), which were characterized by narrow cytoplasm and a few slender cytoplasmic projections. All cases of type B1 and B2 thymoma examined were composed of wide cortical areas and conspicuous medullary areas. In cortical areas, fascin^{+} large dendriform TCDM, as seen in normal thymic cortex, were regularly distributed among numerous thymocytes. Immunostaining for CK indicated that tumor cells in type B1, B2 thymoma were closely similar to normal cTEC, but largely different from those in type AB thymoma in morphology.
Conclusion: Type A-like areas of type AB thymoma are composed of certain particular type of epithelial cells with fibroblast-like appearace, whose significance should be discussed. Although type B-like areas of type AB thymoma are not mere lymphocyte-infiltration but thymic organoid, they seem to be immature organoid induced by tumor cells with insufficient function of cTEC. In contrast, tumor cells in type B1 and B2 thymoma have sufficient function to induce mature thymic organoid. Thus, type AB thymoma is not a mere mixed tumor of type A and type B thymoma but a distinct type of thymoma.

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.307 PROTEIN EXPRESSION OF EXCISION REPAIR CROSS COMPLEMENTATION GROUP 1 (ERCC1) AND THYMIDYLATE SYNTHASE (TS) IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) PATIENTS UNDERGOING EXTRAPLEURAL PNEUMONECTOMY (EPP)

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Background: Many studies have demonstrated that high TS expression is significantly correlated with higher proliferative activity of tumour cells, while untreated patients with non-small-cell lung cancer tended to have longer survival if the tumour ERCC1 expression is high. We hypothesised that in patients with MPM undergoing EPP, high ERCC1 and low TS are associated with prolonged survival.
Methods: Consecutive MPM patients, who underwent EPP at Royal Prince Alfred and Strathfield Private Hospitals, Sydney, Australia from 1994 to November 2009 were reviewed in the study. Tissue microarrays were constructed from eligible patients and five 1mm cores per patient were taken. TS and ERCC1 protein expression levels were evaluated by immunohistochemistry using the score derived from the percentage of cells labelled positive. The average scores from evaluable cores were assessed and the median score was used to divide the group. Overall survival (OS) from the

time of surgery was determined by Kaplan-Meier method and results compared by log-rank test.
Results: There were 80 patients in the EPP cohort that had undergone radical surgery: median age 58 years (range 22-74); 79% male; 76% epithelial and 24% biphasic subtype; 25% AJCC stage I-II and 73% stage III-IV. The median OS was 18.2 months (95% CI: 11.8-24.5 months) with 80% of patients deceased at the time of analysis. Nineteen patients received neo-adjuvant chemotherapy, 1 patient received adjuvant chemotherapy and an additional 20 patients received palliative chemotherapy in this series. The median TS score was 10.2 (range 0-91.3) while the median ERCC1 score was 35 (range 0-90). There was no correlation between the TS protein expression and OS (13.7 vs. 21.6 months for low and high TS levels respectively; p=0.32). There was a trend between high ERCC1 protein expression and longer OS (27.6 vs. 10.3 months; hazard ratio [HR], 1.63; 95% confidence interval [CI], 0.98 to 2.70; p=0.06).
Conclusion: In this series of MPM patients who underwent EPP, TS protein expression was not associated with survival, but there was a trend for a longer survival in patients with high ERCC1 expression.
Keywords: malignant pleural mesothelioma, excision repair cross complementation group 1, Thymidylate synthase

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P3.308 TYPE B3 THYMOMA CAN BE SUBCLASSIFIED INTO DIFFERENTIATED, INTERMEDIATE, AND ANAPLASTIC SUBTYPES.

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Background: Thymomas are known to be tumors of thymic epithelial cells (TEC) with variety of histological appearances and difficult to be classified. Type B3 thymoma is morphologically and phenotypically heterogenous, and some of B3-thymomas are difficulte to be distinguished from thymic carcinomas. On the other hand, we previously reported the presence of thymic cortex-specific macrophage named thymic cortical dendritic macrophages (TCDMs) in the human thymus as scavengers of apoptotic thymocytes (Immunobiology 213:837 2008). We recently found that TCDMs, as well as thymocytes (THYs) are frequently present in B3-thymoma in varied numbers. Because thymomas are known to be functional tumors, we consider that distributional patterns of these cells in thymomas reflect some functions of TEC. Therefore, using these cells as functional markers, we attempted to classify B3-thymomas.
Methods: We examined 11 cases of B3-thymomas and 11 cases of thymic carcinomas immunohistochemically. We used monoclonal antibodies against cytokeratin AE1/AE3 (CK AE1/AE3), fascin, CD99, HLA-DR, claudin-1 (CLDN-1), and MIB-1(Ki-67). TCDM is defined as fascin$^+$ HLA- DR$^-$ dendriticform cell and THY as CD99$^+$ lymphocyte. CLDN-1 is a member of tight-junction protein family, and is used as a marker for medullary (m) TEC.
Results: B3-thymomas are subclassified into three groups. The first group (4 cases) were characterized by the presence of relatively large numbers of TCDMs and THYs. Tumor cells were CK$^+$ CLDN-1$^-$ polygonal cells, and relatively large numbers of TCDMs and THYs were scattered among tumor cells. MIB-1 index of tumor cells was around 5% in average. These findings suggest that tumor cells of the first group retain functions of TEC in considerable extent, and we regard this group as differentiated subtype. The second group (2 cases) were characterized by the absence of TCDM and THY. Tumors were composed of CK$^+$ CLDN-1$^+$ small polygonal cells distributed densely, and their MIB-1 index was around 20 % in average. These findings suggest that tumor cells of this group almost lack the functions of TEC, and we regard the second group as anaplastic subtype. The third group (5 cases) were characterized by the presence of a considerable number of TCDMs and a paucity of THYs. Tumor cells were CK$^+$ CLDN-1$^-$ large polygonal cells arranged in epithelioid pattern, and their MIB-1 index was around 5% in average. These findings suggest that tumor cells retain minimal functions of TEC, and we regard the third group as intermediate subtype. In all cases of thymic carcinomas examined, neither TCDM nor THY were detected, and tumor cells were positive for CK and CLDN-1 strongly, and their MIB-1 index was around 32.1% in average.
Conclusion: Because tumor cells of differentiated and intermediate subtypes of B3-thymoma are

thought to retain some TEC-functions, we consider that these tumors should be called "thymoma". Because tumor cells of anaplastic subtype of B3-thymoma thought to lack TEC-functions, it is reasonable to consider that tumors of this type are carcinomas rather than thymoma. The present study also suggested that CLDN-1 is closely associated with malignancy rather than medullary origin in B3-thymomas.

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P3.309 PROGNOSTIC FACTORS IN MALIGNANT PLEURAL MESOTHELIOMA (MPM) IN A COHORT OF PATIENTS COMPENSATED BY THE DUST DISEASES BOARD

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Background: Survival in MPM patients is variable. There are few validated factors that can be used to stratify patients. We aimed to investigate potential prognostic factors in a cohort of MPM patients who received financial compensation from the Dust Diseases Board (DDB), New South Wales, Australia.
Methods: MPM patients applying for compensation at the DDB from March 07 to March 09 were included. After obtaining informed consent, DDB files were reviewed and where necessary, treating physicians and hospitals were contacted for additional information. Overall survival (OS) from diagnosis was determined by the Kaplan Meier method. Prognostic factors under investigation included: age, gender, histological subtype, AJCC stage, duration of symptoms, certainty of pathological diagnosis, the immunohistochemical (IHC) profile, and the neutrophil-to-lymphocyte ratio (NLR) at the time of the diagnosis. The prognostic value of these variables was examined using Cox regression analysis and all factors were entered into a multivariate model to determine their independent effect.
Results: DDB reviewed 270 applications in this time period, of whom 159 consented: median age 71 years (range 45-91); 93% male; 60% epithelial subtype; median NLR 3.5 (87 results available). Median OS was 11.7 months (95% CI: 9.3-14.1 months). The following variables were predictive of longer OS: younger age ($p<0.001$); epithelial subtype ($p<0.001$); lower AJCC stage ($p<0.01$); definite pathological diagnosis ($p<0.01$); typical diagnostic IHC stains ($p<0.01$); and low NLR ($p<0.01$). A multivariate analysis (117 deaths) showed the following variables to be independently associated with prognosis: age ≥65 vs. <65 years (HR 1.8; 95% CI, 1.1-3.0; $p=0.03$); epihelial vs. non-epithelial subtype (HR 0.3; 95% CI, 0.2-0.5; $p<0.001$); an increase in one AJCC stage (HR 1.4; 95% CI, 1.1-1.8; $p<0.01$); and NLR ≥3 vs. <3 (HR 2.0; 95% CI, 1.2 - 3.4; $p=0.01$).
Conclusion: The prognostic significance of recognised factors such as age, histological subtype and AJCC stage was confirmed in this study. These factors should be routinely used for stratification in clinical trials. In addition, NLR, an index of systemic inflammation was independently associated with survival, confirming our previous findings and highlighting the importance of inflammation in relation to prognosis in MPM patients.
Keywords: Malignant mesothelioma, prognostic factor, neutrophil-to-lymphocyte ratio

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P3.310 SURGICAL MANAGEMENT OF LOCO-REGIONALLY RECURRENT THYMOMA

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Background: There is no standard treatment for recurrent thymoma, and it has been mostly palliative therapy. In this article, we retrospectively reviewed our experiences, to discuss efficacy of surgical treatment and adequate extent of resection.
Methods: From January 1997 to December 2007, 15 patients underwent surgical resection for locoregional recurrence of thymoma in Samsung Medical Center. There were 7 male and 8 female

patients. age of patients at recurrence ranged from 23 to 63 years. World Health Organization histological classification of tumor at the initial resection was B1 in 2 patients, B2 in 6, B3 in 3 and C in 4. Complete resection was achieved in 12 patients by pleurectomy (n=11) or extrapleural pneumonectomy (n=1).
Results: There was neither perioperative mortality nor significant immediate postoperative morbidity. As follow-up, physical exam and Chest CT scan was evaluated by 3 to 6 months interval and median follow up duration was 45 month. At now, 10 patients survived with (n=5) or without (n=5) re-recurrence (3-year survival = 84.0%) Survival was significantly superior in patients with complete resection compared with those with incomplete resection. (p=0.008)
Conclusion: Surgical resection must be considered in patients with loco-regionally recurrent thymic epithelial tumor because it can be performed safely, and offer a chance of long-term survival in selected patients. To achieve complete resection, more extended surgery must be considered in multiple pleural metastases.
Keywords: recurrent thymoma, Surgery, Thymic Carcinoma
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P3.311 RITUXIMAB IN PRIMARY LUNG LYMPHOMA

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Background: RITUXIMAB IN PRIMARY LUNG LYMPHOMA Diffuse large B-cell lymphoma primary of the lung (DLBCL-PL) is rare presentation of malignant lymphoma an standard treatment if not available,thus we assess if the additionn of rituximab to conventional chemotherapy can improve the outcome.
Methods: Twenty-eigh patients with DLBLC-PL, previously untreated, age 34 to 63 years, stage IE (20) or IIE(8), low or low-intermediate clinical risk and Germinal center B-cell origen, were treated with R-CHOP(rituximab,cyclophosphamide,doxorubicin, vincristine and prednisone) by 6 cycles
Results: Complete response (CR) was achieved in 26 patients (92%), with a median follow-up of 42.6 months (range:21 to 67 months), actuarial curves at 5-years showed that progression free-survival (PFS) was 84 % and overall survival (OS) was 82 %, these results were better when compared to historical patients treated with CHOP alone: CR: 88%, PFS:64 % and OS: 55 % in 67 patients. Acute and late toxicities were minimal .
Conclusion: The addition of rituximab to conventional chemotherapy in limited DLBCL-PL appear to improve PFS and OS, limited number of patients did limited the performed controlled clinical trials.
Keywords: primary lung lymphoma, rituximab

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.312 PLATINUM AND THIRD-GENERATION ANTICANCER AGENT DOUBLET CHEMOTHERAPY IN FRONT-LINE CHEMOTHERAPY FOR ADVANCED THYMIC CARCINOMA

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Background: Thymic carcinoma is rare malignant mediastinal tumor and definitively distinguished from thymoma because of wide extensiveness and poor prognosis. At present, cisplatin based triplet or quartet with the second-generation antitumor drugs referred to Einhorn's protocol of germ cell tumor are availed in the front-line setting for advanced thymic carcinoma since 1990's. However, no optimal chemotherapeutic regimen is realistically determined and recent small case studies with carboplatin and paclitaxel doublet demonstrate the similar efficacy with less toxicity than those of previous regimens. Also, platinum-doublets chemotherapy is the recommended standard treatment in front-line setting for advanced non-small-cell lung cancer. And efficacy outcomes associated with cisplatin-based and carboplatin-based doublets are almost similar, the decision about which platinum-based doublet to use is based on tolerance. We retrospectively evaluated effectiveness and toxicity of platinum and the third-generation anticancer drugs combination (platinum doublet) for patients with advanced thymic

carcinoma in clinical practice for over nine years in our institution.
Methods: Between January 1, 2002 and January 31, 2011, we identified patients with advanced thymic carcinoma, who treated with platinum and the third-generation anticancer drugs doublet chemotherapy from our database and medical records retrospectively. The objects of this study were set in response rate, disease control rate, progression free survival, and overall survival. We also assessed any significant hematological and non-hematological toxicity.
Results: A total of 13 patients who treated with platinum doublets chemotherapy (cisplatin/irinotecan;10 cisplatin/gemcitabine;1 carboplatin/gemcitabine;1 carboplatin/paclitaxel;1) were identified in the front-line chemotherapy. The clinical response rate was achieved in 61.5 %. The disease control rate was achieved in 92.3 %. The median progression-free survival was 7.9 months (95% CI 1.3–10.0) and median overall survival was 33.8 months (95% CI 8.3–45.9). The toxicity profiles of platinum doublets demonstrated Grade 3/4 hematological toxicities were observed in 2 patients (18%). Grade 3/4 non-hematological toxicities were seen in 2 patients (18%). No febrile neutropenia and toxic death was recorded. The data will be updated in the presentation.
Conclusion: We concluded that platinum doublet chemotherapy is active and tolerable for advanced thymic carcinoma in the front-line setting with regard to efficacy, toxicity, and usage in clinical setting.
Keywords: Thymic Carcinoma, Chemotherapy, Cisplatin, the third anticancer agent

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P3.313 MESOTHLIOMA IN NORTH EAST LONDON: A REVIEW OF SERVICE PROVISION, MANAGEMENT AND OUTCOME

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Background: The North East London Cancer Network (NELCN) has the second highest incidence of mesothelioma in the UK. The NELCN has a population of 1.6 million, who are young and ethnically diverse with high levels of deprivation. The now defunct local asbestos processing factories, large motor manufacturing plants and commercial dockyards have lead to a high incidence of asbestos related lung disease in the region. The 2010 ERS/ESTS guidelines for the management of malignant pleural mesothelioma have subjected the evidence to systematic review. With such a significant change in the evidence based management of this condition it was felt that the network should audit its own service provision and processes.
Methods: Each hospital in the network provided data for mesothelioma diagnosed between 1st April 2009 and 31st March 2010.
Results: There were 52 new cases of mesothelioma in the NELCN over the audit period. Full data was received on 34 patients. Of these patients 91% were pleural and 9% peritoneal. Over 90% was confirmed histologically, 59% via video assisted thoracoscopic (VATS) biopsy; 70% was epitheliod, 9% sarcomatoid. All patients were discussed in a multidiciplinary team meeting (MDT). Just over 50% received chemotherapy, although it was planned in 74%. All patients who had a VATS biopsy had a surgical pleurodesis. At the end of the audit deadline 11/34 patients had died including all patients with sarcomatoid histology. This is in line with NCIM data 2002-2006, with 33-37% dead at 1 year.
Conclusion: NCIN data suggests that despite good compliance with cancer targets, lung cancer patients in North East London have poor survival figures. It is thought that this may be partly due to late presentation with advanced disease. In this audit, only 41% of patients came through a respiratory specialist as a first port of call, and only 35% as urgent cancer referrals. Histology was obtained for 94% of patients via a high number of thoracoscopic biopsies were performed in line with the recent ERS/ESTS guidance. Staging and performance status were well documented. Chemotherapy was offered to three quarters of patients, half went on to have it. In the majority of cases of those who

did not have chemotherapy, the patient was too ill. However in two cases chemotherapy was delayed in order to wait for symptoms. The current ERS/ESTS evidence suggests that early chemotherapy before symptom progression has a better outcome. Port site radiotherapy was given to a third of patients, only those who did not have chemotherapy. This is in line with the BTS 2007 statement, but it is likely that the amount of radiotherapy will fall in future years. The NELCN has a high case load of mesothelioma. Diagnostics are moving uniformly across the network towards early CT biopsy or VATs biopsy. Palliative surgical pleurodseis is common and chemotherapy is being offered to three quarters of patients. Mesothelioma MDTs are operational and assist in optimizing patient pathways.

Keywords: London, outcomes, mesothelioma, service

Poster Session 3 – Mesothelioma, Thymoma and other Thoracic Malignancies Wednesday, 6 July 2011 12:15-14:15

P3.314 RADICAL PLEURECTOMY WITH INTRAOPERATIVE PHOTODYNAMIC THERAPY IN THE TREATMENT OF PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA: TARGETING EGFR AND STAT3 TO ENHANCE LOCOREGIONAL CONTROL

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Background: We have previously shown that with photodynamic therapy (PDT) as an intraoperative adjuvant, the survival of malignant pleural mesothelioma (MPM) patients treated with a lung sparing, macroscopically complete surgical resection (radical pleurectomy, RP) is superior to the survival of similar patients treated with PDT and extrapleural pneumonectomy. However, in this series, the locoregional control of patients treated with RP+PDT was inferior to the locoregional control of patients treated with EPP+PDT. Here, we review our results with an expanded cohort of RP+PDT patients. In addition, we have explored whether targeting Epidermal Growth Factor Receptor (EGFR) and Signal Transducer and Activator of Transcription-3 (STAT3) (respectively expressed in 75% and 79% of MPM) signaling enhances the cancer cell cytotoxicity of PDT and therefore might be a novel strategy to improve locoregional disease control in patients treated with RP+PDT.

Methods: In an Institutional Review Board approved retrospective study RP followed by intraoperative porfimer sodium-mediated PDT (RP+PDT), 38 patients (42-81 yr) with a diagnosis of MPM (31/38 epithelial, 7/38 non-epithelial subtype) were treated from 2004-2009. Treatment and outcome data was reviewed, with locoregional control defined as absence of recurrence in the ipsilateral pleura, lung parenchyma or mediastinal nodes. Cell culture studies were performed using cultured human and murine cancer cell lines and in vitro PDT clonogenic survival assays. Murine tumor experiments were performed with ab12 tumors grown in the flanks of Balb-c mice.

Results: The majority of patients (36/38) had AJCC Stage III/IV disease. Nevertheless, a lung-sparing macroscopically complete RP was achieved in 37/38 patients. At a median follow-up of 18.6 months, the median overall survival has not yet been reached and the 2-year is 72%. In the 21 epithelial patients with N2 metastatic cancer, overall survival was not adversely affected, with a 2-year overall survival of 82%. Despite these excellent results, local control of MPM remains a problem, with 16/19 patients experiencing locoregional failure as a component of disease progression (8 locoregional only, 8 locoregional + systemic progression). In studies of lung and MPM cell lines and tumors, we have found that PDT activates association and nuclear translocation of EGFR and STAT3 and that inhibition of EGFR and STAT3 signaling significantly enhances the cancer cell cytotoxicity of PDT.

Conclusion: In this expanded cohort of 38 MPM patients, we have established that RP+PDT demonstrates an overall survival that is longer than previously published series of similarly staged MPM patients. Nevertheless, local disease progression of MPM remains a major source of treatment failure in these patients. While these results demonstrate the value of PDT for treating patients with this disease who otherwise have few good treatment options, clearly new strategies are still needed. The high

levels of EGFR and STAT3 expression in MPM and the preclinical efficacy of PDT with EGFR and STAT3 inhibition suggest that targeted inhibition of EGFR/STAT3 pathways may improve the locoregional control in MPM patients treated with RP+PDT.

Keywords: photodynamic therapy, malignant pleural mesothelioma, Surgery, intraoperative therapy

Session P4: Poster Session 4

Thursday, 7 July 2011

Poster Session 4 – Early Detection and Screening Thursday, 7 July 2011 10:00-12:30

P4.001 POLISH LUNG CANCER EARLY DETECION TRIAL

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Background: Eight thousands twenty eight individuals with a high risk of developing lung cancer were enrolled into the PILOT POMERANIAN LUNG CANCER SCREENING TRIAL between February 2009 and March 2010. The purpose of this report is the preliminary analysis of the early results.
Methods: The risk group of developing lung cancer was defined as : age 50-75 years, smoking history of at least 20 pack-years without symptoms of the disease. People with family history of lung cancer and occupational exposure to carcinogens were enrolled with a history of 10 pack years. Low dose computed tomography (LDCT) was performed in 8028 individuals between January 2009 and March 2010 . Enrollment to the trial was done via hotline, website and by the medical staff. I-ELCAP screening protocol was applied for the screnning. Patients with detected nodules in LDCT were subjected to consecutive LDCT examinations based on tumor diameter (<5 mm, 5-10 mm and >10 mm).
Results: A high rate (53% - 4257) of positive CT results was observed. Two thousands and nineteen (47,4%) nodules less than 5 mm, 1884 (44,3%) with diameter of 5-10 mm and 354 (8,3%) with diameter of more than 10mm were detected. In 265 individuals the diagnostic work-up was employed. Within the group of 94 surgically treated patients 59 lung cancers were diagnosed. 63 lobectomies (23 VATS - %), 1 segmentectomy, 21 wedge resections and 6 tumorectomies were performed. Fifty (84,75 %) operated patients were in stage I, 4 (6,78%) in stage II, 5 (8,47%) in stage III.
Conclusion: Lung cancer screening with LDCT allows to detect lung cancer in early, curable stage, thus allowing implementation of minimally invasive surgical techniques. The incidence of pulmonary nodules is relatively high and requires follow up.
Keyword: Lung cancer, Early diagnosis, Screening, Computed tomography

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P4.002 DETECTION OF SINGLE TUMOR MAKER FOR EARLY DIAGNOSIS OF LUNG TUMORS THROUGH COMMON FRAGMENT SEQUENCE IN MULTIPLE LUNG TUMOR MARKERS.

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Post Graduation Study/Pakistan

Background: Lung cancer is currently the most frequently diagnosed major cancer in the world and the most common cause of cancer mortality worldwide. An early diagnosis at stage Ia or Ib have very good prognosis in the treatment regimes. Different tumor markers are in clinical practice or clinical trials for the early detection of lung tumors.
Methods: It is a review in which we will discuss the structural common fragment of current tumor markers of lung carcinoma to attain a common amino acid sequence as a single tumor marker for lung carcinoma diagnosis at stage Ia and Ib.
Results: Different lung tumor maker are studied for their structural fragment which can be concluded as single common sequence in multiple tumor markers to achieve a single marker which have more specificity and sensitivity. The tumor makers CYFRA 21-1, PGP9.5, BAX, $p16^{INK4A}$, HER-2/neu, Fucosyl-GM_1, Pro-Gastrin-Releasing Peptide (31-98), ADAM8, Angiopoietin-2 are compared for their structural sequences. These all tumor markers showed some structural common fragments but a specific common serological fragment is seems to be more realistic in the structural resemblance of antibody.

Conclusion: Although different lung tumor markers have some common molecular sequences but these sequences need further verification for the hypothesis of common fragment detection on serological test. But an antibody titer can be more appropriate as common tumor marker through the common fragments of above mentioned lung tumor markers.
Keyword: Tumor marker, CYFRA 21-1, PGP9.5, BAX, p16INK4A, HER-2/neu

Poster Session 4 – Early Detection and Screening Thursday, 7 July 2011 10:00-12:30

P4.003 ASSESSMENT OF HOGG1 SER326CYS POLYMORPHISM AND DNA DAMAGE IN HEAD AND NECK SQUAMOUS CELL CARCINOMA IN NORTH INDIA

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Background: Head and neck squamous cell carcinoma(HNSCC) is the sixth most common cancer world wide. In India, it accounts for 21 % of total cancer burden and here we tested the role of hOGG1 ser326cys polymorphism and oxidative DNA damage in HNSCC patients in North India. hOGG1 8-oxoguanine DNA glycosylase , one of the key members of Base Excision DNA repair pathway , eliminates the mutagenic base oxidation product 8-oxoguanine, which is produced as a result of exposure to reactive oxygen species. Pan masala, gutka , khaini , bhidi and cigarette are commonly used in North India which could account for a higher incidence of HNSCC cases. These tobacco products have clastogenic and carcinogenic effects and are capable of generating free radicals during auto oxidation of polyphenols in saliva of tobacco users. Salivary cells are the first to encounter various environmental products that soon reach the various body organs via blood.
Methods: Genomic DNA from human salivary cells and whole blood of 40 controls and equal number of HNSCC cases was isolated and the polymorphism of hOGG1 was studied by PCR-RFLP method . Blood and salivary DNA adduct (8-OHdG) was measured by ELISA base colorimetric assay.
Results: The results indicated no difference in hOGG1 polymorphism in both blood and saliva samples. However, more apurinic sites was evident in salivary DNA adduct(8-OHdG) than in blood. Direct interaction of salivary cells to tobacco product exposures could be one of the reasons.
Conclusion: Conclusion: The study suggests that salivary DNA adduct is a better indicator of DNA damage in HNSCC patients. The result also suggests that DNA adduct (8-OHdG) is more predominant in oral reason that neck region.
Keywords: OGG1, 8-OHdG, polymorphism, saliva

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P4.004 MANAGING LUNG CANCER : SHIFT IN STRATEGY

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Background: Elderly patients of Lung cancer provide challenging situation for oncologists. We undertook this two year old project targeted at geriatric cancer patients from rural/ tribal India. Since geriatrics specialty is unheard of in rural India, we decided to address this burning issue of geriatric Lung cancer patients. A standardized geriatric evaluation is essential for the multidisciplinary approach of cancer Rx in patients with Lung cancer. In developed nations geriatric as well as an oncological evaluation are mandatory to offer to these patients the best therapeutic option and improve their prognosis as well as their quality of life. But this facility is a luxury in Asian/African nations. Hence our Cancer NGO team evaluated frailty and suggested plan to include it in lung-cancer care of rural health set-up.
Methods: 6 tertiary care hospitals and two NGOs included in study. 64 healthcare providers given questionnaire on needs of geriatric cancer patients, their needs. 132 terminally ill geriatric Lung cancer patients with a life expectancy of 2 yrs were interviewed/evaluated by Geriatric Depression Scale used for the geriatric evaluation. A standardized geriatric evaluation is essential for multidisciplinary discussion of elderly patients with Lung cancer. A geriatric as well as an oncological evaluation are mandatory to offer to these patients the best therapeutic option and improve their prognosis as well as their quality of life Patients were asked to mark cancer care as satisfactory or non-satisfactory and asked to rate incidence/severity of depression

on diagnosis of Lung-Ca. Due to enormity of project we had initially taken frailty/depression as primary parameter for evaluation. Then responses of cancer service providers were rated against suggestions given by patients.
Results: 132 patients over 2-year period. mean age 58.2 ± 3,6 years old), 82% male, 18% females. 72% subjects had symptoms of cognitive disorder [Folstein MMSE]. The mini-GDS used to detect depression, was positive in 72% of the evaluations. We can clearly identify frailed patients (72%) who did not received any counseling/psychotherapy. 86% patients pointed to lack of psycho-social care. counseling as major lacunas in current set-up. Inadequate patient education on nutrition, social support and absence of trained psychologist were mentioned as dominant factor in responses by 64 healthcare providers who participated in our project. We present our NGO project finding in printed chart-form at 14th WCLC-2011 conference, Amsterdam.
Conclusion: Our two year on-hand experiences clearly show need and benefit of close collaboration between geriatricians and oncologist. Sadly counseling/geriatric care is virtually non-existent in India. In daily management of elderly patients, alteration are needed in 72% of patients by geriatric assessment. We need strong platform like IASLC-2011-conference to show our findings to researchers/activists from developed world and get their guidance on this difficult issue. Government must carry out supportive-care-programmes with NGO-counselors to bring down incidence of frailty/depression in thoracic cancer patients.
Keywords: counseling, psychotherapy, Lung cancer

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P4.005 LOW-EXPRESSED RIN1 INDICATED POOR PROGNOSIS AND NEGATIVELY-CORRELATED WITH SNAI1 IN NSCLC

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Background: The RAS effector RIN1 activates ABL tyrosine kinases and RAB5 GTPases to regulate cytoskeletal remodeling and endocytic pathways that promote normal epithelial functions. Silencing of RIN1 leads to increased motility of epithelial cells. Onco-protein Snai1 inhibits the expression of RIN1 in transcriptional level. In breast cancer, RIN1 inhibits the initiation and progression of tumorigenesis, but in lung cancer cells, high-expressed RIN1 stimulates the cell proliferation.
Methods: Real-time PCR and Western blot assays were performed to detect the expression of RIN1 mRNA and protein in Non-small cell lung cancer tumor tissues (TT) and matched tumor-free tissues (TF) and the association with clinical pathological characteristics including survival data was analyzsed. The expression of Snail protein was also explored.
Results: In total 140 patients, the levels of RIN1 mRNA was down-regulated (less than 50%) in 81 patiens (58%), and up-regulated (more than 2-fold) in 29 patients (21%). The levels of RIN1 protein were down-regulated in 74% patients and up-regulated in 26% patients. Correspondently well, Snail protein levels were up-regulated in 81% patients and down-regulated in 19% patients. Moreover, the poor RIN1 mRNA expression was closely correlated with higher pathological N-stage ($P = 0.004$), poorer pathological TNM stage ($P = 0.008$) and significantly shorter progression free survival.
Conclusion: The expressions of RIN1 mRNA were down-regulated in the majority of NSCLC, and low-expressed RIN1 indicated advanced stage and poorer prognosis. The expression of RIN1 protein was also down-regulated in the majority of NSCLC, and negatively correlated to Snai1 protein well. RIN1 may act as tumor suppressor in NSCLC.
Keywords: RIN1, SNAI1, Prognosis, Non small cell lung cancer

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P4.006 UNITED KINGDOM LUNG CANCER SCREENING (UKLS) TRIAL

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Background: Lung cancer kills more people worldwide than any other malignancy. Currently 33,500 individuals die each year in the UK from lung cancer. Screening patients before they develop symptoms is a control measure urgently requiring evaluation as early surgical resection offers the best chance of cure. The overall aim of UKLS is to provide data required for an informed decision about the desirability of introducing population screening for lung cancer in the UK. This involves establishing the impact of screening on lung cancer mortality, determining the best screening strategy, assessing physical and psychological consequences and determining health economic implications of screening. The UKLS pilot trial starts in 2011. It will randomise 4,000 high risk patients identified by the Liverpool Lung Project (LLP) Risk Prediction Model. If progression criteria are met, and funding available, we plan randomising a further 28,000 subjects from seven centres in the UK. Subjects are selected if they have a 5% risk of developing lung cancer over 5 years as predicted by the LLP risk model.
Methods: The "Wald Single Screen" Design (Baldwin et al 2011) has been chosen for the UKLS trial. Individuals meeting the inclusion/exclusion criteria will be sent invitations to participate and selected on the basis of the LLP risk questionnaire (Cassidy et al 2008). Before consenting, participants are shown a DVD and offered the opportunity to ask questions. After consenting, the research nurse will undertake spirometry and the participant asked to provide blood, buccal swab, nasal brushings and sputum samples and to complete baseline lifestyle, psychosocial, and health economic questionnaires. Consenting participants are randomised to receive a single low dose Computed Tomography (CT) scan on the study arm or usual care on the control arm. Both arms will be followed-up for lung cancer incidence and mortality, psychosocial consequences, and health economic implications. Individuals with a smoking history will receive smoking cessation advice.
Results: Establishing and maintaining accurate CT interpretation is crucial for the trial's success. CT scans will be read locally and centrally (double reading) optimising the sensitivity and specificity of CT screening. UKLS employs volumetric analysis, where possible, with a single initial screen design. Follow-up includes repeat CT for indeterminate nodules and calculation of volume doubling time. Mortality will be measured after 10 years of follow-up. This modelling has resulted in the development of the UKLS care pathway to manage identified abnormalities (Baldwin et al 2011). The pilot study aims to optimise reporting methods including investigating efficacy of different methods of training observers and appropriateness of radiologists versus non-radiologists as local readers.
Conclusion: The aim of the main UKLS trial is to demonstrate a mortality advantage of 30 percent and cost effectiveness in the UK. This project was funded by the NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series. Visit the HTA programme website for more details to project page. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.
Keywords: lung cancer screening, Wald Single Screen Design, CT screening

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P4.007 THE LUCED TEST FOR DETECTION OF EARLY LUNG CANCER: A CRITERION TO COMPLETE THE TEST WITH HIGH SENSITIVITY

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Background: The Cell-CT imaging platform produces 3D volumetric cell images based upon computed tomography as shown in the figure. The Cell-CT's cell-by-cell morphological analysis in 3D overcomes obscuration issues and biases associated with perspective and focal plane selection

inherent to slide imaging and 2D analysis. Thus, regression of 3D cell features to expertly identified cell type produces a classifier that almost perfectly distinguishes cancer from normal cells. This Cell-CT classifier forms the basis of VisionGate's LuCED test to triage the population at high risk for lung cancer to X-Ray CT for tumor localization and treatment. Since LuCED evaluates mostly normal cases, a criterion is needed to determine when to discontinue analysis of additional cells while preserving high sensitivity for cases with diagnostic (dysplasia and cancer) cells. This criterion can be found by assessing the prevalence of diagnostic cells and other normal epithelial cells in sputum. These results are presented here.

Methods: Specimens were obtained from an FDA phase III trial to assess a sputum expectorant. Patients were enrolled based on high likelihood of lung cancer and contributed spontaneous and/or induced sputum. Cancer presence and type was established through biopsy 120 days after the trial completion. A portion of each sputum was stained and deposited on a slide. These slides were scanned by a cytotechnologist to produce counts of various cell types. Results were analyzed to determine the proportion of diagnostic cells to normal epithelial cells. 147 patients comprised our study group that produced 180 specimens with diagnostic cells. Sputum from 44 patients with adenocarcinoma, 68 with squamous cancer, and 68 with other types of lung cancer were analyzed.

Results: Statistical characteristics of diagnostic cells and normal epithelial cells were assessed across many sputa to determine a criterion to terminate the LuCED test. Results show that 90% of the sputum specimens have at least one diagnostic cell per 100 epithelial cells irrespective of tumor type.

Conclusion: Our results show that analysis of sputum by the LuCED test should proceed until 100 epithelial cells have been examined. Doing so establishes an efficient way to discontinue LuCED sputum processing for normal cases, and ensures that the patient is forwarded for additional testing if the sputum contains diagnostic cells.

Keywords: Lung cancer, Early Detection, 3D, Optical Projection Tomography

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P4.008 EFFECTIVENESS OF CHEST X-RAY SCREENING FOR LUNG CANCER IN SMOKERS. A POPULATION-BASED COHORT STUDY IN VARESE, ITALY

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Background: The effectiveness of screening for lung cancer (LC) on a population level is unknown. In this study the effectiveness of chest x-ray (CXR) screening offered to a population-based cohort of smokers was estimated by the LC standardized mortality ratio (SMR).

Methods: In July 1997 all the asymptomatic cigarette ever smokers of more than 10 pack-years, aged 45-75 years, of both genders, registered in the medical records of 50 National Health Service (NHS) general practitioners of the Varese Province (Italy), were invited to annual CXR screening for four years, free of charge. The further eligibility criteria were: subjects without diagnosed or suspected LC and fit for thoracic surgery. Overall 5,815 smokers were invited to the screening (median 32.8 pack-years) and formed the population-based cohort of this study. 21% of the cohort (1,244 subjects) self-selected to participate in screening, undertaking the baseline CXR exam in the years 1997-2001 median 3 screening rounds instead of the five expected); 79% (4,571 subjects) did not participate. The cohort received NHS usual care, with addition of screening CXR to participants. The cohort was followed-up until December 2006, all LC deaths being recorded. We estimated the LC SMR of the cohort in the eight-year period 1999-2006, based on the LC mortality recorded in smokers in the Varese Province (reference population) receiving NHS usual care, matched by location, age, gender, smoking history and calendar period.

Results: In the period 1999-2006 the annual LC mortality progressively decreased in the cohort

compared to the mortality observed in the reference population; cumulatively the LC deaths observed in the cohort were 172 in comparison to 210 expected on the basis of the reference population. The LC SMR was 172/210=0.82 (95%CI 0.67-0.99; p=0.048), showing 18% reduction of LC mortality in the study cohort.
Conclusion: In a population-based cohort of ever smokers the specific LC mortality decreased significantly after implementation of CXR screening.
Keywords: chest x-ray (CXR) screening, smokers, population-based study, standardized mortality ratio

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P4.009 GROUND-GLASS NODULES DETECTED BY CT LUNG CANCER SCREENING: RESULTS OF AN EVALUATION OF PROGRESSION DURING A 5-YEAR FOLLOW-UP PERIOD

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Background: To evaluate the progression of ground-glass nodules (GGNs) during a 5-year follow-up period after detection by computed tomography (CT) lung cancer screening.
Methods: During 2004, 3606 individuals underwent a low-dose CT lung cancer screening examination at the Research Center for Cancer Prevention and Screening. A total of 166 screenees in whom at least one GGN equal to or larger than 5 mm in diameter had been detected were followed-up in our clinic. Follow-up CT scans were generally performed at three months and nine months after the baseline CT scan, and then every year thereafter except in the event of GGN progression. The GGNs were classified into four types according to changes in size and attenuation: a growing type, in which the size of the GGN increased regardless of whether there was an increase in GGN attenuation, or, in which a solid component(s) developed regardless of whether there was an increase in GGN size; a shrinking type, in which the size of the GGN decreased regardless of whether there was an increase in GGN attenuation; a fluctuating type, in which the size of the GGN increased, but later decreased, and then increased again; and a stable type, in which the size and attenuation of the GGN were stable.
Results: CT screening detected 258 GGNs equal to or larger than 5 mm in diameter (mean size, 6.9 mm; range, 5-20 mm) in 95 females and 71 males (mean age, 59.8 years; range, 41-78 years). The median follow-up period was 69 months (range, 16-80 months). During follow-up, 29 GGNs (11.6%) in 27 patients (16.8%) increased in size (growing type), eight GGNs (4.8%) in eight patients (4.8%) decreased in size (shrinking type), one GGN (0.4%) had decreased in size at six months after having increased in size and in attenuation (fluctuating type), and 220 GGNs (85%) in 130 patients (78%) remained stable (stable type). Five of the 29 growing-type GGNs had been resected by October 2010. The histopathological diagnosis was invasive adenocarcinoma in four of them and adenocarcinoma in situ in one.
Conclusion: The natural history of some of the GGNs detected by CT screening was revealed during a 5-year follow-up period, and the results showed that 85% of the GGNs equal to or larger than 5 mm in diameter had remained stable. A limitation of this study is that the diagnosis of only 2% of the GGNs has been determined pathologically.
Keyword: lung, ground-glass nodule (GGN), CT, screening

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P4.010 THE ROLE OF A CONVENTIONAL BRONCHOSCOPY IN THE WORK-UP OF SUSPICIOUS CT SCREEN DETECTED PULMONARY NODULES

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Background: The objective was to investigate prospectively the diagnostic value of a conventional white-light bronchoscopy in the Dutch-Belgian lung cancer screening trial; and to determine whether a bronchoscopic evaluation could be eliminated form the standard work-up of a suspicious pulmonary nodule. The cost-effectiveness of a screening program could be enhanced and the potential harms of a bronchoscopy avoided.
Methods: All consecutive participants with a positive test result between April 2004 and December 2008 were enrolled. The diagnostic sensitivity and negative predictive value (NPV) were calculated at the level of the suspicious nodules. Gold standard for the outcome of the bronchoscopy was in 95% of the nodules based on the surgical resection specimens.
Results: A total of 318 suspicious lesions have been evaluated by bronchoscopy in 308 subjects. The average diameter was 14.6 mm (SD: 8.7) and only 2.8% of nodules were > 30 mm in diameter. The sensitivity of bronchoscopy was 13.5% (95% confidence interval (CI): 9.0%-19.6%), the specificity was 100%, the PPV was 100% and the NPV was 47.6% (95% CI: 41.8%-53.5%) Of all cancers detected, 1% was detected by bronchoscopy only and retrospectively invisible on both low-dose CT and CT with intravenous contrast.
Conclusion: Conventional white-light bronchoscopy should not be routinely recommended for test positive participants of a lung cancer screening program.
Keywords: bronchoscopy, lung cancer screening, Pulmonary nodule, Tomography, Spiral Computed

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P4.011 COMBINE CYTOLOGY AND FLUORESCENT IN SITU HYBRIDIZATION (FISH) OF SPUTUM CELLS FOR EARLY DETECTION OF LUNG CANCER

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Background: Lung cancer is difficult to detect in its early stages and therefore has a poor prognosis. The treatment of early-stage tumors is more effective. Low-dose spiral CT is capable of detecting lung neoplasms in asymptomatic individuals however, it suffers from low specificity which forces unnecessary biopsies or surgery for diagnosis. Some of the genetic changes associated with lung cancer development were shown to be expressed in exfoliated cells in sputum. In pervious studies combination of cytology and genetic analysis of two FISH biomarkers located at 3p22.1 and 10q22.3, proved to be sensitive and specific even in early-stage lung cancer.
Our hypothesis is that combination of cytology and FISH in induced sputum samples, will lead to the development of an effective aiding tool for early detection of lung cancer in patients with suspicious radiological findings.
Methods: Induced sputum was collected from lung cancer and high-risk (i.e. heavy smoker, COPD) patients and healthy non-smoking controls (3, 19 and 5 respectively).
All high risk patients were screened by low-dose CT and followed-up 12 month later. If suspicious nodules were found at baseline CT, an additional CT scan was performed 3 months later. Biopsies were performed if indicated.
Cells were isolated from sputum, stained in Papanicolaou, scanned and analyzed using automated scanning station (Duet™ BioView Ltd, Rehovot, Israel), allowing the analysis of the same cell under two different staining **Methods:** morphology and FISH. During the morphology scan, "Target cells", cells derived from the lower airways and the lungs, were selected. Subsequently, cells were hybridized to a 3-color probe mixture containing two locus-specific probes (located at 3p22.1 & 10q22.3) and a centromeric 10 probe. Then, the slides were scanned again and target cells were relocated and analyzed by their FISH pattern.
Results: The FISH results were compared to the clinical diagnosis based on the CT findings. Genetic abnormalities detected from lung cancer patients were significantly higher than in healthy controls (15.04 and 4.62 respectively, P=0.0001).
Four lung cancer patients were tested – 3/4 were diagnosed prior to the CT and 1/4 was diagnosed by the CT. All patients were identified correctly by FISH (100% sensitivity).
1/23 non-cancer patients had false-positive FISH result (95% specificity). This patient was also highly suspected for cancer by CT but the presence of cancer was ruled out in biopsy.
In 7/19 high-risk patients, suspicious nodules were

found at baseline CT. Final diagnosis confirmed cancer in one patient and ruled out the presence of cancer in the other six. The FISH identified correctly the cancer patient and ruled out 5/6 negative patients.
Conclusion: The combined analysis using morphology and biomarkers for chromosomes 3p22.1 and 10q22-23 was found to be a highly sensitive and specific. The test was able to diagnose or rule-out the presence of cancer in patients with suspicious radiological findings. These preliminary results imply on the potential of using this assay as a non-invasive test for early detection of lung cancer as an adjunct method to the currently accepted CT scan and need to be further validated.
Keywords: Biomarkers, Induced Sputum, Non-invasive testing, fluorescence in situ hybridization

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P4.012 AWARENESS OF LUNG CANCER SCREENING AMONG MEDICAL STUDENTS AT THE UNIVERSITY COLLEGE HOSPITAL, IBADAN

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Background: Worldwide, lung cancer is the most common cancer and the leading cause of cancer related mortality. In Nigeria, lung cancer is rising and patients are relatively younger and often with more advanced disease at presentation compared to developed countries. These poorer prognostic factors make cancer prevention and treatment a priority. This study therefore assessed the knowledge of lung cancer screening and treatment modalities among medical students.
Methods: A cross sectional study was carried out among 302 clinical students of the University of Ibadan. Respondents were chosen using a stratified sampling method. Information was obtained from participants using semi structured, pre-tested self administered questionnaires. Data on respondents' knowledge of lung cancer, screening measures for lung cancer and treatment modalities were collected. Data were summarized using proportions, and χ^2 test was used to explore associations between categorical variables. Level of statistical significance was set at $p < 0.05$.
Results: Majority of the respondents were males (65.9%) and the mean age was 22.45± 1.91 years. Two hundred and five (67.9%) had adequate knowledge of the definition, causes and symptoms of lung cancer. Over half (77.2%) knew lung cancer was preventable however, only 31% were aware of lung cancer screening tests. X-ray was recognised by 55.6%, CT scan by 69.2%, and MRI by 57.6% as lung cancer screening tests. The recognised treatment modalities were palliative care (83.1%), surgery (71.9%), and chemotherapy (78.8%). Those in final year had better knowledge of lung cancer ($p<0.005$). Respondents that knew of lung cancer screening tests were aged 25 years and above ($p<0.05$). Age, sex, religion and level of study had no significant association with knowledge of lung cancer screening test ($p>0.005$).
Conclusion: Majority of medical student were knowledgeable about lung cancer however a few could identify the screening tests for lung cancer. Further educational efforts should be targeted towards the training of this group to be able to give adequate care to their patients.
Keywords: Lung cancer, Screening, University College Hospital

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P4.013 EARLYCDT(TM)-LUNG TEST: AUDIT OF THE FIRST 1000 PATIENTS IN CLINICAL PRACTICE

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Background: EarlyCDT-Lung measured autoantibodies (AABs) to a panel of six tumor associated antigens (TAAs) (p53, NY-ESO1, CAGE, GBU4-5, Annexin1 and SOX2) with a specificity of 90% and a sensitivity of 40% for lung cancer in clinical validation studies. We report on the first 1010 patients in clinical practice who have taken the EarlyCDT-Lung test.
Methods: One thousand and ten (1010) patients in North America at high risk of lung cancer, on the basis of age and smoking history, had EarlyCDT-

Lung measured (start date May 2009) from 293 centers across 40 states and signed a HIPAA release agreeing to their clinical information being accessed as part of this prospective audit. For patients with a positive test their physician was contacted to establish what course of action had followed the test and regular contact maintained until a definitive decision had been made. For patients with a negative test the physician was contacted after 6 months and 18 months to ascertain if the patient had developed a cancer; in the interim if a patient's physician pro-actively provided such information this was recorded. For patients submitting samples in the first 12 months the 6 month follow up is 98%.

Results: Of the 1010 patients, 26 (2.6%) have been diagnosed with lung cancer of whom 10/26 were positive for EarlyCDT-Lung giving a sensitivity of 38.5%. Of the 10 lung cancers positive for EarlyCDT-lung two were stage 1A non-small cell lung cancer (NSCLC) both of which were resected. A total of 173/1010 patients were positive for EarlyCDT-Lung giving a specificity of 82.9%; for the first and second 500 samples the figures were 81.7% and 84% respectively.

In this prevalence round 10/173 positive EarlyCDT-Lung tests have a lung cancer giving a PPV of 5.8% (1 in 17.3). In patients with EarlyCDT-Lung negative tests 16/837 (1.9%) were found to have a cancer (i.e., 1 in 52.3). This represents a threefold difference in the risk of lung cancer. Of the 837 EarlyCDT-Lung negative samples 821 did not have a lung cancer diagnosed (98.1%).

Conclusion: This is the first reported data of EarlyCDT-Lung being used in clinical practice. The results are consistent with the extensive validation datasets previously published on this test with sensitivity for NSCLC at least as high as in the validation studies, including early stage disease. A positive test for EarlyCDT-Lung carried a threefold difference in risk of lung cancer in this population. These figures take no account of occult lung cancers which may present over the next few years as cancers have been shown to stimulate a cancer antigen specific autoimmune response up to 5 years before detection by current imaging methods. Any "yet to present" cancers will likely increase sensitivity and specificity for this cohort. This information can/could be used to help stratify high risk patients in diagnostic algorithms.

Keywords: antigen, Lung cancer, biomarker, autoantibodies

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P4.014 EARLY INDICATORS OF MORTALITY IN ASBESTOS WORKERS

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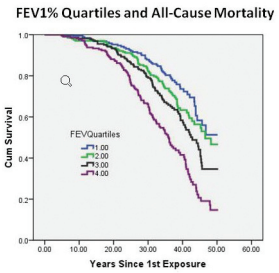
Background: From 1954 to 1972 an asbestos pipe insulation manufacturing plant was operated in Tyler Texas, USA. A cohort of approximately 1100 men were exposed to intense levels of amosite asbestos dust. Exposure duration ranged from one day to 20 years, with most of the men exposed only a few months. This cohort has been followed intensively since 1976 as part of the Tyler Asbestos Worker Program. This presentation looks at the relationship of early clinical findings in this heavily exposed group and their subsequent mortality experience during the 50 years since opening of the plant.

Methods: In 1976 the Tyler Asbestos Workers Program was charged with identification of all individuals exposed at the manufacturing plant and offering them screening with fulmonary function testing, sputum cytology and chest radiographs. In 2003 we attempted to establish the current vital status of all the workers examined by the surveillance program. Death records were obtained from the National Death Index and various state Bureaus of Vital Statistics. Cause of death was reviewed independently and coded by the International Classification of Disease Code, version 9 (ICD-9) by two occupational epidemiologists. Conflicting results were resolved by concensus. Data analysis was performed by Kaplan-Meier survival curves and Proportional Hazards regression, for three specific outcomes: lung cancer mortality, non-lung cancer mortality and all cause mortality. The regression tested the relationship between mortality and the early clinical findings while adjusting for confounding variables such as age, race, smoking and exposure history. The men were examined multiple times during the program, but this analysis uses the clinical results from the first four examinations conducted in the 1970s. Sputum results were dichotomized into moderate atypia or worse versus normal, squamous metaplasian or mild atypia. Radiographic findings were collapsed into

any asbestos related abnormalities and any pleural abnormalities.
Results: Of the 1130 men identified and examined in the program 513 deaths were documented up to 2004; 76 of the deaths were due to lung cancer, 437 were due to other causes. The analysis found that all three of the clinical modalities, cytology, radiology and spirometry, were significantly associated with the long-term mortality outcomes. Pulmonary function testing and sputum cytology were significantly associated with lung cancer and all cancer mortality, $p < 0.002$. Radiographic findings were also associated with lung cancer and all-cause mortality, but less significantly so than cytology and pulmonary function, $p < 0.05$. Only pulmonary function was significantly associated with non-lung cancer mortality, $p < 0.001$. FEV1% was the most consistent early clinical finding related to mortality. This is illustrated in the figure which shows the relationship of FEV1% quartiles to all-cause mortality. Quartile #1 is the highest quartile, #4 is the lowest.



Conclusion: Pleural changes in chest radiographs, moderate sputum atypia or worse, presence of ferruginous bodies in sputum, and decreased pulmonary function (especially FEV1) are each significantly related to subsequent mortality. Early screening with these clinical measures may help identify those workers at highest risk of dying from lung cancer and other diseases.
Keywords: asbestos, sputum cytology, Pulmonary function, mortality analysis

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P4.015 PREVALENCE OF CENTRAL TYPE SQUAMOUS CELL CARCINOMA OF THE LUNG IS DECREASING IN HEAVY SMOKER

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Background: Cigarette smoking is well known to be the cause of lung cancer especially squamous cell and small cell type. The abnormal epitheliums that show to be the precursor of squamous cell carcinoma are demonstrated in central bronchus and correlated with history of smoking. Reported adenocarcinoma cell type of lung cancer is growing in its prevalence and overcome the prevalence of squamous cell type in some area. This study aims to find the prevalence of early lung cancer and cell type in heavy smoker risk population.
Methods: Population were anyone who smoked cigarette more than 20 pack-year, aged more than 40 -year-old and did not have active pulmonary infection or previous diagnosed of lung cancer. The initial screening for lung cancer were chest X-ray and sputum cytology. If abnormal cell was found by sputum cytological examination, high resolution computerized tomography of the chest and autofluorescence bronchoscopy were performed. The final diagnosis was made from any significant abnormality found.
Results: There were 171 participants. All except one were male. Their mean age and amount of pack-year were 56.6(SD 9.9) and 51.1(SD25) respectively. Sixty had positive sputum cytology. The autofluorescence bronchoscopy could find abnormal lesions in average 3.1lesions per person. Most of the pathology result of these lesions was squamous metaplasia. Stage 4 peripheral type adenocarcinoma lung cancer was found in one participant. No squamous cell carcinoma in situ and squamous cell carcinoma were found.
Conclusion: The prevalence of lung cancer was 0.6%. There were no carcinoma in situ or squamous cell carcinoma found in this study. The prevalence of central type lung cancer was decreased in smoker. The suspected reasons included the different compositions and manufactured of cigarette. This finding needs confirmation in larger population.
Keyword: central type squamous cell carcinoma of the lung

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P4.016 PATTERNS OF MALIGNANT DISEASES'S TREND IN GEORGIA

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Background: 7 000 new cases of cancer are reported annually in the country. A vast majority of the cases are primarily detected and diagnosed in the advanced stage (IV - incurable). Taking into account the severe economic conditions in the country for over the past two decades it presented an interest to determine structure, trend and stages of malignant diseases in order to make appropriate changes in the strategy and tactics of the malignant diseases' control and prevention program.
Methods: Descriptive epidemiological study was conducted. Trend of malignant diseases was analyzed for the past two decades from 1988 to 2009. Surveillance data and medical records of primarily diagnosed cases were reviewed. Structure of malignant diseases was determined by site and sex. Incidence rates were calculated by age and sex for all and leading malignant diseases. M/F ration was calculated for all malignant diseases. Statistical tests were employed for statistical significance of the results.
Results: During the first five years of the analyzed period incidence rates of all malignant diseases were high ranging between 119.5 and 143.0 per 100 000 population. Beginning from 1984 morbidity with all the malignant diseases declined significantly, mean incidence rate composed 93.5 (range 60.1 – 101.8). An upward trend was observed since 2001. Incidence rate began to increase gradually and in 2005 it exceeded the highest level, observed in 1988 (136.8 per 100 000). The same patterns of the trend were characteristic for the diseases in men and women. No statistically significant changes were determined in incidence rates by sex, although more cases were observed in male than in female subjects. According to the structure by sex and tumor site, breast cancer in women and respiratory tract (brunches, trachea and lung) cancer in man and colorectal cancer – in both were found to be mainly spread malignant diseases. An upward trend of the advanced cases was observed in all three leading diseases. It was rather dramatic with regard to respiratory tract cancer than with breast cancer and colorectal cancer. For instance, if in 1990 proportion of advanced cases of respiratory tract cancer in men was 43.4%, in 2009 – it reached 67.1%, as for breast cancer in women - proportion of the advanced cases increased from 6.5% to 23.3%. IV stage of colorectal cancer in both sexes increased – from 25.4 % to 45.0% accordingly. The most vulnerable ages were from 45 to 70. Over two fold increase in lung cancer cases in men have been observed in the age group 45-49 for the last three year.
Conclusion: 1. An upward trend of malignant diseases has been observed. 2. Respiratory tract (brunches, trachea and lung) cancer in man and colorectal cancer are mainly spread malignant diseases. 3. Significant proportion of the primarily detected cases was detected in advanced stage (IV -incurable). Recommendation: Public heath strategy should be focused on the expansion of screening programs throughout the country for early detection of malignant diseases cases.
Keywords: Malignant diseases, Trend, Lung cancer, advanced stage

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.017 IMPROVING LUNG CANCER SPECIFIC OUTCOME WHEN ACCESS IS THE KEY–ARE WE THERE YET ?

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Background: Access to specialist cancer care services is pivotal to improve lung cancer specific outcome. Barriers include travel times and disadvantaged socioeconomic status. We analysed the 5 year lung cancer specific survival in a population based study from the second largest state of Australia.

Methods: We identified all patients with newly diagnosed primary lung cancer and their respective treating physicians, registered in the Queensland Cancer Registry (QCR) Australia, from 1 July 2004 to 31 December 2004. Results were linked with the Queensland Integrated Lung Cancer Outcomes Project (QILCOP) to extract data on stage, treatment modalities and outcome. QILCOP captures prospective data on approximately 40% of all new lung cancer patients notified annually through multidisciplinary teams from major public and private institutions in Queensland state. To collect outcome data on those who were not captured through QILCOP we developed survey forms which were posted out to the treating physicians. Data on initial diagnosis and specialist consultation, treatment intent, treatment modalities planned, delivered and toxicity were documented. Travel time to the closest radiation facility was calculated based on usual residence of patients. Incident cases were matched with the National Death Index and the Registrar of Births, Deaths and Marriages. For analyses patients were categorized into quintiles of area-level disadvantage based on the Index of Relative Advantage and Disadvantage (IRSAD) generated by the Australian Bureau of Statistics. Cox regression was used to analyse differences in cause-specific survival with follow up date censored at 31 December 2009.
Results: 856 cases were identified and 829 were eligible for our study. After linking with QILCOP database, survey forms were posted to 407 physicians with a 60% response rate. Final data for analysis was available for 773 patients. Median age at diagnosis was 70 years, 63% were male, 46% had ECOG ≤1 with ECOG unknown in 34%. 73% were non small cell lung cancer, 11% were small cell lung cancer and 16% unknown. In the entire cohort, only 63% had staging data and TNM stage was documented in 74% for non small cell lung cancer. 65% were reviewed by a Respiratory physician or Cardiothoracic surgeon, 33% by a Medical Oncologist and only 10% by a Radiation Oncologist. Those who had access to a radiation facility within 2 hours travelling time were more likely to consult a lung cancer specialist. 5 year cause-specific survival for female vs male was 20% vs. 17% respectively (adjusted HR 0.76, $p<0.001$). In univariate analysis older age, poor ECOG and advanced stage predicted for inferior outcome ($p<0.001$). Different quintiles of area level disadvantage and increased travel distances to radiation facility did not show statistically significant impacts on outcome in either univariate or multivariate analyses.
Conclusion: Despite a trend towards inferior outcome for patients residing in disadvantaged socioeconomic areas or less access to specialists, our results were not statistically significant when adjusting for demographics and other prognostic factors. Prospective studies are warranted to determine impact of access to specialist care on lung cancer outcomes.
Keywords: improving lung cancer specific outcome, access to specialist services, area level socioeconomics

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P4.018 EXTRAPULMONARY MALIGNANCIES DIAGNOSED AT LOW-DOSE CT SCREENING FOR LUNG CANCER

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Background: Incidental findings are a challenge for physicians as these could lead to potential benefits for patients as well as pose additional costs, patient anxiety and iatrogenic injury for clinically negligible conditions. The aim of this study was to retrospectively assess the detection rate, the histology and the clinical stage of the CT screening-detected extrapulmonary malignancies in high risk population for lung cancer.
Methods: 5,203 asymptomatic current or former heavy smokers, aged 50 years or above, underwent an annual low-dose chest CT for 5 consecutive years. The study was approved by our institutional Ethics Committee and all participants signed a written informed consent form. All the patients with at least one "potentially significant extrapulmonary incidental finding (PS-IF)" screening detected were extracted from the study database. An extrapulmonary finding were defined "potentially significant" if it required a further diagnostic and/or clinical evaluation. As our screening protocol included a PET-CT scan to characterize pulmonary nodules larger than 8mm, in the present study we also included all incidental malignancies

detected when performing this additional PET-CT. In retrospect all clinically relevant information, including diagnostic workup and final diagnosis of the PS-IF were collected. Based on the information collected, only histological proven extrapulmonary malignancy screening-detected were eventually included in this study.
Results: At the end of the fifth year of CT screening, 27 unsuspected extrapulmonary malignancies were diagnosed, which represent 0.5% (27/5201) of volunteers enrolled and the 6.2 % (27/436) of PS-IF. This means that unsuspected cancers were diagnosed with a frequency of one case per 200 individuals screened. Eight malignancies were diagnosed at the 1st year of screening, nine at the 2nd year, four at the 3rd year, two at the 4th year and four at the 5th year. Six (22%) malignancies were diagnosed by PET-CT scan. When compared to the 5-year cumulative detection rate of lung cancer of the screening trial (n=186, 3.5% of cohort), on average every 7 lung cancers diagnosed 1 extrapulmonary malignancy was found. The most common extrapulmonary primary tumor was renal carcinoma (n=7), followed by lymphoma (n=5), thyroid cancer (n=3), thymoma (n=2), pancreatic tumor (n=2), Schwannoma (n=1), hepatocellular carcinoma (n=1), gastrointestinal stromal tumor (n=1), prostate cancer (n=1), transitional cell carcinoma (n=1), breast cancer (n=1), pheochromocytoma (n=1) and ovarian cancer (n=1). The clinical follow-up interval was at least 1 year for all patients (range 12–67 months). Twenty-four of the 27 patients in whom a malignancy was diagnosed were alive and all of them were disease free at the most recent follow-up, except for one patient affected by pancreatic tumor.
Conclusion: A considerable number of unsuspected extrapulmonary malignancies can be detected at a pre-clinical stage in lung cancer screening trials. A careful evaluation of extrapulmonary structures, with particular attention towards kidneys and lymph nodes, is recommended.
Keywords: incidental findings, Lung cancer, Screening, CT

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P4.019 JAPANESE GENERAL SCREENING STUDY FOR ASBESTOS-RELATED DISEASES (JG SARD): RESULTS OF BASELINE SCREENING

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Background: The number of patients with pleural mesothelioma and lung cancer associated with asbestos exposure has recently been increasing in Japan. The aim of this study was to evaluate the results of baseline screening for asbestos-related diseases in a group of Japanese general population.
Methods: This prospective study was approved by the institutional review board; informed consent was obtained. Between March in 2006 and December in 2008, 9810 people (5283 men and 4527 women; mean age, 57 years) underwent chest radiography and low-dose CT examinations in 26 institutions in Japan. Clinical information such as histories of smoking and asbestos exposure was reviewed. Chest radiographs and CT scans were interpreted independently by 15 experienced pulmonologists or chest radiologists.
Results: The history of asbestos exposure was definitely present in 1253 (12.8%) individuals, possibly present in 2058 (21.0%), and absent in 6499 (66.2%). On chest radiograph, pleural plaque and pleural thickening were seen in 61 (0.6%) and 65 (0.6%) individuals, respectively. On low-dose CT, pleural plaque and pleural thickening were identified in 264 (2.7%) and 245 (2.5%) individuals, respectively, and non-calcified pulmonary nodule/ mass was seen in 1003 (10.2%). Furthermore, lung cancer was identified in 29 (0.3%) individuals. The history of asbestos exposure was not confirmed in 77 out of 264 individuals (29.2%) having pleural plaques on low-dose CT. Based on the logistic regression analysis, pleural plaque on low-dose CT was significantly correlated with male, age more than 60 years, a history of asbestos exposure and smoking. Similarly, lung cancer was significantly correlated with age more than 60 years, a history of asbestos exposure, and presence of pleural plaques.

Conclusion: Our results indicate that the detectability of pleural lesions on low-dose CT is approximately 4 times higher than that on chest radiographs, and that about 30% of individuals with pleural plaques on low-dose CT are not aware of the asbestos exposure.

Keywords: CT screening, Lung cancer, asbestos-related diseases, pleural mesothelioma

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P4.020 A PILOT LUNG CANCER EARLY DETECTION STUDY IN A PRIMARY CARE PRACTICE IN KNOWSLEY, MERSEYSIDE: THE LIVERPOOL LUNG PROJECT PRIMARY CARE IMPLEMENTATION PROGRAMME (LLP-PCIP)

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Background: More than 90% of people diagnosed with lung cancer in the UK die within a 5-year period. The poor survival is partly linked with late diagnosis often at an advanced stage when various treatment options are less efficacious. The cornerstone of early diagnosis includes prompt identification of high risk individuals, necessitating a need for a validated screening approach that could be used in the primary care setting to target people before onset of symptoms The LLP-PCIP was set up in Knowsley, which has amongst the highest rates of lung cancer in the UK, as a pilot study evaluating the combined role of the LLP risk model, lung function test, sputum cytology and methylation profiling in complementing Bronchospic/CT for early diagnosis of lung cancer. We will describe the design, progress, limitation and expectation of this pioneer initiative.

Methods: The study utilises a prospective cohort design with annual follow up for incident of lung cancer and mortality. In a first step, the LLP risk model is used to assess lung cancer risk for patients aged 50-80 years attending the General Practitioner. Eligibility into the intervention arm is dependent on the LLP risk model score (5-year risk ≥5%) and lung function test (FEV_1/FVC<0.70) results. Also, patients in the intervention arm receive sputum cytology (suspicious or malignant) and chest X-ray (suspicious or malignant) investigations. Based on a positive or suspicious result, a broncoschopy followed by a CT scan and surgery are recommended in succession for definitive diagnosis. Disease free participants in the intervention arm are invited annually for follow-up clinical investigations. All participants are regularly follow-up through the GP and/or record linkage with routine data from cancer registry and death registration. All participants diagnosed with lung cancer are managed by the GP following the NHS standard treatment pathway.

Results: Since study start in January 2009, the LLP risk model has been applied to 1192 patients, and 271(23%) have been identified as high risk of developing lung cancer within 5 years (i.e. 5-year risk ≥5%). Lung function test was performed in 175 (65%) of high risk patients, of which 142 (81%) had FEV_1/FVC<0.70. To date, no lung cancer cases have been identified in the intervention arm, but 11 suspicious patients are undergoing clinical investigation (bronscoscopy/CT scan). The first annual recall for sputum cytology investigation and methylation profiling are now underway.

Conclusion: The LLP-PCIP investigates the effectiveness and clinical feasibility of the combined role of the LLP risk model, lung function test, sputum cytology and methylation profiling to complement Brochoscopic/CT scan for diagnosis of lung cancer, thereby providing a mechanism for early detection before onset of symptoms. An evaluation of the study progress has provided insight on the aspects which need improvement; in particular, how to recruit the hard-to-reach and reducing withdrawal. The experience gained from this study will be very valuable in the planned population-based UK Lung Screening trial (UKLS) currently under pilot in Liverpool and Cambridge

Keywords: Early Detection, Epidemiology, Lung cancer

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P4.021 EARLY LUNG CANCER DETECTION USING DECISION SUPPORT SYSTEM BASED ON DIFFERENT SYMPTOMS ON CHEST RADIOGRAPHS

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Background: Lung cancer is one of the most frequent causes of death in the World with especially high incidence in Hungary. Lung cancer can appear in an early stage not only by nodules, but infiltrates and some other signs on X-Ray images. Therefore the main goal is to detect lung nodules and infiltrated areas on chest images by a newly developed CAD (computer aided detection) system and this way increase the efficiency of the reader performance.
Methods: Our neural network based algorithms find dense, approximately circular shapes and blurred infiltrated areas on chest radiographs. After preprocessing suspicious areas are enhanced by various image processing algorithms, different filter methods find small nodules (diameter of 5mm to 35mm) large nodules (diameter of 30mm – 75mm) and infiltrated objects of arbitrary size. The last step involves the fusion of the filter outputs and false positive reduction. The latter is utilized by an adaptive learning classifier that is trained on validated findings of pulmonologists. The final findings are displayed on the chest radiograph with an approximate segmentation to attract attention to suspicious areas giving a second opinion for the readers.
Results: We tested our system on healthy radiographs and also images containing lung nodules and infiltrated areas validated by a second reader using other test methods (CT, US, etc.). Overall sensitivity was 70% on approximately 1000 images, while producing on average 3 false positives per image. We compared our solution to a previous version not sensitive to infiltrates and examined a clear improvement. We also compared our system to first reader sensitivity where CAD results turned out to be slightly more sensitive; however false positive rates were much higher as first readers mark only one false finding only in more than 50 images on average.
Conclusion: These results enable the CAD system to be used as a second reader and might improve the accuracy of the diagnosis made by the pulmonologist at the diagnostic procedure. Furthermore we see that targeting CAD systems not only at lung nodules but also infiltrated areas may be useful in clinical practice.
Keywords: Decision support system, Chest X-Ray images, Early Detection, Reader efficiency

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P4.022 LUNG CANCER SCREENING: CLINICAL RISK PROFILING WITH LUNG FUNCTION TESTS TO IMPROVE EFFICACY

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Background: Reports from NLST state that LDCT screening can reduce lung cancer (LC) mortality. Despite screening 'very high risk' participants, most studies have baseline cancer prevalence of 1-2% and up to 50% 'false positive' rates. Obstructive spirometry and CT-detected emphysema (CTE) indicate lung damage and hence tobacco-smoke susceptibility. Both are independently associated with LC. Current risk stratification for screening does not account for markers of lung damage. Gas transfer (DLCO) has not been studied in LDCT screening but may correlate with CTE better than spirometry, which may be normal in mild CTE.We hypothesized that participants with normal or near-normal gas transfer have low levels of lung damage and could be safely excluded from LDCT screening. This will 'enrich' cancer prevalence in the screened group and increase efficacy.
Methods: We recruited healthy volunteers aged 60-74 years with smoking history ≥ 30 pack years (current or quit within 15 years) and

FEV1>50%predicted. Volunteers received one prevalence scan (Phillips Brilliance 64-slice multidetector scanner at 0.9mm slice width). Two radiologists independently reported scans. One or more nodules ≥4mm diameter defined a positive scan. Spirometry and gas transfer were measured according to ATS/ERS guidelines. CTE was considered present if >1% of the total lung volume was below a -950 HU threshold (Phillips Brilliance software).

Results: (Median, range). Between December 2007 and December 2010, 256 volunteers were screened: men 66.8%; age 64 (59-75) years; current smokers 45.3%; pack-years 54 (22-235); FEV_1 %predicted 95 (46.6-155.5); DLCO %predicted (n=128) 75.1 (40.0-129.9). 53% of baseline scans were positive. Five LC were diagnosed (prevalence 1.95%). CTE correlated with lung function (FEV1/FVC ratio, FEV_1, DLCO and KCO r=0.57, 0.38, 0.35, and 0.34 respectively). Mean KCO was lower in participants with LC; Receiver Operating Characteristic area under the curve was significant for KCO.(Table 1). Table 1.

	No cancer N=123	Lung cancer N=5		ROC analysis	
	mean (SD)		p value 2-tailed t-test	Area under the curve	P value
KCO % predicted	82.5 (16.1)	66.0 (16.7)	0.03	0.77	0.04
DLCO % predicted	76.9 (15.1)	65.0 (13.1)	0.08	0.73	0.08
FEV1/FVC ratio % predicted	92.4 (14.2)	85.3 (16.2)	0.27	0.63	0.31
FEV1 % predicted	89.8 (18.6)	81.9 (14.4)	0.35	0.65	0.27
CT emphysema % total lung volume	10.4 (5.4)	9.3 (9.4)	0.68	0.61	0.43

A KCO threshold of >90%predicted would exclude 30.4% participants from LDCT screening with no cancer missed. Extrapolating to the full cohort, baseline LDCT cancer prevalence would have increased to 5/180 or 2.8%.

Conclusion: Although based on small numbers this study suggests that lung function testing prior to LDCT screening is worth exploring in larger studies. Even modest reductions in participants requiring LDCT could have significant cost benefits at a population level. Supported by a Queensland Smart State Grant, NCARD and NHMRC.

Keywords: lung cancer screening, lung function test, low dose CT

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.023 IDENTIFICATION OF EPIGENETICALLY SILENCED MICRORNAS IN LUNG TUMORIGENESIS.

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Background: Lung cancer is the leading cause of cancer mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for almost 80% of such deaths. Nevertheless, relatively little is known about what molecules specifically mediate the initiation and progression of NSCLC and therefore a few are used for molecular targeted therapies. Recently, aberrant expression of microRNA (miRNA) has been reported in various cancers. Its role in tumorigenesis would be through suppression of translation and/or affaecting the stability of target messenger RNAs (mRNAs).

Methods: To explore the roles of miRNAs in lung tumorigenesis, we performed miRNA microarray analysis. We treated HDAC inhibitor, SAHA to lung cancer cell lines, Calu-6 and H358.

Results: Through this experiment, we found that the expressions of 27 miRNAs were significantly changed after SAHA treatment in both lung cancer cell lines. In addition, we analyzed the changes of miRNA expression between normal and tumor lung tissues from patients to confirm the role of these miRNAs in lung tumors. The expression of several miRNAs were also reduced in tumor tissues from patients. We also analyzed the changes of miRNA expression between untreated and 5-aza-2'-deoxycytidine (5-aza-CdR) or SAHA-treated lung cancer cell by qRT-PCR. Through these experiments, we found that the expression of one miRNA was reduced in both cell lines and tumor tissues. To study the function of this miRNA in lung tumorigenesis, we transfected Pre-miRNA to Calu-6. After transfection of Pre-miRNA, a significant reduction of cell growth was observed , indicating that this miRNA might have lung tumor suppressive effect. Further, we analyzed the methylation status of this miRNA in lung cancer cell s and tissues by COBRA assay to explore the mechanism of silenced miRNA.

Conclusion: These results suggest that the miRNA palys a role for the inhibition of lung tumor progression. To clarify the function of miRNA on cancer cell growth, determination of the target mRNAs are under investigation.

Keywords: Lung cancer, HDAC inhibitor, micro array, miRNA

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P4.024 EVALUATION OF THE EFFECT OF SAMPLING OF SPONTANEOUS SPUTUM OVER A PROLONGED PERIOD ON THE SENSITIVITY FOR LUNG CANCER.

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Background: Lung cancer is the most common fatal cancer worldwide with an average 5-year survival of 12%. This is mainly due to the advanced stage of disease at time of diagnosis. Secondary prevention strategies are expected to increase the 5-year survival rate by 3-4 folds. Recently, the National Lung Screening Trial reported that spiral CT screening of lung cancer leads to a reduction of lung cancer mortality. CT screening, however, is costly and has a high false-positivity rate. Therefore, a clear need exists for alternative screening assays. Many studies indicate that sputum could be a promising remote medium for early detection of lung cancer, in particular when combined with DNA-methylation based diagnostic assays. Nonetheless, to date all evaluated gene promoter methylation marker panels for early detection of lung cancer in sputum suffer from insufficient sensitivity. We hypothesized that sensitivity for detection of lung cancer may improve when sputum is collected over multiple days. Therefore, this study was set out to determine whether the detection rate of RASSF1A gene promoter methylation is influenced by duration of sputum collection.
Methods: Sputum samples were prospectively collected from 51 lung cancer patients (71% male, mean age 66.8 ± 10.1 years) and 50 controls (74% male, mean age 71.2 ± 8.1 years), recruited at outpatient clinics in the regions around Amsterdam and Nieuwegein, The Netherlands. Cases collected sputum before treatment, or at the time progressive disease was evident after treatment. Controls were patients with COPD without lung cancer in the preceding three years. Spontaneous sputum was collected at home during nine consecutive days in three separate canisters, each representing three successive days. DNA was isolated separately from all three samples per patient. Each DNA isolate was bisulphite treated and subsequently subjected to quantitative methylation-specific PCR (qMSP) to assess methylation status of the RASSF1A gene promoter. As quality control, amplification of housekeeping gene MYOD1 was carried out. All samples were tested in duplicate. Statistical analyses were conducted using chi-square tests.
Results: All subjects provided the requested sputum samples (n=3x101), and all DNA isolates were suitable for qMSP analysis. Analysis of each canister separately showed RASSF1A methylation in samples of day one to three, four to six, and six to nine in 29%, 35%, and 33% of cases, respectively. These figures were significantly lower for control samples, i.e., 2%, 6%, and 2%, respectively (all P-values <0.001). Cumulative analysis of RASSF1A methylation, i.e., combining methylation positivity outcomes for day to six, and day one to nine, revealed RASSF1A methylation in 39% and 47% of cases, respectively, versus 8% and 8% of controls, respectively.
Conclusion: Our study suggests that sputum collected over multiple successive days results in a gain in sensitivity, at the expense of a small loss in specificity, for the detection of lung cancer. Given these findings, it might be considered feasible and legitimate to collect sputum during multiple days for future screening purposes.
Keywords: Lung cancer, Screening, Sputum, Molecular biomarkers

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P4.025 FREQUENCY OF INTERIM-DIAGNOSED LUNG CANCER IN THE SCREENING TRIALS

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Background: The aims were to report the frequency of interim cancer in the CT screening trials and X-ray screening studies, and to present the cell-type and stage distribution of interim cancer in both trials.
Methods: The interim cancers in the low-dose CT and X-ray screening were documented through New York Early Lung Cancer Action Project (NY-ELCAP) database review, literature search through a computerized database (PubMed) and email contact with the research PI.
Results: There were 9 low-dose CT and 3 X-ray screening trials included in this study. The proportion of interim cancer versus total cancer identified was 2.4% in the NY-ELCAP, and from 0% to 5.3% in the other 8 CT screening studies. The proportion was between 20% and 39% in the three X-ray studies. In CT screening study, small cell carcinoma and adenocarcinoma were the most frequent cell types (38% in each); In X-ray screening study, adenocarcinoma was the most frequent cell type (35%), followed by squamous cell (23%), small cell (23%) and other cell type (19%). 78% and 72% of interim cancers found in the CT and X-ray screening studies were stage III-IV cancer.
Conclusion: The proportion of interim cancers in the CT screening study was significantly lower than in the X-ray study. Interim cancers were mostly advanced cancers in both studies. Adenocarcinoma and small cell carcinoma were the most frequent cell types in the CT screening studies. In the X-ray screening studies, there was a wide distribution of cell types.

Table 1 Frequency of interim cancer

Study	Baseline	Interim 1	1st repeat	Interim 2	2nd repeat	Interim 3	3rd repeat	Interim 4	4th repeat	Total (Repeat)	Total (interim)	Total	Interim/ Total
CT screening													
NY-ELCAP	101	3	20	0						20	3	124	2.4%
Cosmos Italy	55	0	38	1	40	0	36	2	16	130	3	188	1.6%
NELSON	70	4	54	3						54	7	131	5.3%
LSS	30	0	8							8	0	38	0%
Hitachi Japan	37	0	4							4	0	41	0%
Milan Italy	11	0	11							11	0	22	0%
Mayo Clinic	31	-	-	-	-	-	-	-	-	34	3	68	4.4%
Toronto * Canada	44	-	10	-	6	-	2	-	-	18	3	65	4.6%
Sone S Japan	23	-	27	-	10					37	0	60	0%
X-ray screening													
Lung Screening Study (LSS)	7	4	9							9	4	20	20%
Memorial Sloan (Randomized) ¤	30*	-	-	-	-	-	-			70	44	144	31%
	23* *	-	-	-	-	-	-			65	56	144	39%
PLCO #	120	46	53	65	62	68	71			186	179	485	37%

Keyword: Lung caner screening

Poster Session 4 – Early Detection and Screening Thursday, 7 July 2011 10:00-12:30

P4.026 SELF REPORTING OF SYMPTOMS AND DELAYS IN PATIENTS PRESENTING TO A RAPID ACCESS LUNG CANCER CLINIC (RALCC)

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Background: The rapid access clinic at our hospital is aimed at expediting the work up and diagnosis of patients with suspected thoracic malignancies. The vast majority of patients (98%) are seen within 2 weeks of referral and the current case find rate is 42%. We aimed to explore the pathway prior to presentation at our RALCC so as to identify common presenting features and potential causes of delays in presentation to the clinic
Methods: We offered a self-reported questionnaire to consecutive patients on their first visit to our RALCC. The questionnaire contained questions about patient's perception of why they were attending the clinic, symptom type and duration of symptoms before seeking medical attention, the time to referral to the RALCC and risk factors for lung cancer
Results: 154 patients participated, 81 male and 73 female, mean age 63 years (21-86 years). General practitioners made the most referrals 134/154 (87%) and 105/159 (68%) perceived abnormal radiology to be the main reason for their attendance to the RALCC. The majority were symptomatic 132/149 (88.6%) with 57% reporting ≥3 symptoms. Cough was the most common presenting symptom at 61%. Others were fatigue 52%, dyspnoea 45%, chest infection 45%, chest pain 40%, weight loss 32%, hoarseness 30%, anorexia 31% and haemoptysis 25%. Patients with haemoptysis had the least delay in presenting to a health care provider (mean 30 days, range 2-120 days) whereas patients with cough, dyspnoea and chest pain had a longer delay

averaging 4.5 months. The average delay between seeking any medical attention and being seen in the RALLC was 14 weeks. The majority of the patients referred had at least 1 risk factor for lung cancer. 72% were current or ex-smokers and 21% reported at least one first degree relative with lung cancer.
Conclusion: There were significant delays between symptom onset and presentation to a health care provider. The duration of delay varied depending on symptom type. The bulk of the delay was before patients sought medical attention but there was still a sizeable delay between presentation and referral to the RALCC. One in 5 patients had a first degree relative with lung cancer and one in ten had two or more first degree relatives with lung cancer indicating that this may have been a factor in the decision to refer. Our study highlights the need for increased public awareness regarding the presenting symptoms of lung cancer and there exists the opportunity to reduce delays in diagnosis resulting in better patient outcomes.
Keywords: Lung cancer, presenting features, delays in presentation

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P4.027 OUTCOMES OF PATIENTS PRESENTING TO A RAPID ACCESS LUNG CANCER SERVICE

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Background: A new cancer care-pathway was developed in Ireland as laid out in the national cancer control strategy delineating a clear organisational structure and formally linking thoracic surgery centers with 8 regional cancer centers. Site-specific multidisciplinary teams are at the centre of this organisational structure. The aim of Rapid Access is to assist in the provision of timely and evidence-based multidisciplinary lung cancer care, to increase the number of patients seen in the early stage of their disease when they are candidates for curative treatment and to increase the opportunities to offer patients clinical trials and studies.
Methods: The first 500 patients referred to the rapid access lung cancer clinic in our institution were studied. Data was collected prospectively and entered into a patient tracking database. The parameters analysed included patient demographics, investigations and patient outcomes. All patients had a baseline dynamic CT thorax and bronchoscopy. Patients where bronchoscopy failed to yield a tissue diagnosis had a CT-guided or surgical lung biopsy. Staging investigations included PET/CT, endobronchial ultrasound and endoscope ultrasound guided fine needle aspirate or mediastinoscopy. Patients with a cancer diagnosis were then discussed at a weekly multidisciplinary team meeting were a management plan was made.
Results: Median age was 68 years (range 18-89) and 301 (60.2%) were male. The median time from referral receipt to first rapid access clinic assessment was 5.5 days (range 0-26). Patients with a malignancy were discussed in a multidisciplinary team meeting a median of 5 days from first clinic assessment (range 0-31). 206 patients (41.2%) were diagnosed with a malignancy. Of the remainder, 79 patients (26.8%) were identified as having suspicious nodules that required further surveillance. 68 patients (23.1%) had an alternative respiratory disease and 29 patients (9.9%) had a non-respiratory condition and were referred to the relevant specialists. The remaining 118 (40%) were reassured that there was no evidence of malignancy and discharged to their referring doctor with no pathology found. One hundred and seventy nine (35.8%) patients were diagnosed with primary lung cancer with a further 27 (5.4%) patients diagnosed with secondary lung cancer and other thoracic tumours.

As part of the diagnostic work up for malignancy, 64 patients (29%) required a CT guided biopsy and 21 patients (10.2%) required a surgical biopsy to yield a tissue diagnosis in suspected lung cancer. Histological staging was achieved in 123 patients (84%) with NSCLC

For those patients in whom active treatment was recommended, 44 (27.9 %) had surgical resection, 39 (30.2%) chemotherapy and 15 (11.6%) radiation monotherapy. Thirty-one patients (24%) received chemotherapy, 5 (3.9%) had surgery with chemotherapy and 3 (2.3%) had treatment with all 3 modalities.
Conclusion: Thoracic malignancy is identified in over 40% of patients this study shows that appropriate patients are being referred to rapid access. A higher percent of early stage lung cancers are being identified when compared to figures from

National Cancer Registry of Ireland. Twenty five percent of referrals will require ongoing assessment for pulmonary nodules. This will pose significant challenges with regards workload for the service in the future.

Keywords: Epidemiology, Patient outcomes, Multidiplinary Team, Rapid access lung cancer clinic

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P4.028 PRELIMINARY RESULTS FROM A FOUR YEAR LONGITUDINAL CHEST CT SCREENING STUDY FOR LUNG CANCER IN AN URBAN COHORT OF HIV HEAVY SMOKERS

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Background: Within the HIV population, the incidence of non small cell lung cancer (NSCLC) is estimated to be 2-4 times that of the general population. Of the non AIDS associated malignancies, lung cancer is the leading cause of death among HIV patients who develop malignancy because of its advanced stage at presentation. The United States National Lung Cancer Screening Trial recently reported a 20% reduction in mortality for heavy smokers undergoing low dose computed tomography (CT) screening, but individuals with HIV diagnosis were excluded. We report the results of a single arm observational pilot study of lung cancer CT screening in a cohort of HIV who are heavy smokers that explores the efficacy of CT screening to detect lung cancer at an earlier stage in HIV patients.

Methods: In 2006, a prospective longitudinal study was initiated on a cohort of 185 asymptomatic individuals over 25 years old with confirmed HIV diagnosis who had a smoking history of greater than 20 pack-years. All participants had baseline (prevalence) chest CT scanning and 107 patients (58.2%) also received at least one subsequent annual (incidence) examination of the chest. In the CT scans of 136 patients, 3D CT reconstruction and software were used to quantify, in a blinded fashion, the attenuation values of all the pixels on each scan so that pixels with abnormally low attenuation, that represented emphysematous lung (attenuation volume below –950 Hounsfield Units), could be discriminated from normal lung by a discrete emphysema score.

Results: Of the 185 individuals, 31.4% were females, 90.3% African-Americans, 8.7% Caucasian, and 1.1% Hispanic. The median age at enrolment was 48 years, and the median number of pack-years was 34. Non-calcified nodules ≥4mm were detected in only 4 participants (2.1%) by prevalent CT and no new nodules were observed on incident scans. Only one patient with biopsy proven NSCLC was detected and this was a large hilar mass seen on incident scanning (0.94%). The stage of the NSCLC at the time of CT detection was advanced. No biopsies were undertaken for benign disease. Additional CT findings of clinical importance were noted in the chest in 132 (71.7%) patients and extrathoracically in 30 (16.3%) of patients, respectively. On the prevalent scans, the median emphysema attenuation score for the screened HIV smokers without malignancy was 1.09% (range, 0.43-22.8%) whereas the single HIV patient with NSCLC had an emphysema attenuation score of 25.2%. The patient with NSCLC had a 35 pack year smoking history.

Conclusion: This is the first reported CT lung cancer screening trial in HIV smokers. Our results show that not only is CT screening feasible in an urban population of smokers with HIV, but also that the rate of lung cancer detection is in line with other single arm CT screening studies in HIV indeterminate patients. Our preliminary data of quantifiable CT emphysema attenuation scores generate a future exploratory hypothesis that the susceptibility of a HIV patient to lung damage by cigarette smoking may be a predictor of risk of developing subsequent NSCLC.

Keywords: HIV, Non small cell lung cancer, CT screening

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Early Detection and Screening Thursday, 7 July 2011 10:00-12:30

P4.029 IMPACT OF LUNG NODULE CLINIC IN TIMELINESS OF LUNG CANCER, DIAGNOSIS AND TREATMENT

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Background: Following hurricane Katrina, the New Orleans VA Medical Center outpatient pulmonary clinic was not reopened until late 2006. Many challenges in the care of patients with suspicious findings for lung cancer were found in the years following this natural disaster. The need to outsource diagnostic procedures and some radiographic evaluations caused a significant delay in the diagnosis and treatment of this disease. A pulmonary lung nodule clinic (LNC) was created in the fall of 2009 to centralize, expedite and direct the care of patients with suspicion of lung cancer. Our study is aimed to measure the impact of this clinic in the timeliness of diagnosis and treatment of lung cancer and to compare these results with the correspondent national VA standards in quality of care.
Methods: A retrospective chart review was performed for lung cancer cases diagnosed in the Southeast Louisiana Veterans Health Care System (SLVHCS) from 2007 to 2010. Cases were divided in two groups: pre-lung nodule clinic (January 2007 to September 2009), and post-lung nodule clinic (October 2009 to 2010). Primary outcomes consist of two quality indicators addressing timeliness of care for all incident lung cancer cases: Time from suspicion to diagnosis (T1) and time from diagnosis to treatment (T2). Inclusion criterion was a new lung cancer diagnosis during the above-mentioned time in the SLVHCS general pulmonary and Lung Nodule clinics. Exclusion criteria were: absence of pathologic confirmation, and a non-diagnostic biopsy result. Data was reviewed for comparison of T1 and T2 between pre and post Lung Nodule Clinic creation, and with available national VA lung cancer care standards. A T test was used to evaluate the differences in T1 and T2 between the two groups.
Results: From an initial population of 151 newly diagnosed lung cancer cases, a total of 128 patients were eligible after exclusion criteria were applied. T1 (suspicion to diagnosis) pre-LNC was 53 days and post-LNC was 35 days (P=0.04). T2 (diagnosis to treatment) pre-LNC was 32 days and post-LNC was 38 days (P=0.39). The available national VA quality indicator rates indicate a median time from initial suspicion of lung cancer and a pathologic diagnosis of 32 days, and from diagnosis to initial treatment of 35 days.
Conclusion: The creation of a dedicated lung nodule clinic in the SLVHCS improved significantly the timeliness of lung cancer diagnosis making our center comparable with the national VA standards despite of the disrupted infrastructure as a consequence of hurricane Katrina.
Keywords: Lung cancer, diagnosis, TIMELINESS

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Early Detection and Screening Thursday, 7 July 2011 10:00-12:30

P4.030 TERT PROMOTER METHYLATION IN BLOOD SAMPLES AS LUNG CANCER RISK MARKER?

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Background: The identification of lung cancer risk groups is an important prerequisite for successful lung cancer screening programmes. Lung Cancer genome-wide association (GWA) studies have identified TERT as a candidate lung cancer susceptibility gene, but the causal mechanisms have not yet been identified. Epigenetic mechanisms

play an important role in mediating environmental influences on gene expression, and promoter methylation is involved in lung carcinogenesis. TERT promoter methylation was thus investigated as a promising lung cancer risk biomarker.
Methods: A discovery (n=34) and a validation (n=48) set of non-small cell lung cancer (NSCLC) tumors, adjacent normal lung tissue and blood samples were assessed for TERT methylation and genotype. Additionally, comparative genome-wide methylation analysis after MCIp-enrichment was performed on blood samples from lung cancer cases and controls using whole genome CpG island arrays (Agilent). Quantitative high throughput TERT promoter methylation analysis using MALDI-TOF MS (Sequenom) was performed on DNA isolated from blood samples from lung cancer cases (n=866) and controls without lung cancer (n=506).
Results: TERT promoter hypermethylation was observed in tumors vs. adjacent normal lung tissue ($p<001$). Methylation at one TERT promoter CpG unit was significantly correlated with the genotype at rs421629 ($p=0.002$). In blood samples of cases compared to controls, the TERT amplicon investigated showed a statistically significantly increased average methylation ($p<0.0001$). In the genome-wide blood-DNA methylation screen, TERT was one of the genes identified as differentially methylated between cases and controls.
Conclusion: The association of tumor-specific *TERT* methylation with *TERT* genotype points to a possible mechanism of the association with lung cancer risk for this GWA-identified susceptibility locus. Our finding of significantly increased methylation in blood samples from lung cancer cases vs. controls makes *TERT* methylation a potentially interesting epigenetic marker for early diagnosis and/or lung cancer risk.
Keywords: methylation, epigenetics, NSCLC, lung cancer risk

Poster Session 4 – Chemoprevention Thursday, 7 July 2011 10:00-12:30

P4.031 ILOPROST IMPROVES ENDOBRONCHIAL DYSPLASIA IN FORMER SMOKERS: IMPLICATIONS FOR PHASE II CHEMOPREVENTION TRIAL DESIGN

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Background: We conducted a multi-center, double-blind, placebo controlled Phase II trial of iloprost in subjects at risk for lung cancer and found a positive result in the primary endpoint, average histologic score, in former smokers. Secondary analyses revealed results with potentially important design implications for future similar Phase II trials.
Methods: Entry criteria included: current or former smoker (>20 pack-years); at least mild dysplasia on sputum cytology; no previous history of lung cancer. Autofluorescence and white-light bronchoscopy was performed with 6 standard endobronchial sites biopsied, along with other abnormal appearing areas. Subjects were then randomized to oral iloprost (in escalating doses) or placebo for 6 months and a second bronchoscopy with repeat biopsy of all areas sampled on the first bronchoscopy, as well as any new areas suspicious for dysplasia. The predetermined primary endpoint for the study was average bronchial histologic score (based on WHO classification) in all subjects, as well as in current and former smokers separately.
Results: The accrual goal of 152 subjects was reached and 125 completed both bronchoscopies (60/75 iloprost, 65/77 placebo). Treatment groups were well matched for age, tobacco exposure, airflow limitation, and baseline histology. Histology was summarized within patients using 3 separate measures: average of all biopsy scores (Avg), worst biopsy score (Max), and dysplasia index (DI- the percentage of biopsies with a score of at least mild dysplasia). 74% of subjects had at least one biopsy displaying mild dysplasia (WHO score 4.0) or worse

on initial bronchoscopy. A reproducibility study with two independent pathologists demonstrated that 85% of readings were within one histologic grade. Baseline histology was significantly worse for current smokers (Avg 3.0) than former smokers (Avg 2.1). Former smokers receiving oral iloprost exhibited a significant improvement in Avg (-.41, p = 0.01), Max (-1.10, p = 0.002) adn DI (-12.45%, p = 0.006). No histologic improvement occurred in former smokers. Prespecified secondary analyis restricted to only the 6 standard sites demonstrated similar outcomes to all site analysis, demonstrating that in this Phase II trial, autofluorescence bronchoscopy was not necessary for achieving a positive outcome. Restricting the analysis to sites sampled on both the firest and second bronchoscopies resulted in a similar treatment effect. The largest treatment effects were achieved when analysis was restricted to non-normal sites that were sampled on both bronchoscopies, but this analysis is biased towards a faveorable treatment effect as normal biopsies that progress to abnormal were excluded.

Conclusion: Oral iloprost significantly improves endobronchial dysplasia in former smokers. Secondary analysis demonstrates that in this trial autofluorescence bronchoscopy was not required for achieving a positive outcome, possibly due to prespecification of at least 6 biopsy sites and the high incidence of dysplasia in this population. It remains to be proven whether histologic summarization measures will predict a true chemopreventive effect in Phase III trials, but Max exhibited the largest treatment effect and therefore might be the preferable primary endpoint.

Keywords: prostacyclin, chemoprevention, Lung cancer, premalignancy

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.032 LUNG ADENOCARCINOMA INCIDENCE RATES AND THEIR RELATION TO AIR POLLUTION

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Background: There may be a relationship between air pollution and the incidence of lung adenocarcinoma. The objective of this study is to evaluate the possible influence of air pollutants on the incidence rate of lung adenocarcinoma.

Methods: The study included 8 counties of the Center of Portugal, where information on concentrations of air pollutants was available. We collected data on air pollutants (NO_2, NO, NOx, SO_2, O_3 and CO) from 1999-2008 and correlated it with the incidence rates of lung adenocarcinoma in the same period. Statistical analysis consisted of Spearman correlation between the average levels of air pollutants and the incidence rates of lung adenocarcinoma.

Results: There was a positive correlation between NO_2 concentrations and adenocarcinoma incidence rates in one county (correlation coefficient = 0,900; 95% CI). On the other hand, we observed a negative correlation between O_3 average levels and the incidence of this type of lung cancer (correlation coefficient = - 0,857; 95% CI). The influences of NO, NOx, SO_2 and CO were not statistically significant.

Conclusion: Although we observed significant correlations between NO_2 and O_3 concentrations and the incidence rate of lung adenocarcinoma, the study does not allow us to conclude that there is a causal relationship. The retrospective nature of the study and the size of the sample are important limitations and results must be interpreted with caution.

Keywords: lung adenocarcinoma, air pollutants

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.033 CANCER WAITING TIMES: ASSESSMENT OF ONE MONTH WAIT TARGET FROM DIAGNOSIS TO TREATMENT OF ALL CANCERS IN ENGLAND

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Background: Over the last few years, National Health Service (NHS) in UK has focussed its attention on reducing waiting times of all the cancer patients. The NHS cancer plan 2000 lays out the ways of improvement. By 2008, the ultimate target was that no patient should wait longer than one month from an urgent referral by their GP for suspected cancer to the start of treatment.

Methods: Data regarding all cancer patients including breast, lung, upper and lower GI,

skin, gynaecological, urological, head and neck, haematological malignancies, children's cancers, sarcomas and others in England were collected from the department of health records. All cancer patients treated during the period (Oct. 2007 to Oct. 2008) which fall under the category of one month wait target were counted. This also included the total number of patients treated during the quarter by referral type i.e. urgent GP and other referrals in England. The data were analyzed using the excel spread sheets.

Results: Based on all the urgent GP referrals, 80% were received with in 24 hours. The highest number of referrals were received for breast cancer followed by lower GI, skin, lung and head and neck cancers. The percentage compliance of 31 day target in these cancers was 98-99%. The rest of 19% urgent referrals which were received after 24 hours had percentage compliance of 90% in 2007 and early 2008 but was noted to be improved to 94% in the last quarter of 2008. The referrals which did not meet the target were mainly dermatological followed by breast, lower GI, urological, gynaecological and head and neck.

Conclusion: Around 220,000 people are diagnosed with cancer each year in England, and the disease causes more than 128,000 deaths. The total number of new cases of cancer is increasing by 1.4% per year, as the UK's ageing population grows. The NHS Cancer Plan (2000) proposed that targeting 'cancer waiting times' and providing referral guidelines would lead to an improvement in the outcome of patients with cancer. The 31 day target is indeed a challenging target and it has certainly highlighted and focused on those patients who have been given the diagnosis so that the treatment could be initiated as quickly as possible After taking into account of the statistics, Better Cancer Care – An Action Plan was launched in October 2008. Central to this is development of a comprehensive programme of work to assure the quality of care delivered. Two key and complimentary strands of this work are assuring compliance with national clinical standards and guidelines through robust clinical governance and delivery of two new cancer targets, one of which is 31-day target from decision to treat to first treatment for all patients diagnosed with cancer irrespective of their route of referral and has been expanded to cover subsequent treatments for all cancer patients including those diagnosed with recurrence. The agreed tolerance level is 5% for each of these targets, that is the stated waiting time must be met for 95% of all patients covered by the target. These new targets have to be achieved from October – December 2011.The recommendations made to achieve the target are development and implementation of effective clinical pathways across organisational boundaries and sustainable delivery by continuous development of data management system so that resources are not diverted and data capture is complete and as robust as possible. .

Keyword: Cancer Waiting Times

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P4.034 FAMILY HISTORY OF LUNG CANCER AMONG CHILDREN WITH ACUTE LEUKEMIA

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Background: Family history of cancer may represent shared genetic and environmental risk factors for leukemia.

Methods: We examined associations of family history of lung cancer among children acute leukemia incidence (main group) by using data on 192 patients identified at diagnosis and 192 population-based controls in the West Ukraine (Lviv region) during 1995-2010.

Results: In 192 families with acute leukemia lung cancer has been met in 28 (14,6%) families from 1 to 4 cases. In main group lung cancer families has been met often - 28 cases than in the control group - 19 cases ($P<0.05$) regardless of the degree of relationship to proband.

Among 35 relatives of probands with acute leukemia who have been diagnosed with lung cancer, this pathology was found in females in 14(40%) cases and in 21 cases (60%) in males. Both groups has been met in lung cancer 1.5 times more often in men than in women. In both groups, no difference was found for the oldest and youngest family members with this diagnosis ($P> 0,05$).

Comparing families of basic and control groups there wasn't revealed significant difference for other families in cancer ($P> 0,05$).

Conclusion: As in families of maingroup lung cancer was detected more frequently than the control group, we can assume that carcinogenesis in the group with acute leukemia in children a slightly

different way than in population. It is likely that the mutation that runs cancer in children, focusing on other gene loci than the general population.
Keywords: Lung cancer, acute leukemia, children, family

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.035 EPIDEMIOLOGY OF LUNG CANCER CASES IN A TERTIARY CARE CANCER HOSPITAL - SOUTH INDIA

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Background: Lung cancer is a major Public health problem in developed countries. The epidemiological cause for the increase in lung cancer cases for the past 10 years is mainly due to lifestyle factors, tobacco smoking and air pollution due to urbanisation and industrialisation. The lung cancer cases in developing countries are increasing every year. This is due to the tobacco smoking habit, and smoking for long duration. Globally, 85% of cases in men and 46% in women are due to smoking. In developed countries the proportions are 91% for men and 62% for women and in developing countries 76% for men and 24% for women. The objective of our study was to see the prevalence lung cancer cases in the year 2010.
Methods: The study was conducted in a 300 bed cancer hospital attached to tertiary care teaching hospital located in the state of Karnataka, South India. The data on lung cancer cases reported in the year 2010 was collected from medical records department and analyzed using SPSS software version 17.0.
Results: In the year 2010, 185 lung cancer cases were reported. According to the ICD-10 classification, 98% of the lung cancer cases were bronchus or Lung unspecified. About 1% had overlapping lesions. Majority (75%) of the cases were reported between the age group 50-70 years. Majority of the cases were reported among males, and most of them were above 50 years of age. About 10% of the lung cancer was reported among females and most of the patients were less than 40 years of age. There was a history of multiple uses of tobacco & its product among 77.1% of the cases.
Conclusion: In our study, majority of the lung cancer cases gave history of smoking. It is a proven fact that smoking leads to lung cancer. The primary prevention need to be emphasized locally, nationally and internationally to control lung cancer. The extensive information, education and behaviour change communication campaign should be conducted by the district health authority with great emphasis laid on young people and school children. The local political system should actively participate in the implementation of legislative and restrictive measures. The de-addiction campaign should be conducted every month in the district. The national and international coordination and commitment is necessary to continue research on different methods of smoking cessation. The screening for lung cancer is not feasible and lack potential for reducing mortality than primary prevention. Therefore, mass screening for lung cancer is not recommended as a routine public health policy.
Keywords: Epidemiology, Lung cancer, control

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.036 DESCRIBING TREATMENT, TREATMENT OUTCOMES, RESOURCE USE AND QUALITY OF LIFE OF ADVANCED NSCLC PATIENTS - THE LUNG CANCER ECONOMICS AND OUTCOMES RESEARCH (LUCEOR) STUDIES

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Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Published international, comparative, real-life data on 1) NSCLC treatment patterns, 2) treatment outcomes,

3) resource utilization and 4) patient reported health-related quality of life (HRQOL) is limited. The LUCEOR studies will provide insight into all four areas of research.
Methods: The LUCEOR-1 study will retrospectively collect information on healthcare resource use (inpatient/outpatient care, hospice care, emergency room visits, laboratory and mutation testing), treatment and treatment outcomes (tumor response, overall and progression free survival). Information will be collected from 2,200 patient charts of deceased advanced stage (IIIb/IV) NSCLC patients. The LUCEOR-2 study will prospectively collect HRQOL data (using the EuroQol questionnaires) from 720 advanced stage NSCLC patients. The LUCEOR studies will be conducted in 10 countries.
Results: 40 sites were recruited in Australia, Belgium, Canada, France, Germany, Italy, Netherlands Sweden, Turkey and the UK. 22 (55%) are University Hospitals, 12 (30%) General Hospitals, 6 (15%) other. On average 173 NSCLC patients (range 25-483) are treated per site per year. 63% of all treated patients are stage IIIb/IV (range 30%-90%). 48% of patients have a performance status of 0-1 at initiation of first line pharmacotherapy. This rate is lower in the UK at 30%. All but one site use CTCAE grading for adverse events. 90% of sites use the RECIST criteria to evaluate response status and 93% of sites assess performance status using the ECOG scale. Information on drug utilization, hospitalization, outpatient visits and adverse events was found in all patient records. 52.5% of sites use a combination of electronic and paper records, 15.0% of sites use electronic records only and 32.5% paper records only.
Conclusion: Sites have been found to routinely collect information on treatment, treatment outcomes and resource utilization. Differences exist in site designation, percentage of patients diagnosed with advanced NSCLC, performance status at initiation of pharmacotherapy and means of storing chart information.
Keywords: Advanced Non-Small Cell Lung Cancer, chart review, Quality of Life

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P4.037 IMPROVEMENTS IN LUNG CANCER SURGERY

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Background: Many lives are lost to lung cancer because patients are not considered for surgery or given appropriate surgical treatment. We explore trends in surgical outcomes up to recent time.
Methods: Using data from the Cancer Registry of Norway we analyzed outcomes and quality indicators of lung cancer surgery in the periods 1994-95, 2000-01 and 2006-07.
Results: For the three study periods 12 616 cases of lung cancer were diagnosed. A total of 2 201 patients underwent surgical resection. The age distribution of resected patients was stable. The proportion of adenocarcinoma was 32% in the first period, increasing to 44% and 42% in the following periods (p for trend<0.001). Surgery was performed at 24 hospitals during the first two periods and at 13 in the last. Resection rates varied among counties from 7% to 31%. From the first to the last period national resection rates increased from 16% to 19% (p for trend =0.001) and one year survival increased from 73% to 82%. The proportion of resected patients in pStage I-II decreased from 87% to 83% (p for trend =0.048), the number of pneumonectomies from 27% to 15% (p for trend<0.001) and the mortality rate within 30 days after surgery from 4.8% to 3.0% (p for trend=0.072). In the first two periods, 31% of these early deaths were caused by surgical complications, whereas in the latter period none were related to the surgical procedure itself. The only unfavorable trend observed was the waiting time from the final diagnostic procedure to surgery, which increased from 29 to 40 days throughout the periods (p<0.001).
Conclusion: Important aspects of lung cancer surgery have improved in recent years except for waiting times which increased.
Keyword: lung cancer surgery

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P4.038 PROGNOSTIC INFLUENCE OF THE SIMPLIFIED COMORBIDITY SCORE (COLINET) IN PATIENTS WITH LUNG CANCER: A POPULATION BASED STUDY.

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Background: Many patients (pts) with lung cancer have smoking and lifestyle-related comorbidities which may affect survival independently of their cancer and treatment. This study was undertaken to determine if a Simplified Comorbidity Score (SCS) reported by Colinet et al (Br J Cancer 2005; 93: 1098) provided prognostic information in addition to the established prognostic factors (sex, stage, performance status, age).
Methods: Retrospective survey of all pts identified by the Victorian Cancer Registry who were diagnosed with lung cancer in the 6 month period 1/2003- 6/2003. Data collection including prognostic factors, SCS, treatment given and survival was performed retrospectively in 2008.
Results: There were 921 pts, and 841 (91.3%) for whom data were available. 63.1% were male and median age was 72 years (range 30-94). 89.9% had a tissue diagnosis, of which 86.6% were non-small cell (NSCLC), and 13.4% small cell carcinoma (SCLC). Stage group: NSCLC – I - 17.7%; II – 5.0%; III – 25.8%; IV – 51.5%. SCLC stage: limited – 33.3%; extensive – 66.7%. Performance status (ECOG): 0 – 11.5%; 1 – 35.8%; 2 – 13.0%; 3 – 14.4%; 4 5.7%; unknown 19.6%. Comorbidities on which the SCS is based were distributed: cardiovascular 54.6%; respiratory 38.9%; neoplastic 19.9%; renal 4.6%; diabetes 11.7%; alcoholism 5.5%; tobacco 83.1%. In pts with NSCLC, higher SCS score (>9) was associated with increasing stage, ECOG performance status, male sex, increasing age, tobacco consumption and not receiving treatment. On univariate analysis, SCS as a continuous variable had no significant effect on survival ($p > 0.05$ log rank test for trend both all pts and NSCLC). In all pts, an SCS score ≥ 9 predicted worse survival (p=0.048), but not in pts with NSCLC (p=0.075). Using Cox regression, survival was analysed by SCS score after adjusting for the effect of age, sex, cell type (NSCLC, SCLC, no histology), ECOG performance status and stage for all patients and then restricted to NSCLC. As a continuous or dichotomous ($\leq$ or > 9) variable, SCS was not a significant prognostic factor for all pts or when restricted to NSCLC. If ECOG performance status was removed from the model, SCS > 9 predicted worse survival both for all cases (HR 1.17, P=0.047) and NSCLC (HR 1.20, p=0.037).
Conclusion: In this retrospective analysis of population based registry pts, SCS did not provide additional information beyond established prognostic factors in pts with lung cancer. ECOG performance status may be a substitute for the effect of comorbidity.
Keywords: Lung cancer, prognostic factors, comorbidity

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P4.039 HISTOLOGICAL SUBTYPES OF LUNG CANCER IN OPERATED PATIENTS

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Background: Lung cancer takes the first place both for morbidity and mortality in Latvia and worldwide. Adenocarcinoma becomes the most common subtype of lung cancer in many countries, however in Latvia it is squamous cell lung cancer.
Methods: We have made a retrospective analysis of all lung cancer patients operated at the Department of Thoracic Surgery in the Clinic of Tuberculosis and Lung Diseases of Latvian Centre of Infectology between 2001 and 2010. We have analysed demographic data and histological subtypes of these operated patients and performed statistical analysis using Microsoft Office® Exel and EpiInfo6 statistical tools.
Results: 1198 lung cancer patients were operated during last 10 years: among them 262 (21.9%) female and 936 (78.1%) male. Mean age of female patients was 60.1(±11.9), but for male patients – 61.6(±9.2) years. The highest incidence of patients was in age group between 61 and 70 – accordingly in 36.3% of female and in 43.1% of male patients. Altogether squamous cell lung cancer was diagnosed in 551 (46%) cases, adenocarcinoma – 384 (32.1%), mixed or other type of non small cell lung cancer – 97 (8.1%), small cell lung cancer – 90 (7.5%), carcinoid – 51 (4.3%), sarcoma – 14 (1.2%), other – 11 (0.9%).
For female patients the most common subtype of lung cancer was adenocarcinoma (54.6%), second – carcinoid (14.1%) and only third – squamous cell

lung cancer (13.7%). For male patients squamous cell lung cancer was diagnosed most frequently (55%), weather adenocarcinoma was second (25.7%).
During last 10 years the frequency of adenocarcinoma has grown, and the frequency of squamous cell carcinoma has decreased: comparing the first (between 2001 and 2003) and the last (between 2008 and 2010) 3-year periods the frequency of adenocarcinoma was accordingly 22.8% and 37.9% ($p<0.001$), but the frequency of squamous cell lung cancer – 48.3% and 40.6% ($p<0.05$).
Conclusion: In operated patients during last 10 years, squamous cell lung cancer is mostly diagnosed among men and all patients together, but adenocarcinoma – among women. We observed the statistically significant growth in the incidence of adenocarcinoma and decrease in the incedence of squamous cell cancer among operated lung cancer patients.
Keywords: Lung cancer, hystological subtypes, Adenocarcinoma

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P4.040 LUNG CANCER INCIDENCE AND SURVIVAL IN ENGLAND: AN ANALYSIS BY SOCIO-ECONOMIC DEPRIVATION AND URBANISATION

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Background: Most previous studies have investigated either socio-economic deprivation or urbanisation in relation to lung cancer incidence or survival. We investigated the association between socio-economic deprivation, urbanisation and lung cancer incidence and survival in England.
Methods: We extracted data on patients diagnosed with lung cancer (ICD-10 C33-C34) between 2003 and 2007 who were resident in England. We assigned each patient to an urbanisation score and to a socio-economic quintile based on their postcode of residence. We calculated age-specific incidence rates and age-standardised incidence rates (per 100,000 European standard population) by sex, urbanisation and socio-economic deprivation group. We used Kaplan-Meier survival analysis to compare the survival of patients from urban and rural areas by socio-economic deprivation.
Results: A high proportion of urban areas in England were classified as deprived, and rural areas were mostly affluent. The incidence of lung cancer was higher in urban areas than in rural areas. However, when incidence between urban and rural areas was compared by socio-economic deprivation, this different disappeared. Survival from lung cancer was slightly higher in affluent areas than in deprived areas. Survival from lung cancer in urban and rural areas was similar across all socio-economic deprivation quintiles.
Conclusion: The difference in incidence between urban and rural areas can be explained by the differences in the distribution of socio-economic deprivation quintiles in the two urbanisation categories. When socio-economic deprivation is taken into account little difference is seen between both the incidence and survival of lung cancer in urban and rural areas.
Keywords: Lung cancer, urbanisation, socio-economic deprivation, incidence and survival

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P4.041 TRENDS IN INCIDENCE OF SMALL CELL LUNG CANCER AND ALL LUNG CANCER

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Background: The incidence of small cell lung cancer (SCLC) is often quoted as 'around 20%' of all lung cancers but is reportedly decreasing over time. We analysed the trends in incidence of SCLC and compared these with the trends in lung cancer overall among males and females in South East England.
Methods: We identified 237,792 patients diagnosed with lung cancer (ICD-10 C33-C34) between 1970 and 2007. We used a Poisson regression age-cohort model to estimate the age-specific rates in the 1890 to 1960 birth cohorts and the 1970 to 2007 calendar periods. We computed age-standardised incidence rates using the European standard population. In addition, we analysed the trends of lung cancer

subtypes according to morphology.
Results: In the most recent time period, SCLC accounted for 10% and 11% of cases of all lung cancer among males and females, respectively. Among the morphologically specified lung cancers, SCLC accounted for 15% and 17% among males and females, respectively. There was a decrease of SCLC incidence over time and by birth cohort in both sexes. The decrease in SCLC was more marked than that in all lung cancers.
Conclusion: The decrease in SCLC incidence rates may reflect decreases in the prevalence of cigarette smoking, and changes in the type of cigarettes smoked.
Keywords: incidence, Small Cell Lung Carcinoma, Lung neoplasms, Smoking

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P4.042 YOUNG WOMEN WITH NON SQUAMOUS, NON SMALL CELL LUNG CANCER (NSCLC).

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Background: Women under age 50 with NSCLC make up approximately 5% of all lung cancer in the U.S. These cases have a disproportionately high impact since patients are often raising families and in the most productive time of their lives.
Methods: We reviewed a cohort of young women with thoracic carcinoma to assess patterns of disease at presentation and outcome. 1450 consecutive unselected thoracic oncology patients treated by a single Oncologist (DDK) at our institution from 2003 - 2010 were analyzed for smoking status, histology, stage and patterns of metastases (METS), and survival.
Results: A total of 51 patients seen were women under 50. Pts with squamous (5) and small cell (2) were virtually all heavy smokers. Other histologies (11) consisted of neuroendocrine cancer, carcinoid, mesothelioma, and thymoma. The remaining 33 had ADENO or unspecified non small cell (NOS). Smoking status was never = 13, former = 11, and current = 9. Age ranged from 22 to 48 (median 42). 23/33 (70%) had Stage IV, 6/33 (18%) had IIIA/B, and 4/33 (12%) had stage I or II. Adenocarcinoma was 29/33 (88%) and NOS was 4/33 (12%). Overall survival was 11.6 mo while survival for never-smokers was only 10.7 months. At presentation, 16 pts had pleural effusion (48%) and 5 (15%) had brain METS . No pt had adrenal METS at time of diagnosis. 12/13 (92%) never smokers had stage IV disease. 4 never smokers had a distinctive (miliary) pattern of innumerable small nodules.

Smoking Status	Total Number	Bulky Pleural Disease	Innumer. Small Nodules	Other	IV	IIIB	IIIA	I/II	Adeno	NSC/ NOS
Never	13	7	4	2	12	0	0	1	13	0
Former	11	6	0	5	3	4	1	3	9	2
Current	9	6	0	3	8	1	0	0	7	2

Conclusion: Young women with NSCLC were likely to have bulky advanced disease. Unlike other settings, non-smokers did not seem to fare better than current or former smokers. The miliary pattern of innumerable bilateral small pulmonary nodules was only seen in never-smokers.
Keywords: Young women with lung cancer, metastatic patterns

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P4.043 INITIAL SYMPTOMS AND DELAY BETWEEN INITIAL SYMPTOMS, DIAGNOSIS AND ONSET OF SPECIFIC TREATMENT IN ELDERLY PATIENTS WITH LUNG CANCER.

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Background: Lung cancer is the leading cause of death due to cancer. Epidemiological data show that more elderly patients are diagnosed with lung cancer.
Methods: The objectives were to describe 1) the initial symptoms of lung cancer in elderly patients (≥ 75 years of age) and 2) the time between the initial symptoms and the first visit with a thoracic oncologist, the time between the initial symptoms and the beginning of the specific treatment of the cancer, and the time between the first visit with a thoracic oncologist and the beginning of the

treatment. These data were compared with those observed in younger patients (<75 years of age).
Results: One hundred and ninety-three consecutive patients with lung cancer, diagnosed between 2006 and 2008, were included. Fifty-nine (31%) were 75 years old or older. There were 26 small-cell lung cancers and 167 non-small cell lung cancers (94 adenocarcinomas, 23 large-cell carcinomas, 11 undifferentiated carcinomas, 36 squamous cell carcinomas, 2 large-cell carcinomas with neuro-endocrine component, 1 adenosquamous carcinoma). We found no statistical difference in sex ratio, tobacco status, histological distribution, and TNM staging between elderly patients and other patients. Elderly patients had more co-morbidities (median Charlson score = 2 (IQR 1-3) versus 1 (IQR 0-2) in younger patients, p<0.001). The performans status (PS) was higher in the elderly group (PS 2: 31% versus 9% in the younger patients' group; PS 3-4: 12% versus 5% in the younger patients' group, p<0.0001). The most frequent initial manifestations in elderly patients were general symptoms (37%), cough (29%), dyspnea (29%), pain (14%), respiratory infection (10%). No statistical difference was found between the 2 groups concerning the symptoms, except for dyspnea (more frequent in elderly patients, p=0.05). Diagnosis was fortuitous or obtained by a screening test in 20% elderly patients vs 24% in younger patients (p=0.57). The delay between the initial symptoms and the first visit with a thoracic oncologist was similar between the 2 groups (median of 1.1 months [IQR 23 days – 3 months] in elderly patients vs 1.4 months [IQR 19 days – 3 months], p=0.99). The time between the initial symptoms and the beginning of the specific treatment of the cancer was similar in the 2 groups (median 2.5 months [IQR 1.7 months – 5.8 months] in elderly patients versus 2.7 months [IQR 1.6 months – 4.2 months] in younger patients, p=0.51). The time between the first visit and the beginning of the treatment was also similar in the 2 groups (median 1.2 months [IQR 20 days – 2.1 months] versus 1.1 months [IQR 14 days – 1.9 months], p=0.35). These three time periods did not differ between the 2 groups, irrespective of the histological type and the staging. Eighty percent of elderly patients were actively treated with chemotherapy, surgery and/or radiotherapy, compared with 98% of younger patients (p<0.0001).
Conclusion: We found no difference regarding the initial symptoms of lung cancer between elderly and younger patients in our population, except dyspnea, more frequent in elderly patients. Diagnosis and treatment delays were similar in the 2 groups.
Keywords: elderly patients, Lung cancer, initial symptoms

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P4.044 ADHERENCE TO ANTI-CANCER TREATMENT : UNIQUE STUDY METHOD FOR DEVELOPING NATIONS

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Background: Adherence to lung cancer treatment is complex multi-factorial issue. A clinical audit aims to improve patient care and outcomes through systematic review of care against explicit criteria. Very few studies done to understand this issue.
Methods: A large-scale audit was conducted to assess adherence to the lung cancer treatment guidelines. Case records of 210 lung cancer patients (identified from patient databases and pharmacy records) who initiated anti-cancer therapy sequentially from early 2007 to late 2010 were examined retrospectively from 4 sites. Information was collected on treating physician, patient demographics, ART regimen, and guideline recommendations for patient management, monitoring and clinical outcomes. Only data explicitly stated in the medical records was abstracted. Patient de-identified information was entered into collective database over 3 months by trained data collectors.
Results: The key changes in lung cancer therapy guidelines over time were summarized. This audit has demonstrated successful measurement of adherence to guidelines for lung cancer therapy initiation. Barriers include inadequate infrastrustre for such study, resource, time involved and need for data collectors with good lung cancer therapy experience and knowledge.
Conclusion: The results of audit will enable feedback on clinical practice to improve patient care in participating sites and the audit can be repeated in future, perhaps in a simplified format, to assess changes in adherence to treatment guidelines. There is potential to extend the guidelines audit to other sites that manage lung cancer in future.
Keywords: Lung cancer, adherence, therapy

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P4.045 IMPROVING CLINICAL RESEARCH, RESOURCES, SUPPORT SERVICES AND HEALTH RELATED QUALITY OF LIFE IN AGE-SPECIFIC THORACIC CANCER PATIENTS

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Background: A retrospective analysis was done at M. D. Anderson from 1985 until 1994. The comparison between 157 patients (pts) younger than 40 years with adenocarcinoma of the lung and the counterpart older than 50 years with the same diagnosis didn't show any differences in the outcome of the disease in terms of overall survival or progression-free survival. As a conclusion authors stated that these pts should be treated similarly to older pts. However, the common perception is that this is a distinct category of pts, who requires a different approach during diagnosis and treatment, mainly due to a complex psychological environment. Unlike paediatric cancer pts, few young adults with lung cancer are involved in clinical trials. Furthermore, only 20 to 35% of pts between 15 to 19 years are treated at institutions that are involved in NCI-sponsored treatment clinical trials and only 10% of them are enrolled in trials. By contrast only 1 to 2% of pts aged between 20 to 39 year-old are entered into NCI-registered clinical trials taking into consideration that this small percentage could be due to the fact that few clinical trials are available for this category of pts. To overcome this limit and to enhance understanding biological features we planned to create a database dedicated to young pts with thoracic malignancy.

Methods: We performed a retrospective analysis at the Thoracic Oncology Unit of San Luigi Hospital from 2007, January the 1st to 2010, December the 31st, identifying 12 pts with thoracic carcinoma aged between 15-39 year-old.

Results: In this population, mean age was 36 years old.

patient	histotype	age at diagnosis	gender	smoking habit	clinical trials	biomolecular features
1	adenocarcinoma	37	F	no	yes	NA
2	adenocarcinoma	35	M	no	yes	NA
3	adenocarcinoma	34	M	current	yes	NA
4	squamous ca	39	F	current	no	NA
5	adenocarcinoma	33	M	current	no	EGFR+
6	adenocarcinoma	36	M	current	yes	NA
7	squamous ca	38	M	current	no	NA
8	adenocarcinoma	39	M	no	no	EML4/ALK+
9	MPM	35	M	former	no	NA
10	adenocarcinoma	36	M	no	no	EGFR-
11	adenocarcinoma	39	F	current	yes	NA
12	SCLC	39	F	no	yes	NA

Conclusion: pts aged 15 to 18 years are unlikely to have tumour biology or host physiology that is different from those over age 18, yet they usually are excluded from first line adult drug development studies. Furthermore, while nearly all paediatric cancer treatment trials include pts at least to age 18, a 15 year-old have a disease that is not covered by paediatric trials but is ineligible for adults trials and the same could happen for young adult pts. A dedicated database would be the first step to better understand cancer biology and specific features of those cancers that occur in this age group, with the purpose to develop more specific approaches to these pts and personalized clinical trials.

Keywords: thoracic malignancies, young patients

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P4.046 THE CHANGING LUNG CANCER INCIDENCE IN HEALTH AREA NINGBO , CHINA

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Background: A previous study demonstrated that lung cancer incidence in Ningbo area had increased in the past years. We expanded the original data set to determine if this increase had continued between 2007 and 2010. Objective of this study is to identify incidence, mortality rate and characteristic of diagnosed lung cancer, and to estimate whether it develop work load to health organizations and influence health benefit.

Methods: A retrospective observational study based on hospital admission/discharge records and pathological department data on lung cancer was brought to Ningbo No.2 Hospital between

01/01/2007 and 31/12/2010.

Results: According to the hospital data the number of diagnosed lung cancer carried to Ningbo No.2 Hospital was 1605 during study period. Of all malignant tumor (10139) collected, 15.8% were lung cancer which ranked the highest in every study year. Average age of the sample was 62.2 years .The incidence of lung cancer was fluctuated from 367 (2009) to 440 (2008) in the hospital records, 371(2007) and 427 (2010) respectively. Mortality rate was from 20.8% (2010) to 35.9% (2008) .General bed occupancy of lung cancer were 32597 days which possessed 14.78 % among all hospitalized patients during study years. Referring to the pathological department data only 822 cases were diagnosed as lung cancer which represents just 51.2% of the admission/discharge data (1605) at the same period. Proportion of diagnosed lung cancer cases was unbelievably low .The main reason for the above difference between hospital admission/discharge data and pathological department is found to be that the number of post operated patients from other health organizations and chemotherapy cases were not taken into account at pathology departments. According to pathological records, male to female ratio was 2.2 (567) : 1 (255). A significant rise was observed in women in 2010(83) comparing those diagnosed in 2007(38) , men patients were increased 1.88 times from the first year (109) to fourth year(202).Of all ages the most popular group happened to 50-60 years (278/33.8%) and 60-70 years (269/32.7%) . There was no significant difference in average age in each study year. According to the pathological analysis, the most frequent histological characteristics were adenocarcinoma (50.3%/413) and squamous cancer (28.4%/233).Only 22 females in squamous within 4 years, however, the number of females (168) were close to males(132) in adenocarcinoma cases.

Conclusion: Lung cancer is a health problem of the first order in Ningbo area, results reveal that lung cancer remains to be the leading cause of cancer death in both men and women, female victims increased dramatically in malignant tumors. Lung cancer has resulted in a big workload of Ningbo No.2 hospital. Mean age of the appearance of the disease was within the national range, the majority of the cases being age over 50 years. The most common histology type was adenocarcinoma cell carcinoma. With a sustained burden of lung cancer projected for the coming years, a method of early detection that could effectively reduce incidence and mortality from lung cancer would potentially have an enormous public health benefit.

Keywords: Lung cancer Incidence, Work load, mortality, health benefit

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.047 MODIFICATION OF LUNG CANCER IN A FRENCH MONOCENTRIC COHORT BETWEEN 1990 AND 2010

Fabien L. Vaylet[1], Jacques Margery[1], Alexa Mairovitz[1], Herve Le Floch[1], Frederic Riviere[1], Ignes N'gampolo[1], Wanda Gaspard[1], Francois Pons[2], Rene Jancovici[2], Jean Philippe Arigon[2], Patrick Saint Blancard[3], Claude Marotel[1], Jean-Christophe Pouget[4], Pierre L'Her[1]

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Background: Authors report the analysis of monocentric cohort of 1400 patients with lung cancer followed between 01.01.1990 and 31.12.2009.

Methods:

Cohort	1990-1994	1995-1999	2000-2004	2005-2009	Global
Sex-ratio M/F	7.3	3.6	2.9	2.7	3.3
Median age	63	65	65	67	65
Non smoker	4 %	8 %	8 %	12 %	8 %
Adenocarcinoma	30 %	39 %	52 %	57 %	47 %
Epidermoid	41 %	32 %	23 %	19 %	27 %
Small cell	10 %	10 %	9 %	8 %	9 %
Stade I	17 %	29 %	22 %	22 %	23 %
Stade II	9 %	8 %	4 %	4 %	6 %
Stade III	40 %	35 %	25 %	24 %	28 %
Stade IV	32 %	29 %	44 %	50 %	40 %
Diagnosis by endoscopy	73 %	60 %	43 %	44 %	52 %
Diagnosis by punction	3 %	9 %	21 %	21 %	15 %

Results: This cohort is the largest single center in French literature. The analysis over 20 years shows epidemiological and histological changes.

Conclusion: This analysis shows the increase of adenocarcinoma with increase of female patients, of non smoker-status and increase of diagnosis by TDM punction. Non small cell is stable. Median age of diagnosis is a little bit increasing. The increase of stage IV and the decrease of stage III is due to a best staging with the routine use of PET and Brain RMI procedures since 2000.

Keywords: Lung cancer, Epidemiology, histology

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.048 SURVIVAL OF LUNG CANCER IN A FRENCH MONOCENTRIC COHORT BETWEEN 1990 AND 2010: IMPROVEMENT AND HOPE.

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Background: Authors report analysis of monocentric cohort of 1400 patients with lung cancer followed between 01.01.1990 and 31.12.2009.
Methods: Kaplan -Meyer and Foucher methods are used.
Results: The survival with Kaplan-Meyer method is 56 % at 1 year, 23 % at 5 years and 17 % at 10 years. Analysis of relative survival, taking into account the mortality of the general population without lung cancer, is 57% at 1 year, 26% at 5 years and 22% at 10 years (Method of Foucher, on 1990-2005 population).

	Relative Survival at 1 year	Relative Survival at 5 years	Relative Survival at 10 years
Stage I	94 %	76 %	64 %
Stage II	71 %	51 %	38 %
Stage IIIA	60 %	30 %	21 %
Stage IIIB	56 %	22 %	16 %
Stage IV	34 %	6 %	3 %

The period analysis shows an improvement on overall relative survival.

	Relative Survival at 1 year	Relative Survival at 5 years	Relative Survival at 10 years
1990-1994	50 %	16 %	14 %
1995-1999	59 %	27 %	22 %
2000-2004	59 %	30 %	*
2005-2009	*	*	*

*Insufficient delay. The period analysis shows an improvement in relative survival at 5 years by stage.

Relative Survival at 5 years	1990-1994	1995-1999	2000-2004
Stage I	57 %	65 %	64 %
Stage II	37 %	28 %	47 %
Stage IIIA	8 %	20 %	35 %
Stage IIIB	7 %	8 %	26 %
Stage IV	0 %	1 %	5 %

Conclusion: This analysis shows a very interesting increase of the relative survival of lung cancer patients since 1990, global and by stage (1997 WHO Classification).
Best staging by PET and RMI and best medical strategies explain this results, specially for Stage III and Stage IV: An Hope for this pathology
Keywords: Lung cancer, Epidemiology, survival

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.049 IMPROVEMENT OF THE SURVIVAL OF STAGE IV LUNG CANCER IN A FRENCH MONOCENTRIC COHORT BETWEEN 1990 AND 2010. AN HOPE.

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Background: Authors report the analysis of relative survival of stage IV patients from a monocentric cohort of 1400 patients with lung cancer followed between 01.01.1990 and 31.12.2009.
Methods: The analysis is done for 367 patients stage IV on the 991 lung cancers diagnosed (1997WHO Classification), over only the period 1990-2004 to have a sufficient delay. 52 % are adenocarcinomas, 15 % squamous, 10 % large cell and 16 % small cell. Sex ratio Male/Female is 3. Median age is 63 years. 9 % are non smoker status. Diagnosis is obtained by

endoscopy in 57 %, by pleural (7 %), parenchyma (13 %) and metastasis (12 %) biopsies. PET-CT and Brain RMI are used in routine since 2000.
77 % received first line chemotherapy, 46 % a second line chemotherapy, 6% a biotherapy (after 1995).
Results: The global Kaplan Meyer survival of these patients is 31 % at one year, 5.8 % at 3 years and 3 % at 5 years. The global relative survival, taking into account the mortality of the general population without lung cancer is 34 % at 1 year , 6 % at 3 years and 3 % at 5 years. The period analysis shows an improvement in relative survival:

	Relative Survival at 1 year	Relative Survival at 3 years	Relative Survival at 5 years
1990-1994	23.7 %	0 %	0 %
1995-1999	28.2 %	2.8 %	1.4 %
2000-2004	38.5 %	10.4 %	5.4 %

Conclusion: The multivariate analysis made by the method of Cox and the Esteve shows an improvement of the survival respectively with an odds ratio to 0.79 (p = 0.0418) and 0.70 (p = 0.0012) for the period 2000-2004 compared to 1990 -1994. It 's possible to explain this result by the best selection of patients after PET and RMI and by best therapeutic strategies (more of first line chemotherapy, more of second line chemotherapy and beginning of biotherapy) available in the recent period. An hope for this pathology.
Keywords: Lung cancer, Epidemiology, survival, Metastasis

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Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.050 THE INFLUENCE OF GENETIC POLYMORPHISM OF CYP1A2, GSTT1, GSTM1, NAT2 AND MDR1 ON LUNG CANCER PREDISPOSITION

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Background: At present a rise in oncologic diseases including lung cancer (LC) is associated with increasing environmental pollution with xenobiotics. Penetrating into organism xenobiotics are subjected to biotransformation processes. Change in the activity of xenobiotic biotransformation enzymes related to the existence of genetic polymorphism results in increased susceptibility of organism to deleterious effects and, in consequence, to a rise in a risk of developing various oncopathologies. One of the causes of tumor development is known to be disbalance of activation, inactivation and removal of toxic compounds. On this connection it is necessary to take into account the total contribution of polymorphic variants of genes encoding enzymes of I and II xenobiotic biotransformation phases as well as P-glycoprotein in detecting predisposition to LC.
Methods: The study comprised 118 LC patients undergoing treatment at Minsk Oncologic Dispensary over the period from 2003 to 2009. The control group includes 329 persons without oncopathology permanently living in the area of Belarus. PCR-RFLP and multiplex PCR methods were used for studying polymorphism of genes: CYP1A2 (C734A) – the activation phase; GSTT1 (deletion), GSTM1 (deletion), NAT2 (C481T, G590A and G857A) – the detoxication phase and MDR1 (C3435T) – the removal phase. The examined individuals were divided into "fast" and "slow" acetylators according to the results of genotyping for three NAT2 sites (C481T, G590A and G857A). The association of genotypes with predisposition to LC was estimated odds ratio (OR) and 95%confidence interval (CI).
Results: The combination of genotypes «734CACYP1A2/ GSTT1(+)/ GSTM1(+)/3435CTMDR1» was revealed to exert a protective effect when the genes CYP1A2 and MDR1 are represented with heterozygote and the genes GSTT1 and GSTM1 do not contain homozygous deletion. The risk of LC development is increased in the individuals with the genotype combinations «734AACYP1A2/GSTT1(-)» or «GSTT1(-)/3435CCMDR1». The combination «734AACYP1A2/GSTT1(-)/3435CC MDR1» is of the highest risk importance, especially when the carrier of such a combination is a "slow" acetylator. Table – The most important combination of polymorphic gene variants of xenobiotic biotransformation enzymes in formation of predisposition to lung cancer

Genotype	OR (95%CI)
734CACYP1A2/GSTT1(+)/ GSTM1(+)/ 3435CTMDR1	0,37 (0,16-0,91)
734AA CYP1A2/GSTT1(-)	3,26(1,61-6,60)
GSTT1(-)/ 3435CC MDR1	3,63 (1,33-9,96)
734AA CYP1A2/GSTT1(-)/3435CC MDR1	11,37 (2,25-57,39)
734AA CYP1A2/GSTT1(-)/"slow" acetylator/ 3435CC MDR1	15,49 (1,71-110,56)

Conclusion: Thus, the study of genetic polymorphism of enzymes at all phases of xenobiotic biotransformation in an individual increases the degree of prognosis accuracy of his predisposition to LC. Association of homozygous GSTT1 gene deletion with predisposition to LC was detected in residents of Belarus. Combinations of polymorphic gene loci of biotransformation enzymes exert a modifying effect on risk importance of GSTT1 genotype in lung cancer development.

Keywords: Lung cancer, genetic polymorphism, xenobiotic biotransformation enzymes

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P4.051 LUNG CANCER AS A SOCIAL DISEASE

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Background: Apart from a clear association with tobacco, other factors of importance for development of lung cancer have received little attention. We present a case-control study focusing on social variables and comparing lung cancer patients to those with large bowel cancer.

Methods: The research project was carried out during 2009 and 2010. A written questionnaire was completed by 248 consecutive patients with lung cancer and 244 patients with large bowel cancer treated at our institute. The two groups were balanced for gender and age. Data on place of birth, smoking history, diet and alcohol intake, body weight and height, profession, housing conditions and family income were collected and analysed. Statistical analysis was performed by using descriptive statistics, Mann-Whitney U test, chi-square test and logistic regression.

Results: There were significant differences between the groups regarding smoking status: non-smokers 7% vs. 52.3%, ex-smokers 70% vs. 38.6%, and current smokers 20.1% vs. 9.1% for lung and large bowel cancer respectively ($p<0.001$). The share of immigrants in patients with lung cancer was higher (19.8% vs. 11.1%, $p = 0.005$) compared to large bowel cancer patients. The proportion of patients working as industrial workers, construction workers or in other polluted working environment was also higher among lung cancer patients, as compared to large bowel patients (63.4% vs. 48.5%, $p = 0.001$). Especially striking is the difference in metal industry workers (35.3% vs. 18.2%, $p<0.001$). There were no statistically significant differences regarding housing conditions, family income, diet and alcohol consumption. The importance of smoking and polluted working environment was confirmed by a multivariate analysis.

Conclusion: When compared to patients with cancer of the large bowel, the group of lung cancer patients included a higher proportion of immigrants and a higher proportion of those working in polluted environment. While there is no doubt about the role of smoking in lung cancer carcinogenesis, social factors such as pollution in the working environment also play a role. The influence of polluted working environment on lung cancer incidence will be evaluated in detail in our future research work. In addition, adjusting our programmes to the needs of a low social class is essential for effective communication and should be considered when planning every step, from prevention to palliative care.

Keywords: social status, Epidemiology, Lung cancer, colon cancer

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P4.052 FEMALE LUNG CANCER: RE-ANALYSIS OF NATIONAL SURVEY OF LUNG CANCER IN KOREA, 2005

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Background: Female lung cancers have different clinical features and therapeutic results. The aim of this study was to analyze the differences in between women and men in Korean lung cancer.

Methods: We re-analyzed the result of national survey of lung cancer conducted by Korean Association for the Study of Lung Cancer (KASLC) at 2005.

Results: Of the 8,788 patients, 2,124 (24.2%) were

female. The mean age at the diagnosis was 62.5 years for females and 64.8 years for males, (p
Conclusion: Women with lung cancer were relatively overrepresented among younger patients and smoked less intensively, raising the question of gender-specific differences in the lung carcinogenesis. Over-representation of adenocarcinoma was observed in the women regardless of smoking status. Women with lung cancer had a better prognosis than men; however smoking female showed the worst prognosis. Gender and smoking status are clearly important factors in lung cancer approach.
Keywords: Female, Lung neoplasms

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P4.053 LUNG CANCER DISEASE PATHWAY MANAGEMENT IN ONTARIO, CANADA

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Background: Cancer Care Ontario (CCO) is the government agency responsible for continuously improving cancer services across the province of Ontario through 14 regional cancer programs. In addition to using funding levers, a defined performance management cycle and clinical engagement, CCO introduced a disease pathway management (DPM) approach in 2008 to improve cancer care. Its 4 objectives are to integrate all provincial quality improvement initiatives on a specific tumour type (guideline development, clinical quality improvement initiatives, performance indicator measurement); to systematically evaluate the full continuum of the patient journey and identify gaps in evidence, clinical practice and measurement that impact the quality of care and the patient experience; set and manage regional performance indicators across the pathway; and leverage specific tools to model the impact of policy decisions.
Methods: In 2009, the Lung Cancer DPM began with a draft lung cancer (LC) disease pathway by the project's co-chairs (WKE, YCU) and the establishment of five multidisciplinary working groups that focussed on prevention and screening, diagnosis, treatment and palliative care, end-of-life and survivorship, as well as a patient and family advisory group. Using the draft disease pathway to guide discussion, working groups held five two-hour meetings and developed 17 improvement project ideas across the patient journey. Eight of these were selected for detailed discussion at a provincial consensus conference which voted on priorities for action.
Results: A Priorities for Action Report has been prepared and is being widely circulated. The LC disease pathway has been refined through substantial multidisciplinary discussion, which has helped to standardize diagnostic and treatment approaches across the province. Regional "roadshows" have commenced that share the results of the Action Report and present regional LC care providers with region specific data on LC incidence, smoking rates, stage distribution, wait times for treatment, compliance with treatment guidelines, utilization of a standard symptom assessment instrument and metrics of the quality of end-of-life care. Regional cancer programs have been provided with funding to implement LC specific quality improvement initiatives. In particular, lung cancer diagnostic assessment programs/units with nurse navigators and dyspnea management standards have been the highest priority initiatives that regions have pursued to date.
Conclusion: A lung cancer DPM initiative in Ontario has identified priorities for action to improve the quality and processes of diagnosis and care and the overall patient experience for those touched by lung cancer. Funding is being linked to quality improvement initiatives and to the creation of diagnostic assessment programs that facilitate timely access to diagnosis and treatment.
Keyword: Pathway Management

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P4.054 NON-SMALL CELL LUNG CANCER EPIDEMIOLOGY IN BRAZIL: RESULTS FROM 10-YEAR REGISTRY IN A PRIVATE ONCOLOGIC CENTER.

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Background: Lung cancer is a major burden around the globe and approximately half cases occur in developing countries. According to the Brazilian National Cancer Institute, 27,660 new cases were expected in 2010. However, this figure is probably underestimated, and specific registries in lung cancer are a priority. Capturing these data is crucial to better understand local characteristics, the impact of incorporating novel treatments/technologies, thereby supporting better resources allocation. Access to novel treatments/technologies among cancer patients in Brazil may differ between public and private sectors and features for the latter are not available to date.
Methods: A comprehensive non-small cell lung cancer (NSCLC) registry was conducted in a private oncologic center in Brazil from 1999 to 2010. Pathological diagnosis, disease characteristics, treatment modalities, and outcomes were evaluated. Staging was classified according to the AJCC 6th edition, and survival curves were compared using log-rank. Long-term follow-up was enabled through active surveillance, using telephone contact.
Results: 449 patients were included, and median age was 65 years (range 27-92). Most patients presented with advanced disease, with a 54.2% frequency for stage IV (includes wet IIIB), 25.2% for stage III, 5.6% stage II, and 14.4% stage I. 25% were never-smokers, and adenocarcinoma was the most frequent histology (49.1%), followed by squamous cell carcinoma (20.5%). Surgery was performed in 26.1% of patients, adjuvant chemotherapy in 11.7%, and neoadjuvant chemotherapy in 7.3%. 251 patients (56.5%) received palliative chemotherapy, and 127 (50.6%) were also treated with second-line. 51.8% of patients received radiation therapy in some moment during disease treatment. After 10.7 months median follow-up, the overall survival was 17.6 months (95% CI, 15.7-19.6). According to tumor stage, the median survival was not reached, 99.7, 20.2, and 13.8 months for stages I, II, III, and IV, respectively (P=.0001). The estimated 3-year overall survival according to tumor stage was 83.1%, 69.8%, 32.8%, and 19.7%.
Conclusion: The described features are in line with the current worldwide literature in NSCLC, and outcomes are favorably similar to descriptions from developed countries.
Keywords: Lung neoplasms, Epidemiology, Registry

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P4.055 THE MYTH ABOUT ASBESTOS AND PHARAOHS: HOW WE IN THE NATURAL SCIENCES DO NOT CHECK NON-MEDICAL "FACTS"

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Background: Over the years many times presentations on the medical aspects of asbestos have started with the sentence: "Asbestos was used in old Egypt to protect the mummies of their pharaohs". When challenging this, the answer is: it is on the net. We decided to further investigate this.
Methods: A search of the net and investigating whether there is any reality behind this claim.
Results: In Google, a search on "asbestos and pharaoh" yields 488 000 hits in 0.44 seconds. A random search of some of these show that many are from lawyer´s offices offering help to asbestos victims who start with an historic review. Many others are similar reviews from other sources. If there are any references, they are cross-references – i e to each other, and none goes back to any reference from Egyptology or archeological sources. The oldest we have found is from 1947, a medical paper giving no reference at all. In the world of egyptology, nobody has ever heard of asbestos being used anywhere or for anything in the old Egypt. Notably, Wikipedia (which is more careful about references) does not mention anything about pharaohs in its review of asbestos history.
Conclusion: In the medical sciences, we are very careful about medical facts, making sure that we have reliable references. However, we are much less careful about non-medical "facts", which we do not bother to check very thoroughly.
Keywords: asbestos, history, old egypt, mummy

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P4.056 ARE LUNG CANCER TREATMENT AND SURVIVAL RATES IMPROVING IN THE UK? RESULTS FROM THE NATIONAL LUNG CANCER AUDIT.

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Background: Lung cancer treatment rates and survival previously reported in the UK are low by international comparison, with significant geographical variation noted. The national lung cancer audit aims to address this via the collection of detailed data, case mix adjustment and feedback of results to drive local improvement.
Methods: Data are presented at cancer network level for patients in England and Wales submitted to the audit in 2009, with results for 2008 shown for comparison. Casemix adjusted logistic regression models were performed for sex, age, stage, performance status and deprivation. The models compare the odds of an outcome occurring in one cancer network compared to the population average.
Results: 32,068 cases were submitted, which represents over 97% of expected cases. 76% were histologically/cytologically confirmed. Cell types were non small cell 59%, small cell 11%, mesothelioma 5% and carcinoid 1%. The mean, range and case-mix adjusted odds ratios for key outcomes (excluding mesothelioma) are shown in the table.

				Case-mix adjusted odds ratios	
		mean	range	minimum	maximum
Histology confirmed	2009	76%	64-87%	0.56	2.18
	2008	72%	56-88%	0.47	3.37
Active treatment	2009	59%	41-69%	0.36	1.71
	2008	54%	39-68%	0.46	2.06
Surgery in confirmed NSCLC	2009	18%	13-24%	0.60	2.13
	2008	14%	5-32%	0.31	3.71
Chemotherapy SCLC	2009	65%	35-79%	0.28	2.18
	2008	62%	39-84%	0.32	3.45

Median survival was 189 days (range 150-224 days). Following case mix adjustment, the hazard ratio of risk of death varied from 0.78 to 1.26. In 2008 the median survival was 174 days (range 147-222 days) with a hazard ratio range of 0.74 to 1.22.
Conclusion: Treatment rates for lung cancer patients seen in 2009 have increased when compared to 2008, with a reduction in national variation. This is associated with a small increase in overall median survival. However, national variation persists, even after case mix adjustment. Possible explanations include differences in co-morbidities that are not linked to deprivation, or variations in lung cancer pathways. Organisations are encouraged to continue to examine their own results and review their local guidelines and care pathways in order that regional variability is reduced and outcomes are improved.
Keywords: Audit, treatment, survival

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P4.057 IS THERE AN ASSOCIATION OF THE SPECIALTY OF THE DIAGNOSING PHYSICIAN ON DELIVERY OF GUIDELINE-BASED THERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC) IN THE US?

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Background: Previous studies have shown that a referral to an oncologist is the strongest predictor of chemotherapy treatment in patients diagnosed with advanced NSCLC. No studies have addressed whether the specialty of the physician involved in the diagnosis of NSCLC affects the likelihood of subsequent delivery of guideline-based therapies. Using a nationally representative US sample of NSCLC patients, we investigated the association between the specialty of the physician involved in the initial diagnostic work-up and receipt of guideline-based therapy for stages IIIA/B and IV NSCLC.
Methods: We performed a retrospective cohort study using the SEER-Medicare database. Inclusion criteria consisted of patients with newly diagnosed stages IIIA/B and IV NSCLC without prior cancer history, who were diagnosed between 01/01/2000 and 12/31/2005. Patients had to be alive at least 2

months after diagnosis and have Medicare claims data available. We linked the physicians' unique physician identification numbers (UPINs) available in Medicare claims to the American Medical Association (AMA) masterfile database to obtain information on physician primary specialty. We defined the diagnosing physician as the one whose UPIN was listed in the closest billing claim for NSCLC-related CT scans (93% chest CTs) that preceded or were within 45 days of the cytological or histological diagnosis of NSCLC. A multi-level mixed logistic model was used to measure the association of the diagnosing physician specialty with receipt of guideline-based therapy within 4 months of diagnosis, defined as chemotherapy with surgery, chemoradiation, or chemoradiation and surgery for stage IIIA, chemoradiation for stage IIIB/NOS, and chemotherapy for stage IV, adjusting for patient covariates, including year of diagnosis, age, gender, race, co-morbidity, geographic area, median household income (census tract level), tumor histology, stage, and patient clustering around physicians. We estimated odds-ratios (OR) with respective 95% confidence intervals.

Results: 30,234 NSCLC patients were included in the analysis. Mean age was 75.6 (SD 6.1), 16,005 (53%) were male, 25,146 (83%) were white, and 15,505 (51%) had stage IV disease. The number (percentage) of patients treated with guideline-based therapies within 4 months was as follows: 1,716 (38%) for stage IIIA (80% chemoradiation, 9% chemotherapy and surgery, and 11% chemoradiation and surgery); 2,643 (26%) for stage IIIB/NOS (chemoradiation); and 7,917 (51%) for stage IV (chemotherapy). The six most common diagnosing physicians' specialties were internal medicine (10,391, 34% patients), family practice (5028, 17%), pulmonology (3,671, 12%), emergency medicine (1380, 5%), cardiology (1282, 4%), and hematology-oncology (1,064, 4%). Relative to internal medicine, patients who were diagnosed by hematologists-oncologists were more likely to receive guideline-based therapies for any stage (absolute difference of 16%; adjusted OR=1.6; 95% CI= 1.4 to 1.8). Other specialties were not statistically different than internal medicine in regards to the likelihood that their patients received guideline-based therapy. The associations were similar across all stages.

Conclusion: This observational study showed that advanced NSCLC patients managed during the peri-diagnostic period by hematologists-oncologists were more likely to receive guideline-based therapies. These results suggest an opportunity for improvement in timely referral of NSCLC patients to cancer specialists in order to optimize their access to appropriate therapies.

Keywords: diagnosis, SEER-Medicare, Lung cancer, physician specialty

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P4.058 INCIDENCE AND CHARACTERISTICS OF BRONCHIAL COLONIZATION AT THE TIME OF LUNG CANCER DIAGNOSIS: A PROSPECTIVE STUDY.

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Background: Bronchial colonisation is frequently reported in patients with lung cancer. These colonisations could influence patient therapeutic management and prognosis. The aim of our study is to refine prospectively incidence and nature of bronchial colonisations in patients presenting with lung cancer.

Methods: Two hundred and twelve patients with lung cancer underwent a flexible bronchoscopy at the time of diagnosis of lung cancer. Bacterial, mycobacterial and fungal investigations were systematically performed for all patients. Type and frequency of these colonisations were analyzed and correlated with patients and tumours characteristics and outcome.

Results: Microbiological data were available for all patients (n = 212). Potential pathogens were found in 48.6% of samples. It is noteworthy that we still found 20.3% of infection by using a threshold at 10^5 UFC/ml. We identified Gram-negative bacilli (Haemophilus influenzae 4.2%, Enterobacter sp. 3.8%, Escherichia coli 8.5%, Serratia 3.2%, Pseudomonas Aeruginosa 2.4%, Klebsiella 3.3 %) but also gram positive bacilli (Staphylococcus 12.3%, Streptococcus pneumonia 3.3%). In addition, we found 0.5% of atypical mycobacteria, 42.5% of Candida albicans, and 4.7% of Aspergillus fumigatus. Our study highlighted that aged patients

(p=0.005) with COPD (p=0.02) were significantly more often colonized. At the contrary, tumor stage, atelectasis, bronchial stenosis and abnormalities of chest X-Ray were not associated with a higher rate of colonizstion. Squamous cell carcinoma were more frequently colonised than other histological subtypes but it was not statistically significant (p = 0.11). Survival data were avalaible for 198 patients. Bacterial colonisation was associated with a worse survival when compared with patients without colonisation even if the difference was not statistically significant (p = 0.36).

Conclusion: Colonisation of airways is reported in almost half of the patients presenting with a lung cancer. This colonization is more frequently observed in fragile patients. Collecting colonisation status of patients at the time of diagnosis may help clinicians to better predict prognosis and subsequent infectious complications of lung cancer.

Keywords: bronchial colonisation, infection, Lung cancer, bronchoscopy

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P4.059 EPIDEMIOLOGY OF LUNG CANCER IN CROATIA IN A 23-YEAR PERIOD (1985-2008)

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Background: Worldwide, lung cancer is one of the most common cancers in terms of both and mortality (around 1.4 million new cases per year and around 1 million deaths). Rapid increase of lung cancer over the last century from a relatively rare disease to an epidemic is attributed to the exposure to tobacco smoke and other risk factors. Recently published epidemiological indicators put Croatia at the top of the list of countries with high mortality rates from lung cancer.

Methods: The aim was to demonstrate epidemiological indicators for lung cancer in Croatia (International Clasification of Diseases, 10th revison, codes C33-C34) in the period between 1985 and 2008 and to compare our results with other European countries. We used a wide range of statistical data sources (obtained from cancer registry websites or annual reports), ranging from those of World Health Organisation (WHO) to the data of Croatian National Cancer Registry (CNCR).

Results: According to CNCR, approximately 33% of all deaths in Croatia are caused by cancer. Among male population, lung cancer takes 18% and among female population 6% of the total number of patients diagnosed with cancer. Among males, incidence of the lung cancer is in the first place and also in the first place by the cause of death. Among females, incidence of lung cancer is in the third place. The 5-year survival for all stages and histological types is approximately 12%. The peak incidence is between the ages of 70 and 75, with the disturbingly increasing trend above the age of 60, when 90% of cases are diagnosed. In 2008, according to data of CNCR, the overall incidence of lung cancer was 57.1/100 000 (94.6/100 000 for men and 22.3/100 000 for women). In 1985, according to the data of WHO, there were 1919 lung cancer deaths (1664 men (76.9/100 000) and 255 women (11.05/100 000)). In 2008, number of deaths among men was 2139 (100.42/100 000) and among women 611 (26.65/100 000), which represents the total cumulative increase of the mortality rate of 44.5% (31% for men and 142% for women) in the 23-year period. WHO ranked Croatia as the 12th in the world and as 7th in Europe on the list of countries with the highest mortality from lung cancer for the year 2008.

Conclusion: The overall cumulative rate in mortality from 44.5% in the period between 1985 and 2008 is shocking. Despite all efforts in the diagnosis and treatment of lung cancer, 80% of patients are diagnosed in the advanced stage of the disease. The main risk factor is cigarette smoking. In Croatia, 27.4% of the population are declared smokers, which represents a disappointing fact. Although contemporary oncology has very effective way of treatments, an increased mortality rate is caused by late detection of the disease. The first preventive step in the fight against lung cancer in Croatia was made in 2009 by the legal prohibition of smoking in all public places. The effects of this law will be visible in the future.

Keywords: Epidemiology, mortality, Lung cancer, incidence

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P4.060 EGFR/KRAS MUTATIONS IN AFRICAN AMERICANS (AA) VERSUS CAUCASIANS (CA) IN PATIENTS (PTS) WITH NSCLC: A COMPARATIVE ANALYSES OF THE SOUTH CAROLINA EXPERIENCE.

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Background: AAs with NSCLC has inferior survival compared to CAs. We sought to discern whether differences in incidence of EGFR or KRAS mutations between races could partly explain these differences.
Methods: Pts with NSCLC who were seen at the Hollings Cancer Center (HCC) and underwent EGFR and KRAS mutation testing in 2010 were included. Microdissected formalin-fixed paraffin-embedded tumors from 89 patients with NSCLC were analyzed for EGFR/KRAS mutations by allele-specific PCR. Data were compared with previously reported experiences from Memorial Sloan Kettering Cancer Center (MSKCC), Case Western Reserve (CWR), and Louisiana State University Health Sciences Center (LSU). We estimated the percentage of EGFR+ and KRAS+ AA and CA subjects using exact binomial confidence intervals, and compared proportions using Fisher's exact test. Aggregate estimates were obtained using inverse variance-weighting and random-effects modeling to account for study heterogeneity.
Results: Of the 89 pts, 63 were CAs and 26 were AAs. In AA population, 24/26 pts had successful EGFR and KRAS analysis. In the CA population 59/63 pts and 61/63 pts had successful EGFR and KRAS testing, respectively. Data are in the table below. A weighted aggregate are also compiled.

	EGFR	Status		KRAS	Status	
	N+/Total N (%; 95% CI)	N+/Total N (%; 95% CI)	p	N+/Total N (%; 95% CI)	N+/Total N (%; 95% CI)	p
	AA	CA		AA	CA	
HCC	2/24 (8; 1, 27)	10/59 (17; 8, 29)	0.49	6/24 (25; 10, 47)	16/61 (26; 16, 39)	>0.99
MSKCC	23/121 (19; 12, 27)	61/476 (13;10, 16)	0.11	21/121 (17; 11, 25)	125/476 (26; 22, 30)	0.04
CWR	1/53 (2; 0, 10)	15/89 (17; 10, 26)	0.005	12/53 (23; 12, 36)	16/76 (21; 13, 32)	0.83
LSU	NR	NR		22/60 (37; 25, 50)	10/51 (20; 10, 33)	0.06
Aggregate	26/198 (10; 0, 21)	86/624 (14; 11, 16)	0.51	61/258 (25; 16, 33)	167/664 (25; 22, 28)	0.92

CI = Confidence intervals; NR = Not Reported
Conclusion: Overall, the incidence of EGFR and KRAS mutations were similar for AAs and CAs. The observed differences in survival between AAs and CAs cannot be explained by differences in the molecular entities examined. Detailed demographic and survival data will be provided at the meeting.
Keywords: EGFR, Kras, Mutation

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.061 DELAY IN DIAGNOSIS OF LUNG CANCER IN SOUTHERN INDIA – AN ANALYSIS

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Background: Lung cancer is one of the most common cancer disease in India. Nevertheless it has been diagnosed at a verly late stage, for which curative approach is not available. Hence we have thought of identifying the reasons for delay in diagnosis of Lung cancer.
Methods: A Prospective study was done on stage III and Stage IV patients who had presented to our hospital during January 2009 and December 2010 ,with symptoms of more than one month. Identified patients were asked to fill a Questionnaire,mentioning the details for delay. The results were tabulated and analyzed.
Results: During the study period 156 patients were evaluated in our outpatient clinic,out of which only 122 patients were found to be eligible for the study and were offered the Questionnaire. Hundred and one(82.78%) patients were males and 21(17.22%) patients were females.Patients age ranged from 32 to 78 years(mean – 54.15years). Eight patients had taken self medication and had not visited a Physician. Fifty one(41.8%) patients were evaluated by chest X-ray by the Family physician of which

21(17.21%) patients X-ray did not show any finding. Remaining 30(24.59%) patients were presumed to have tuberculosis and was treated empirically with antitubercular drugs. Thirty (24.59%) patients were advised evaluation by their physician, but did not have radiographs done due to financial reasons. Twenty eight(22.95%) patients symptoms were ignored by the family members. 17(13.93%) patients did not proceed for further evaluation as their symptoms disappearad after their visit with the Physician.10(8.19%) patients were not evaluated with chest radiograph as they had symptoms not related to chest. Almost one half (48%) of the patient had a combination of factors for delay in diagnosis.
Conclusion: Several reasons for delay in diagnosis were found. High prevelance of Pulmonary Tuberculosis and the bias of the Family physician plays a major part in delayed referral. Low socioeconomic status is also a major concern in our patient population.
Keywords: Delay in Diagnosis, Lung cancer,

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P4.062 MANAGEMENT OF LUNG CANCER IN AUSTRALIA: HAVE WE MADE PROGRESS?

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Background: Lung cancer outcomes in Australia remain very poor. We aimed to document management and compare to a 1993 population-based survey, which had indicated poor compliance with guidelines.
Methods: Patients diagnosed during 6 months of 2003 were identified from the Cancer Registry and data obtained from source documents
Results: Data were available for 841 patients (82% of eligible pts): median age 72 yrs and 63% male. Most were ex-smokers (57%), with 8% never smokers (71% female). For smokers, the median exposure was 37 and 52 pack years for females and males respectively (p<0.001). Only 2% were screen-detected. Diagnostic modality was: clinical only 10%; cytology alone 20%, histology 70%. Considering NSCLC (n=655): adenocarcinoma 40%, squamous 23%, large cell 13%; stage I/II 24%, III 26%; PS 0-1 63%; PET scan 43%; invasive staging of mediastinum 8%; specialist referral 99%; discussed at multi-disciplinary case conference (MDM) 33%. Of 206 pts (32%) treated with curative intent, 130 (20%) underwent surgery (lobectomy 82, pneumonectomy 18, segmental resection 30) with 86% of patients having a R0 resection and only 7% adjuvant chemotherapy. With curative intent, 91 pts (48%) received radiotherapy. 311 pts (48%) had palliative treatment while 138 pts (21%) received no therapy. Considering all NSCLC pts, 258 (39%) received chemotherapy and 365 (56%) radiotherapy at some time during their illness. Considering the 101 pts with SCLC, 67% had PS 0-1, 33% limited disease, 99% saw a specialist and 21% discussed at MDM. 9% received no treatment while 27 pts (27%) were treated with curative intent, including 16 (20%) with chemoradiation. For the 85 pts (10%) who did not have a pathological diagnosis, an attempt to obtain tissue was made in 62%. As compared with patients with a tissue diagnosis, these patients were older (79 vs 71 yrs, p<0.001), worse PS (PS 0-1 13% vs 51%, p<0.001), less frequently presented at MDM (11% vs 30%, p=0.001), and more likely to have no cancer treatment (84% vs 20%). Median survival was 1.1mths (SE0.2). Median and 5-year survival were: NSCLC 6.9m (SE 0.42) and 11%; SCLC 7.2m (SE 0.96) and 3%, respectively. Considering all pts, better survival on multivariate analysis was associated with younger age, good PS, no weight loss, early stage, never smoking and better socio-economic status. Changes from 1993 to 2003 were: median 3yrs older (69 vs 72yrs respectively, p<0.001); fewer males (70% vs 63%, p=0.002); less SCLC (14% vs 12%, p=0.10); more adenocarcinoma (32% vs 42%) and less squamous (42% vs 23%, p<0.001). Patients receiving no treatment were similar. Fewer patients went to a definitive surgical procedure, possibly due to use of PET scanning. When adjusted for age and sex, the overall 5yr survival did not change over the decade.
Conclusion: Despite increased use of PET scanning and more multi-modality therapy, lung cancer survival did not improve over the decade. New strategies are required to improve patient outcomes.
Keywords: Lung cancer, population-based, Management Survey, Health outcomes

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P4.063 TRENDS IN LUNG CANCER INCIDENCE AND MORTALITY IN BELARUS, 1970-2009

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Background: Lung cancer is the most frequent cause of cancer mortality among men and takes sixth place in female cancer mortality in Belarus while the prevalence of smoking remains unacceptably high. The objective was to describe main trends in lung cancer incidence and mortality in Belarus population.
Methods: Incidence and mortality trends were assessed by means of data derived from National Cancer Registry. Age-specific rates were investigated and age-standardized rates (ASRs, World) and cumulative risk were calculated. Linear regression analysis was used to reveal main trends.
Results: Overall, lung cancer incidence rates (ASRs) increased more than 100 and 34 % among males and females, respectively. ASRs for males peaked in 1994 (71,8 per 100 000), for females - in 1991 (5,8 per 100 000). ASRs for men were increasing up to 1994. Significant positive slope was revealed (1,83 with standard error SE=0,05) for this period. Then rates started to decrease and showed significant negative slope (-0,62; SE=0,074). In women any clearly defined trend has not been revealed. The rates were stabilized at around 4,7-5,6 per 100,000 women. But for urban women a slight negative slope was revealed while a positive slope was found out for rural women. Crude rates showed more pronounced tendency to increase, indicating that the major part of the growth was due to population ageing. The incidence showed an increase with age and reached peak in age group 70-75 in male and 75-79 in female. Age-specific rates showed steady increasing for elder age groups due to better diagnostics. But there could be a negative upward trend in the middle age groups for rural women. Mean cumulative risk was 9,3% (95% confidence interval 8,5Ã·10,1) for men and 0,99 (95% confidence interval 0,95Ã·1,04) for women. Trends in lung cancer mortality in men have tended to decrease during the last decade (slope -1,11 with SE=0,06). Standardized mortality rates for women were at stable level about 3,3-3,9 per 100 000 during 1999-2009. Mean ratio mortality/incidence was 0,7 for women and 0,81 for men in the last decade.
Conclusion: Lung cancer mortality trends in men are on a downwards path as in most European countries, while female rates may continue to rise, points to an urgent need for national prevention strategies that target tobacco cessation and prevention among women.
Keywords: incidence, mortality, Epidemiology

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P4.064 LUNG CANCER IN SOUTHERN INDIA – A SINGLE CENTRE EXPERIENCE OF PATTERNS OF PRESENTATION AND DISEASE CHARACTERISTICS

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Background: Lung cancer is the leading cause of cancer death in developed countries and is also rising at an alarming rate in developing countries. Very little data is available on the pattern of lung cancer presentation and treatment results among Indian patients. We aim to describe the clinical, histological, epidemiological and treatment characteristics of patients diagnosed with lung cancer in our hospital.
Methods: Ours is a retrospective study of patients treated in the Department of Oncology between January 2008 to December 2010.We did a chart review and collected the demographic, clinical and treatment details of all the patients diagnosed with lung cancer. The data were tabulated and analyzed.
Results: Two hundred and thirty four patients with lung cancer were treated in our department from January 2008 to December 2010.Eighty two percent were males (n=192) while the rest were females. {M:F=4.57:1}.The age of presentation ranged from 31 to 75 years(Mean-57.92 Years).Cough was the main presenting symptom in 41% of the patients.

(n= 96), followed by dyspnea (17.9%),Chest Pain(15.4%), Bone pain(10.3%),Headache (7.7%), Hemoptysis (4.4%) and Swelling in the neck(3.3%). More than two thirds of patients had more than one presenting complaint. Only 30 patients (12.82%) presented to our department within one month of onset of symptoms.132 patients (56.41%) presented within 1-2 months of onset of symptoms while 72 patients (30.76%) presented more than 2 months after onset of symptoms. CT guided Biopsy/ FNAC was the most common diagnostic modality employed(74.4%).Fifty one percent of tumors were right sided while 48.2% of patients had left sided tumors. In 2 patients, the tumors were bilateral. Right upper lobe was the most commonly involved lobe in 46.2% of patients(n=102). Adenocarcinoma was the most common pathology seen in 43.6%(n= 102) patients. Squamous cell carcinoma was seen in 66 patients. Small cell carcinoma was seen in 42 patients(17.9%) while 24 patients presented with poorly differentiated carcinoma.Only 15.4%(n=36) of patients presented with localized/ locally advanced disease while the remaining patients had metastatic disease at presentation.One hundred and twenty six patients(54%) presented with metastasis at single site while 72 patients(31.2%) presented with metastasis at multiple sites.Bone is the most commonly involved metastatic site(36.4%) followed by brain (18.2%) and Liver(18.2%)

Conclusion: More than 80% of lung cancer patients were detected in the unresectable advanced stages (IIIB and IV).Adenocarcinoma is the most frequent histological subtype in our patient population.Bone is the most common site of distant metastasis

Keywords: South India, Lung cancer,

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P4.065 NON-SMALL CELL LUNG CANCER IN NEVER-SMOKERS: EPIDEMIOLOGICAL CHARACTERISTICS AND SURVIVAL. A POPULATION BASED STUDY OF 9215 CASES.

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Background: Tobacco smoking is the major risk factor for lung cancer, but approximately 10% of all patients are live-time never-smokers. Nevertheless lung cancer in never-smokers is an understudied entity and data on this issue are limited. We aim to assess clinicopatological differences and cancer specific survival between smokers, ex-smokers and never-smokers with NSCLC.

Methods: Data was gathered from the Regional Lung Cancer Register in the Uppsala/Örebro region in Central Sweden, a population-based register covering 98% of patients diagnosed with lung cancer during the period 1995-2008. 9215 cases of lung cancer were analysed with regard to gender, age, performance status, histological types, TNM staging and survival.

Results: Of 7177 patients included in the study, 3321(46,3%) were smokers, 2868 (40,0%) were former-smokers and 733 (10,2%) were never-smokers. During 1995 to 2008 lung cancer in never-smokers increased from 8% to 11% among all lung cancer cases. The number of never-smoking lung cancer patients showed an increase with 46%, from 50 to 73 cases. Among never-smoking patients 70% were women. The never-smokers had a higher mean age at diagnosis than smokers (70,4 years versus 65,7 years). Adenocarcinoma was the most common histopatological type among all patients, but it was proportionally more frequent among never-smokers compared to current and former smokers. (69,2% versus 40% and 41,9%). Squamous cell carcinoma was less common among never-smokers than smokers. (11,2% versus 34,7%). There were no significant differences in performace status and TNM stage. Survival outcome was significantly better in female never-smokers with stage IA-IIB and stage IV as well as in male never-smokers with stage IV compared to smokers.

Conclusion: Lung cancer in never-smokers has increased over time, is diagnosed at a higher mean age and is more likely to be adenocarcinoma. Two thirds of the patients are women and there are differences in survival outcome compared to smokers. This suggests that lung cancer in never-smokers and smokers may be considered as two separate disease entities and caused by different carcinogenesis.

Keywords: survival, Non-small cell lung cancer, Never-smoker, tobacco smoking

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P4.066 STANDARD OF CARE THERAPY IMPROVES SURVIVAL TO A SMALL EXTENT IN NSCLC PATIENTS IN THE LAST 20 YEARS IN THE NETHERLANDS

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Background: Treatment of patients with non-small cell lung cancer (NSCLC) has changed over time. The aim of this study was to describe these changes in daily practice in patients with NSCLC in the Netherlands during the period of 1989-2008 and compare these changes to the guidelines. Potential effects on survival were examined.
Methods: All patients with NSCLC diagnosed during the period 1989-2008 were selected from the population-based Netherlands Cancer Registry. The Cochran-Armitage trend test was used to analyze trends in treatment. Relative survival trends were estimated by a multivariable linear regression model. Follow-up was complete up to February 1st 2010.
Results: NSCLC was diagnosed in 139,309 patients, almost 25% being ≥ 75 years. Among stage I, the proportion of younger patients (< 75 years) undergoing surgery increased from 84% in 1989-1993 to 89% in 2004-08 and among elderly (≥ 75 years) from 35% to 49%; for stage II this proportion decreased from 80% to 70% in younger patients and increased from 21% to 28% in the elderly. Adjuvant chemotherapy in stage II increased from 0% to 24% in younger patients, but remained <5% among the elderly. In stage III the proportion of younger patients receiving chemoradiation increased from 1% to 43% and in elderly from 0% to 13%. In stage IV use of chemotherapy in younger patients increased significantly from 10% to 54%, and in elderly from 2% to 21%. Although five-year relative survival for the total group has not increased since 1989, survival has increased within every stage and for patients younger than 60 years. After adjustment for treatment variables, this improvement remained only significant for patients with stage I and III disease, suggesting that changes in survival per stage were mainly caused by better staging at diagnosis and only partly by improvement in therapy.
Conclusion: Therapy as applied in clinical trials with younger patients with good performance status, is still at a distance from the application of therapy observed in daily practice. Standard of care therapy contributed only in a small amount to improvement in relative survival for each stage, without an improvement for the total group.
Keywords: Non-small cell lung cancer, survival, treatment

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P4.067 COMORBIDITY AND FUTURE LUNG CANCER RISK IN A UK HIGH RISK PRIMARY CARE PRACTICE

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Background: Lung cancer continues to be the leading cause of cancer death worldwide. The disease is predominantly common among elderly patients, thus likely to be preceded or accompanied by multiple comorbid conditions. Whilst many studies have reported association between pulmonary diseases and lung cancer occurrence, the role of other chronic conditions that manifest primarily later in life are yet to be elucidated. This study describes the pattern of comorbidities among individuals in a pilot primary care lung cancer early detection study, and explores the influence of these chronic diseases on future risk of developing lung cancer.
Methods: Diagnosed medical conditions for participants in a pilot lung cancer early detection study at a UK primary care practice were obtained. Individual's 5-year absolute risk for future development of lung cancer was estimated from the LLP risk model, which has been successfully

validated in three independent studies. Patients were classified as high or low risk based on a 5-year future risk threshold of 5%. Associations of comorbidity conditions with the future risk were examined using logistic regression analysis.
Results: The median age of participants was 62yrs (range=50-88yrs) and more than half were females (53%). Musculoskeletal and connective tissue disease (85.5%) and respiratory system diseases (82.6%) were the leading comorbid conditions; these were mostly dominated by rheumatism (49.8%) and acute respiratory infection (76.2%) respectively. Prior diagnosis of circulatory disease (OR=1.84, 95% CI=1.36-2.47) and malignant disease (OR=1.45, 95% CI=1.05-2.00) were statistically significantly associated with increased risk of lung cancer whilst infectious disease (OR=0.47, 95% CI=0.35-0.64) and genitourinary system diseases (OR=0.72, 95% CI=0.52-0.94) appear statistically significantly protective. Specifically, COPD (OR=1.85, 95% CI=1.33-2.60) and cardiac diseases (OR=2.57, 95% CI=1.47-3.05) diagnosed in 22% and 21% of patients respectively were significantly associated with increased future risk of lung cancer.
Conclusion: This study demonstrates strong positive relationships between circulatory diseases, cardiac diseases in particular, and COPD with future lung cancer risk. Evidence from our results supports a role for prior diagnosis of circulatory disorders such as ischaemic heart diseases in defining lung cancer high risk individuals. Thus, incorporation of objective measures of these diseases and that of COPD may improve predictions of existing lung cancer risk models. A clearer understanding of the inter-relationship between diseases is critical for developing future prevention, early detection and treatment programmes.
Keywords: Epidemiology, comorbidity, lung cancer risk, primary care

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P4.068 CHANGES IN THE LUNG CANCER MORPHOLOGY DURING 10-YEAR PERIOD IN LITHUANIA: A SINGLE INSTITUTION EXPIERENCE

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Background: Lung cancer is the leading cause of cancer morbidity and mortality worldwide. Over the past years, the frequency of adenocarcinoma has increased, while, squamous cell carcinoma decreased. The aim of the study was to investigate histologic types and other clinical characteristics of patients with lung cancer during 10-year period.
Methods: A retrospective review of 479 patients with lung cancer diagnosed histologically or cytologically in Hospital of Lithuanian University of Health Sciences Kaunas Clinics. The data was collected from 1998-1999 years - period 1 and 2008-2009 years - period 2.
Results: In period 1 were 261 cases: 40 female (15.3%), 221 male (84.7%) and stage I 22(8.4%), stage II 31(11.9%), stage III 125(47.9%), stage IV 83(31.8%) and in period 2 were 218 cases: 25 female (11.5%), 193 male (88.5%) and stage I 21 (9.6%), stage II 24 (11%), stage III 99 (45.4%), stage IV 74 (34%); ($p>0.05$). In period 2 patients were older than in period 1 patients at the time of diagnosis (68.23±4.98 vs 62.35±5.34 yrs, respectively, $p<0.05$). Histological types were: small cell carcinoma 55 (21.1%), NSCLC 206 (78.9 %): squamous cell carcinoma 148 (71.8%), adenocarcinoma 24 (11.7%), large cell carcinoma 1 (0.5%), NOS 33 (16.0%) in period 1 and small cell carcinoma 43 (19.8 %), NSCLC 175 (80.2%): squamous cell carcinoma 6 (38.3%), adenocarcinoma 13 (7.4%), large cell carcinoma 6 (3.4%), NOS 89 (50.9%) in period 2; ($p<0.05$).
Conclusion: During 10-year period NOS and large cell carcinoma frequency increased while squamous cell carcinoma decreased. Sex and stage distribution did not changed during 10-years period.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.069 PROGNOSIS OF LUNG CANCER MORBIDITY BASED ON CHANGES OF ECOLOGICAL SITUATION. SCIENTIFIC SUBSTANTIATION OF METHOD.

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Background: Aim of the project. To check possibility of Ukrainian population's morbidity of lung cancer (LC) prognostication based on data due to air pollution (AP) in previous years.
Methods: In our work we have used official data of the National cancer-register of Ukraine about LC morbidity and data of the State Statistics Committee of Ukraine about AP in Ukraine and its regions. In previous project we have already ascertained, that in Ukraine tobacco smoking level have increased and LC morbidity decreased during last 20 years. Thus, we have started research of major LC risk factors. Investigation of correlation between level of AP and LC morbidity was one of our research lines. Possibility of this dependence based on analysis of LC morbidity in 1995-2004 years and AP level in 1985-1994 years in the same regions. We have used regression analysis method and, as result, deduced a formula, which, in our opinion, represents this correlation (2008 1st European Lung Cancer Conference). For Ukraine in general this formula is as follows: $y = 0{,}0018x^3 - 0{,}0967x^2 + 2{,}0553x + 22{,}98$. The single-type polynomial cubic equation represents this correlation for all Ukrainian regions: $y=ax^3-bx^2+cx+d$ · y – the level of LC morbidity, · x – air pollution level for 10 years by the time of determination of an actual morbidity, · a, b, c – factors, which, according to the authors, were caused by ecologic-climatic conditions, specificity and features of placing manufacture, and others for each territory · d – "Background" level of morbidity (on conditions that air pollution is absent). Based on this formula and data about AP level in 1994-2004, we have calculated forecasted level of LC morbidity for Ukraine and all Ukrainian regions. We have compared the calculated data (155 elements) with standardized actual data.
Results: In 115 pairs of data (74%) calculated rates ware in confidence interval of analogical actual value. In 145 cases (93,54%) Student's coefficient was less than 2, which indicates that absence of significant difference between calculated and standardized actual value. In 85 pairs (54,84%) the difference between calculated and standardized actual value was less than 5%, in 43 pairs (27,74%) this difference was from 5 to 10% and in 27 cases (16,42%) exceeded 10%. In only one case (0,65%) Student's coefficient exceeded 3, which indicates that presence of significant difference between calculated and standardized actual value.
Conclusion: 1. 1. Revealed correlation between lung cancer morbidity and air pollution level, which is represented by single-type polynomial cubic equation for all Ukrainian regions. 2. 2. This formula could be used for a medium-term forecast of lung cancer morbidity and argumentation of prophylactic activities.
Keywords: morbidity prognosis, Lung cancer, air pollution

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P4.070 FIRST RESULTS OF THE PROSPECTIVE SCOT REGISTRY.

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Background: The SCOT (Small Cell Lung Cancer treatment and outcome) registry objective is to describe the patterns of care and patient outcomes in newly diagnosed patients with SCLC.
Methods: Currently 526 patients have been recruited by 56 centres in 14 countries (Europe 13, Asia 1). Patients' baseline characteristics and initial treatment intention are recorded at entry and additional patient information is collected every 6 months for 18 months to track actual treatment, follow-up and outcome. In addition healthcare resource utilisation is captured.
Results: Baseline data and 6 months data for 70% of the patients are available currently. The population was mostly represented by male patients (73%). Patients median age was 65 years. 5% had a previous history of cancer and almost all patients had a smoking history (95%) - 50% were current smokers. Based on the baseline collected, 42% of the patients presented with limited disease (M0) versus 58% with extensive disease (M1). Metastases were most frequently reported in lymph nodes (55%), liver (35%), lung (25%) and bones (24%). Initial

treatment intention for the patients presenting with M0 disease included chemotherapy alone, for 41% of the patients and for 58% the intention was combined chemo-radiotherapy. For the majority of patients with M1 disease the intention was to treat with chemotherapy alone (87%) and 11% with combined chemo-radiotherapy. Of the patients with 6 months of follow-up completed, 30% of patients with M0 disease were actually treated with chemotherapy alone, 62% with combined chemo-radiotherapy, 4% surgery and 33% were treated with prophylactic cranial irradiation. 60% of patients with M1 disease were treated with chemotherapy alone, 28% with combined chemo-radiotherapy and 18% were treated with prophylactic cranial irradiation. For 67.8% of the patients, the initial treatment plan was actually delivered. 13.5% of the patient population with 6 months visit completed (51 patients) had died. 78.3% of the deceased patients had M1 stage disease. 27.5% of the deceased patients had not received any chemotherapy.

Conclusion: More than a third of patients presenting with M1 stage disease received therapies other than chemotherapy alone (chemo-radiotherapy or radiotherapy). In patients with M0 stage disease, 62% were treated with combined chemo-radiotherapy and only 33% received prophylactic cranial irradiation. This preliminary data suggests that treatment based on guidelines is often impossible, highlighting a need for more treatment options.

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.071 RETROSPECTIVE ANALYSIS OF EPIDEMIOLOGICAL AND TREATMENT OUTCOME IN PATIENTS WITH METASTATIC LUNG CANCER AT AN ONCOLOGIC INSTITUTION IN SOUTHERN BRAZIL

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Background: Lung cancer is the most common tumor worldwide and a leading cause of preventable death. In Brazil it is the third most common malignancy with 27,630 new cases estimated for the year 2010, divided in 17,800 men and 9,830 women. There is an increasing incidence in Brazil, especially in females, which is attributed to increased smoking habit in this gender. Risk and prognostic factors influence treatment results and survival in patients with advanced disease. The aim of this study was to identify in our population the epidemiological profile of patients with non-small cell lung cancer (NSCLC) in advanced stage and confront the results of treatment with the data in the literature.

Methods: This retrospective study included 125 patients referred to the Clinical Oncology Service of our hospital, with NSCLC in stage IIIB with pleural effusion and IV and tried to identify the epidemiological characteristics, risk and prognostic factors and the results obtained with treatment through survival analysis using the Kaplan-Meier method.

Results: Of 125 patients enrolled, 52.8% were male, median age 58 years, performance status (PS) less than 1 in 61.3%, weight loss greater than 10% in 83.3% and subtype adenocarcinoma in 59.2% of cases. Most of the patients (83.2%) were smokers or former smokers at the time of diagnosis and the most common initial symptoms were chest pain (76.5%) and cough (69,9%). Bone and brain metastases were detected in 29,6% and 21,4% at diagnosis, respectively, similar to that found in the literature. Among the 104 patients assessable for response, the partial remission rate was 31.7% and the stable disease rate was 16.3%. Patients were treated with carboplatin-paclitaxel in first line in 88,6% and docetaxel in second line in 47,1% The median survival was 8.3 months (95% CI 6.5 to 10.1 months) and there was a significant statistical difference in median survival between patients with performance status less than 1 versus those equal or greater than 2 ($p = 0.014$).

Conclusion: An equal incidence between sexes reflects the increasing number of cases in females following the statistics worldwide. Smoking is still the most prevalent risk factor and is more associated with the epidermoid histological subtype. In our population, the number of cigarretes smoked per day was high although the most common subtype was adenocarcinoma, in accordance with the statistics of growing incidence of this subtype. Overall survival was similar to that found in the world literature. This study shows the epidemiological profile of patients with lung cancer in a Southern Brazilian population and the impact of prognostic factors in treatment outcome.

Keywords: Metastatic lung cancer, southern brazil, Overall survival, prognostic factors

Poster Session 4 – Epidemiology Thursday, 7 July 2011 10:00-12:30

P4.072 THE IMPACT OF PATIENT AND HOSPITAL FEATURES ON SURGICAL RESECTION RATES AND SURVIVAL FOR PEOPLE WITH NON-SMALL CELL LUNG CANCER IN ENGLAND.

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Background: There is evidence that the surgical resection rate and 5-year survival for lung cancer varies between and within countries. We used the National Lung Cancer Audit linked to Hospital Episode Statistics to quantify the extent to which these outcomes were modified by patient and/or NHS Trust features.
Methods: We included all English patients with a histological diagnosis of non-small cell lung cancer (NSCLC). We used logistic regression to quantify the independent influence of patient level features, including a Charlson Index score of co-morbidity, and NHS Trust features on the likelihood of having surgery. We used Cox regression to quantify the impact of the same variables on survival.
Results: There were 34,513 patients with non-small cell lung cancer in our dataset. Increasing age, more advanced disease stage, poor performance status and the presence of co-morbid illness were all independently associated with a reduced risk of having surgery. The 27% of patients first seen in thoracic surgical centres were 51% more likely to have surgery than those seen in non-surgical centres (adjusted Odds Ratio 1.51, 95% confidence interval 1.16, 1.97). Surgery was the most powerful determinant of overall survival, reducing the likelihood of death by more than half (adjusted Hazard Ratio 0.41, 95% confidence interval 0.39, 0.44). Amongst those patients who received surgery, there was no affect on survival based on where they had first been seen, which suggests that the resection rate could be increased to that observed in thoracic surgical centres without a negative effect on survival.
Conclusion: The 27% of patients with NSCLC first seen in a thoracic surgical centre are more likely to have surgery for their cancer and to benefit from the survival advantage this confers. There is an opportunity to improve the outcome for patients with lung cancer in England by improving the care pathway for patients first seen at a non-thoracic centre.
Keywords: surgical resection, survival, co-morbidity, Epidemiology

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P4.073 ASSESSMENT OF THE OFFER OF CLINICAL TRIALS IN THORACIC: A PILOT STUDY

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Background: Rates of participation in clinical trials (CT) among thoracic patients, particularly minority and underserved patients remain suboptimal. Although patient understanding of CTs and identification of barriers from their perspective is a key component of improving access, physician offer of CT and barriers from their perspective has been understudied. Low accrual rates to trials often have the negative impact of prolonging duration of study, delaying analysis of study results, and causing closure of potentially important studies due to lack of timely accrual. The primary objective of this study is to retrospectively assess rates of CT offerings to thoracic patients and secondarily, assess the reasons why a CT was not offered and/or better understand the reasons for participation refusal.
Methods: Conducted a retrospective analysis of 300 thoracic patient records seen during the period of August 2010-October 2010. During the pre-pilot phase, the trained abstractors reviewed 5 cases to ensure inter-rater reliability. The abstractors reviewed records using a data abstraction tool to identify if patients were eligible for a treatment CT, eligible and offered a CT, eligible but not offered a CT and accepted a CT. Abstractors compared each record to eligibility criteria from all treatment CTs

open during the selected time frame.
Results: The pre-pilot phase demonstrated inter-rater reliability (95%) among the abstractors and led to the initiation of the Study Implementation Phase. In this phase, abstractors are reviewing the 300 patient records which were randomly selected from all clinic visits during the selected 3 month period. The study implementation phase is currently underway and results will be available in June 2011.
Conclusion: Previous evidence indicates that there may be many reasons for low clinical trial participation. While understanding participant barriers is clearly important, it is also vital to understand physicians' perceived barriers for referral of patients to clinical trials. Increasing the offer of CTs to more patients may improve participation rates, especially among minority and underserved patients who are often least likely to be offered a trial. We initiated this study to identify our potentially unique reasons or combination of reasons. The conclusions obtained from our data will drive interventions for increasing accruals that are tailored to the address the accrual issues specific in our program. The hope is that this concept could be replicable for others experiencing decreasing rates of CT participation.
Keywords: accrual, study

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P4.074 NON-SMALL-CELL LUNG CANCER SURVIVAL ACCORDING TO HOSPITAL TYPE

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Background: Several studies have shown improved outcomes for non-small-cell lung cancer (NSCLC) patients treated at hospitals associated with teaching or high-volume surgery. These studies however, involved mainly surgical patients, used all stages combined, or were restricted to the elderly population. We conducted a national cancer database (NCDB) to evaluate the stage-specific survival according to hospital type.
Methods: NCDB is a database containing approximately 70% of all cancer patients diagnosed in the United States. All patients with NSCLC and defined stage, diagnosed between 1998 and 2001, were evaluated for survival according to hospital type. Hospitals were divided into Community Cancer Centers (CCC), Comprehensive Community Cancer Centers (CCCC), and Teaching Research Centers (TRC), if they had between 100-649 patients per year, 650 or more patients per year, or were associated with a medical school respectively.
Results: Among the 253,041 patients meeting the inclusion criteria, there were 44,981 (18%) CCC, 127,336 (50%) CCCC, and 80,724 (32%) TRC. Community hospitals (CCC and CCCC) were associated with a higher percentage of patients older than 70 years. In addition, patients with stage I or II were less likely to undergo surgery in the CCC or CCCC hospitals. TRC was associated with a significant improvement in 5-year survival when compared to CCCC and CCC for patients with stage I (48% vs 42.2% vs 36%), II (27.6% vs 23.4% vs 19%), and III (10.6% vs 8.2% vs 7.1%). In patients with stage IV, the 6-month and 1-year survival were also significantly better for patients treated in TRCs (45.1% and 24%) compared to CCCC (40.8% and 20.9%) and CCC (38.4% and 19.1%).
Conclusion: In patients with NSCLC, there is a significant difference in outcomes according to the hospital type. These differences may be due to improved quality of care, patient selection, or both.
Keywords: Non-small cell lung cancer, survival, hospital type

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P4.075 LUNG CANCER IN SENEGAL

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Background: In Africa the incidence of lung cancer is rising rapidly.
Methods: The purpose of this retrospective study

was to analyze clinical, therapeutic, and prognostic features of lung cancer patients treated at the Principal Hospital in Dakar between 2003 and 2010.
Results: A total of 89 cases were compiled over the 7-year study period. Eighty eight percent were male smoker with a mean age of 59.2 years. Histological samples were obtained by bronchial fibroscopy (n=62), CT-guided transthoracic needle biopsy (n=18), or from a metastatic site (n=9). The histological diagnosis was squamous cell carcinoma in 44 cases, adenocarcinoma in 21, large-cell carcinoma in 17, small-cell lung cancer in 5, and bronchiolo-alveolar cancer in 2. Tumor staging demonstrated stage I-II in 7 cases, stage III in 22, and stage IV in 60. Chemotherapy was proposed in 37 cases, radiotherapy for pain relief in 8, and surgery in 1. Symptomatic management was performed in 48 % of patients. Ten patients were lost during the follow-up. Median survival was 7 or 3 months depending on whether or not chemotherapy was performed.
Conclusion: The much higher rate of histological diagnosis than in the sub-region is due mainly to the availability of trained personnel with access to bronchial endoscopy and CT-scan needle biopsy. Administration of cytotoxic drugs is feasible but too expensive due to the lack of universal health care: two-thirds of cases only benefit from symptomatic management whereas chemotherapy significantly improved median survival by 4 months ($p < 0.0001$). Prognosis of the disease is poor because management is undertaken at an advanced stage. Lung cancer is a health issue in Dakar, Senegal. It is absolutely necessary to quickly propose therapeutic standards adapted to the African socio-economic setting as well as an anti-tobacco prevention policy.
Keywords: Lung cancer, africa, Epidemiology

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P4.076 NSCLC IN INDONESIA: TREATMENT PRACTICE & EFFECTIVITY-SHARING EXPERIENCES IN DHARMAIS CANCER HOSPITAL

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Background: Lung cancer is the health problem in developed countries and also in developing countries as well. Lung cancer become the leading cause of mortality in cancer and responsible for about one-third of all cancer deaths. In Indonesia, lung cancer has become in top five rank cancers since 2002. Until now, data about lung cancer in Indonesia still limited. We want to share about epidemiological data in lung cancer especially treatment and survival-related therapy in Indonesian in year 2006-2007.
Methods: We used cross sectional study design and we analyzed survival by using Kaplan Meier analysis.
Results: In period 2006-2007, we gathered 213 lung cancer patients with age varied between 20-83 years, mean age was 58.4 years. Male patients (161/76.2%) were more frequent than female (52/23.8%). More than half NSCLC patients had adenocarcinoma histology (59.1%) and more than 75% patients had advanced stage. Type of therapies was surgery (6.6%), radiotherapy (40.4%), chemotherapy (38.5%) and targeted therapy (12.2%). Median survival time for patients who had chemotherapy was better than not accepted (10.2 month vs 3.2 months). The similar result also happened for targeted therapy (19.9 months vs 4.4 months). One year survival of lung cancer patients in our hospital was 18.3% whereas three years survival was 1.9%.
Conclusion: We conclude that chemotherapy and/or targeted therapy has shown prolong median survival time.
Keyword: lung cancer, chemotherapy, survival, Indonesia

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.077 NON-RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA TREATED WITH CHEMOTHERAPY AT THE UNIVERSITY HOSPITAL OF AARHUS 2000-2010: A RETROSPECTIVE STUDY

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Background: Malignant pleural mesothelioma (MPM) is a rare cancer with a poor prognosis. 80% of the individuals with MPM have been exposed to

asbestos. Other agents are suggested to be DNA-virus SV40 and other silicates. Late diagnosis, staging-difficulties and underlying illness which make the patients unfit for curatively intended trimodal therapy are some of the challenges for this cancer. Over the past years it has been discussed which platin-based doublet-regime one should use as first line palliative treatment. This work aims to study the epidemiologic characteristics and overall survival of patients with non-resectable MPM treated with chemotherapy at the University Hospital of Aarhus year 2000 - 2010.
Methods: Review of journals. Data are structured using the Aarhus Lung Cancer Register and statistics are analyzed using SPSS.
Results: A total of 80 consecutive patients with MPM referred to the oncology department in Aarhus. First line chemotherapy includes cisplatin/vinorelbine (standard first line until summer 2007), cisplatin/pemetrexed (standard first line since summer 2007) as well as monotherapy with pemetrexed. The median age of the 80 patients (69 males and 11 females) at diagnosis was 64 years (range 40-80). 46% of the patients had epithelioid histologic subtype and 54% had non-epithelioid subtype (sarcomatoid, biphasic and NOS). As first line treatment 34% received cisplatin/vinorelbine, 45% received cisplatin/pemetrexed and 21% received pemetrexed as monotherapy. Median overall survival (mOS) for the whole group was 13,1 months (95% CI 10,3-16,0). We found no significant difference in mOS between patients treated with cisplatin/vinorelbine (mOS 15,2 months, 95% CI 9,0-21,4) and cisplatin/pemetrexed (mOS 15,1 months, 95% CI 6,3-24,0). Median OS for patients treated with pemetrexed as monotherapy as first line was 7,4 months (95% CI 4,2-10,8). Patients with epithelioid histologic subtype had a significantly better mOS (15,2 months, 95% CI 11,6-18,8) compared to patients with non-epithelioid subtype (8,9 months, 95% CI 4,9-12,9).
Conclusion: We found that subtype of histology is significantly associated with survival. Patients with epithelioid histology have a better prognosis than patients with non-epitheloid subtype. Our results show no significant difference in overall survival in patients who received different platin-based doublet-regimes. MPM is still a disease with a poor prognosis, and the survival rates in this retrospective study are comparable to other published data.
Keywords: malignant pleural mesothelioma, Chemotherapy, survival

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P4.078 EPIDEMIOLOGY AND SURVIVAL ANALYSIS OF LUNG CANCER - 10 YEARS OF EXPERIENCE IN A PORTUGUESE RESPIRATORY REFERENCE CENTER

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Background: Lung cancer is the third most common in Portugal, and the leading cause of death by cancer. There are no large scale studies reporting its epidemiology and survival analysis in Portugal. With this study we aim to make an epidemiological analysis by gender, histological type and stage of patients diagnosed lung cancer, and determination of overall survival in studied population.
Methods: Retrospective analysis of patients who attended our Pulmonary Oncology Consultation between January 2000 and December 2009.
Results: 1142 patients were followed during that period, with a mean age of 64.1±11.9 years; 944 (82.7%) male. At the time of diagnosis 48.2% were smokers and 19.2% non-smokers. Over the years the incidence of lung cancer in former smokers increased (p=0.001), and decreased in smokers (p=0.001), but it did not vary in non-smokers (p=0.42). Most patients presented performance status 0 and 1 (67.6%). The most frequent histological type was adenocarcinoma – ADC - (450, 39.4%), followed by squamous cell carcinoma – SC - (282, 24.7%), non-differentiated NSCLC (211, 18.5%), SCLC (139, 12.2%) bronchiolalveolar carcinoma – BAC - (22, 1.9%), carcinoid tumor – CT - (22, 1.9%) and large cell carcinoma – LCC - (16, 1.4%). In female gender, the leading histological type was adenocarcinoma (55.6%), followed by NSCLC (37, 18.7%), assuming the other types less preponderance. The most usual histological type in male was adenocarcinoma (340, 36.0%), followed by squamous cell carcinoma (263, 27.9%), NSCLC (174, 18.4%) and SCLC (125, 13.2%). At the time of diagnosis 82.1% of patients were on Stage IIIB and IV. Over the years the number of diagnoses at stage IA-IIIA did not change. Diagnosis at stage IV increased (p<0.001) and at stage IIIB decreased (p<0.001) over time. Considering patients with lung cancer, increasing age

was associated to decreased risk of ADC, LCC and CT (p<0.001), and increased risk of SC (p<0.001). Along the years BAC incidence decreased (p=0.01) and non-differenciated NSCLC incidence increased (p=0.03). Overall median survival was 15.6 months and overall survival at 5 years 16.7% We obtained the following median survival: NSCLC (including non-differentiated NSCLC, ADC, BAC and SC): 15.8 months; SCLC: 7.4 months; Carcinoid tumors: 21.0 months. Male gender and smoking history were associated to worse prognosis (p<0.01 and p<0.05, respectively).

Conclusion: An increase in diagnosis of lung cancer in early stages over the years was not seen. However, the increasing number of diagnoses in stage IV is probably due to the emergence of new and more sensitive staging techniques. Surprisingly, despite more accurate diagnostic and pathology techniques, the number of non-differenciated NSCLC has increased over the years. The median overall survival, as well as for each histological type, falls within the described in literature. Male gender and tobacco use history were associated to worse prognosis. Further studies are needed to enframe these epidemiologic findings in national and international reality.

Keywords: Epidemiology, Lung cancer

Poster Session 4 – Tobacco Control Thursday, 7 July 2011 10:00-12:30

P4.079 THE RISK OF TOBACCO-SPECIFIC LUNG CARCINOGEN AMONG NON-SMOKING RESTAURANT AND BAR WORKERS IN NIGERIA

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Background: To say that tobacco smoking causes lung cancer is an understatement. Smoking causes numerous cancers but has lung cancer on the highest. The alrming issue at the hand is that smoking may accrue to lung cancer among non smokers in work places or elsewhere.

Methods: We examined about 200 restuarant and bar non-smoking staff in four geo-political locations in Nigeria-Lagos, Kano, Port-Harcourt and Abuja from 2005-2009. Secondhand smoke were compared with results from these participants who were exposed to it. We took note of how long each staff had worked in these bars or restuarents and the amount of Environmental Tobacco Smoke (ETS) each of them were exposed to.

Results: Participants exposed to workplace secondhand smoke were more likely to have any detectable level of NNAL (P=.005) and higher mean levels of NNAL (P < .001) compared with non-exposed participants. Increased levels of NNAL were also associated with hours of a single workplace exposure (P=.005).

Conclusion: Non-smoking employees left unprotected from workplace secondhand smoke exposure had elevated levels of a tobacco-specific carcinogen in their bodies. All workers—including bar and restaurant workers—should be protected from indoor workplace exposure to cancer-causing secondhand smoke.

Keywords: Environmental Tobacco Smoke(ETS), Tobacco Control, Cancer, Lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Tobacco Control Thursday, 7 July 2011 10:00-12:30

P4.080 STUDY OF RELATIONSHIP OF AGE AT ONSET OF SMOKING, INTENSITY OF SMOKING (MEASURED IN PACK YEARS), AND DURATION OF SMOKING TO STAGE OF LUNG CANCER, PATHOLOGICAL SUBTYPES AND OUTCOME: SINGLE CENTER EXPERIENCE FROM A COMMUNITY CANCER CLINIC SERVING SUBURBAN AND RURAL POPULATIONS IN SOUTH CAROLINA IN THE US

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Background: This study was aimed at identifying relationship between duration, intensity and quantity of smoking (age when started smoking, number of pack years, type of cigarettes-with or without filters) with stage of lung cancer, pathological subtypes and response to treatment with different subtypes. We intended to carry out multivariate analysis to identify if cigarette smoking at a young age with long history

was an independent risk factor for development of specific type of lung cancer at an advanced stage and carried poor prognosis.
Methods: information regarding smoking history (age when started smoking, duration of smoking, number of packs smoked per day and number of years of smoking) was collected in prospective method for patients presenting at a small community based cancer clinic in suburban and rural South Carolina in the US. Demographic data and other relevant past medical history was collated and analyzed from electronic health records (Enterprise Healthcare by Agastha Healthcare). Statistical methods applied included hazard ration and multivariate analysis.
Results: Data on total of 267 (178 males; 89 females) patients were reviewed in this study. 168 patients were diagnosed with advanced (stage III and IV AJCC classification) cancer. Relative risk of developing advanced stage cancer with early age smoking was 2.82 by hazards ratio. Proportional odds ratio revealed a linear relationship between intensity of smoking (in terms of number of pack years) and advanced stage in lung and head and neck cancer. Multivariate analysis confirmed that age at smoking and intensity of smoking were independent risk factors for advanced stage cancer.
Conclusion: Intensity of smoking (defined as number of packs of cigarettes smoked per day multiplied by number of years smoked = pack years) is a very strong and independent risk factor for development of advanced lung cancer with hazards ratio of 2.82 also confirmed by multivariate analysis. For every incremental increase in smoking intensity, there is an exponential increment in the likelihood of early development of cancer and also advanced stage at presentation. It is very important to plan and carry out aggressive smoking cessation education at elementary and middle school level to target vulnerable population at a very young age.
Keyword: smoking, cigarette, lung cancer, stage

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P4.081 THE BELIEFS, KNOWLEDGE, UNDERSTANDING, ATTITUDES AND TREATMENT ACCESS TO LUNG CANCER AMONGST RURAL DWELLERS IN NIGERIA

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Background: Evidences of lung cancer cases from scientific researches have being on the rise in the last few decades and tobacco which is a major risk factor causes about 90% of lung cancer diagnosed around the world. The need to reduce this scourge has become more important.
Goal: The goal of this study is to ascertain the beliefs, knowledge, understanding, attitudes and treatment access to lung cancer among rural dwellers in Nigeria.
Methods: An interview guide was designed specifically for these studies in which 700 rural dwellers in Nigeria most of which were men, age 45 and over took part in. It contained questions about beliefs, knowledge, understanding and attitudes about Lung Cancer Diagnosis and incidences. In addition, questions assessing the variables of the Health Belief Model and health motivations also were included. The data were obtained during face-to-face interviews in the primary language of the participating people. The interviews were translated into English.
Results: Out of the 700 people who participated, only 7% of the participants knew about lung cancer, 3% had undergone at least one Lung Cancer Diagnosis during their lives, and 90% were not aware of the disease. There was little or no access to treatment even at early detection in these rural areas thereby causing vulnerability to loss of life. Majority of these rural people (95%) said they knew little or nothing about lung cancer. While 15% of the people said detecting cancer early was important, only 3% reported that cancer could be cured. Age, education, or mother tongue showed no statistically significant relationship with the lung health practice scores. However, proficiency with the English language ($p = 0.009$) and number of years exposed to awareness and education ($p = 0.009$) had a significant relationship with the lung health practice scores. The significant explanatory factor for the variable lung health practices was a cue to action ($p = 0.009$).
Conclusion: The level of awareness and treatment access to lung cancer amongst Nigeria's rural dwellers is extremely low thereby making them not to engage in screening and/or detection practices. This alarming situation calls for urgent intervention of medical/health organizations to provide immediate lung cancer awareness, diagnosis and care so as to reduce incidences or threat at early detection.

Tobacco which is known as a major cause of lung cancer (90%) is widely used by these rural dwellers

thereby making them so vulnerable. Awareness is suggested while providing smoking cessation for smokers who intend to quit.
Keywords: tobacco, Rural Nigeria, Lung cancer, diagnosis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Tobacco Control Thursday, 7 July 2011 10:00-12:30

P4.082 TOBACCO USE AND SECONDHAND SMOKE AS RISK FACTORS FOR LUNG CANCER

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Background: Cancer represents a particular problem in highly developed industrial countries. In these countries, a great percent of general population belongs to older age categories, in which the risk of occurrence of this disorder is higher. Lung cancer (LC) is the most frequent malignant disease in the world. Worldwide, about 80% of LC cases in men and 50% in women are caused by tobacco smoking. Other risk factors include secondhand smoke and exposure to asbestos, radon, arsenic, and air pollution. Tobacco also causes deaths among nonsmokers. Exposure to secondhand smoke in the home, workplace, and public areas also kills tens of thousands of nonsmokers every year. Our specific objective was to analyze the role of active and passive smoking in lung cancer risk.
Methods: The investigation was an analytical type of case-control study. It elaborated 185 patients diseased of lung cancer (investigated group-IG), and the same number of persons without malignant disease (control group-CG). Both group members were interviewed during the initial 18-month period of the study. Risk analyses were done using unconditional logistic regression, which provides results in the form of crude odds ratio. The odds ratios and their 95% confidence intervals (CI) were computed.
Results: Among patients were 67% of current smokers (CS), 23.8% of former smokers (FS) and 9.2% of never smokers (NS), compared to 40.5% of CS, 28.7% of FS and 30.8% of NS among controls. The greatest percent of the diseased (44.4%), started smoking up to the age of 15-years. LC patients, in average, smoked almost 29.95±11.03 cigarettes per day (c/day), compared to the controls, in whom the average was 21.35±9.50 c/day. Most of the members in both groups consumed cigarettes with filter (LC-87.1%; CG-97.4%). In the group with LC 33% tried to stop smoking, and their stoppage period, in average, was 9.48±13.04 months. According to the case-control study, CS and FS, together, had 4.40 (95% CI, 2.44-7.93), times as great risk to become ill from LC in relation to the NS. CS who smoked >40 c/day had almost four times (OR=3.56; 95% CI, 1.23-12.64), significantly greater risk to get LC, compared to those who smoked <40 c/day. CS whose length of the smoking period was >40 years, had 3.94 (95% CI, 2.11-7.35), times greater risk to become ill compared to those who smoked <40 years. Exposition to passive smoking was registered in 82.4% from the members of the IG, i.e. 63.2% members of CG. In addition, 42.8% of the diseased nonsmokers inspired the cigarettes smoke at the working place and at home. Exposition to passive smoking lasted longer than 16 years in almost all diseased persons (92.9%). The risk of developing LC is 2.72 (95% CI, 0.7-10.59), times greater in the exposed to passive smoking, compared to the non-exposed.
Conclusion: Lung and other cancers caused by tobacco are often untreatable at the time of diagnosis. The key to reducing these cancers is to prevent initiation of smoking in young people, and to encourage smokers to quit. Quitting smoking substantially reduces cancer risk.
Keywords: cigarette smoking, passive smoking, Lung cancer

Poster Session 4 – Tobacco Control Thursday, 7 July 2011 10:00-12:30

P4.083 TOBACCO CONTROL IN CHINA

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Background: With 350 million smokersin 2002, China accounted for more than one-fourth of the world's annual tobacco consumption and own the world's largest tobacco company.
Methods: The National Prevalence Surveys in 2002 showed that the smoking rate in adult male and female was 66.0% and 3.08% respectively.

From 1984 to 2007, smoking prevalence, especially smoking prevalence of males, remained at high levels. Subsequently, prevalence of exposure to secondhand smoke is also as high as 52.9%. About 540 million suffered from Second Hand Smoking exposure in 2005.
Results: China is a FCTC member country. The 10th Session of the Standing Committee of the National People's Congress officially ratified the WHO/FCTC on August 28th 2005. FCTC took into effect on Jan 9th, 2006. Tobacco Control Organizations in China include: Ministry of Health, China CDC- National Tobacco Control Office, WHO Collaborating Center for Tobacco or Health, China Association On Tobacco Control, National Health Education Institute, China Foundation of Cancer, Think Tank Center and so on. In 2004, Premier Wen Jiabao met general director of the WHO and promised that the 2008 Olympic Games would be tobacco free.
Conclusion: Regulations on no-smoking in public places in Beijing were enacted from May 1st, 2008 before the 29th Olympic Games. Smoking is forbidden in the following public places: 1. Indoor areas of medical organizations; 2. Infant institutions and kingdergartens; 3. Middle schools, primary schools, mid-level vocational schools; 4. Universities and other teaching areas of educational and training organizations. 5. Theatres, music halls, exhibition halls, museums, art galleries, libraries, science and technology museums, archives, children's palaces, memorial halls and other places for science & teaching, culture and art. 6. Business center of commerce, finance, post and tele-communications; 7. Inside buses, taxis, rail transits and other public transportation tools, related ticket offices and indoor platforms; 8. Cultural relics protection units open to the public; 9. Gymnasiums; 10. Contest area and seating area of stadium.
Keywords: Tobacco Control, China

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P4.084 TEENAGERS AS A TOOL AGAINST TOBACCO SMOKING, NOT MODELS FOR TOBACCO INDUSTRIES

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Background: For over twenty years, the tobacco industry has made marketing and distribution of tobacco products to youths a core of its marketing strategy in developing countries.
Methods: This paper will try to educate and expose some of the secret parties of British America Tobacco and how to prevent students and youths from their tricks and secret parties.
Results: Tobacco Control advocates in Nigeria lodged in a hotel which the BATN secret party was held, this recent event was organized to promote the Pall Mall brand of BATN. It was organized in all the six geo political zones in the country and was heavy on young people. Invitation cards were secretly given out in secondary schools and colleges and young girls were encouraged to attend. A seminar was organized by the tobacco control advocates for the same students from different high schools in Ogun and Lagos State to sensitize them on the harmful effect of tobacco smoking. Attendees of the workshop were surprised at the lies of the BATN and many of the high school students were not aware of the chemicals included in cigarette, this facts made students who had intentions to start smoking stopped. Most of the teachers and school head who attended the workshop also realized the damages caused by smoking and immediate actions were taking by creating anti-smoking clubs in high schools.
Conclusion: Teenagers in the developing countries should be encouraged to advocate for tobacco control thereby making them role models and not smoke models. This effort through a report by the print media said to have rescued student for being a cancer patient in the future.
Keyword: Role models, Smoke Models

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P4.085 "TOBACCO INDUSTRIES" A THREAT TO THE YOUTH

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Background: The Tobacco multinationals has turned to a vampire who kills both day and night, the advertisement and secret parties being organized by the big tobacco multinationals especially in the developing world has recruited hundreds of thousands of youths. It was also revealed that the

British American Tobacco (BAT) had conducted several surveys to determine the rate of youth smoking in Nigeria.
Methods: Research and experience has showed various trick and strategies of the tobacco industries. It is therefore appropriate to implement laws that will curb every secret parties and advert used to promote its new product "Pall Mall" in developing countries especially Nigeria.
Results: These methods will creatively counter and expose the enticing ACTIVITIES of tobacco multinationals.
Conclusion: Since the tobacco multinationals are recruiting more teenagers and youths everyday, thereby killing millions to make billions, efforts should be made in monitoring the tobacco industries to reduce both direct and indirect advertisement by the tobacco companies and engage more teenagers and youths in tobacco control activities with materials that will reveal the lies of the tobacco industry.
Keyword: Youth, Tobacco, Tobacco Industries

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P4.086 PREDICTION OF FUTURE SMOKING ATTRIBUTABLE DEATHS FOR LUNG CANCER IN ITALY UNDER PRIMARY AND SECONDARY PREVENTION SCENARIOS

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Background: Cigarette tobacco smoking is well known to be the major cause for lung cancer and for a wide variety of diseases. Smoking prevalence in Italy decreased by 21% from 1986 to now for male and females, as effect of changes in smoking initiation and quit rates, and in part attributable to the development of tobacco control policies. As a consequence, smoking attributable deaths for lung cancer and for other causes decreased in the last years in Italy, mainly for men. Policies not yet implemented in Italy and lung cancer screening (spiral CT scan) may help in further decreasing smoking prevalence, and therefore also in reducing smoking attributable deaths. This work aims to predict the number of future smoking attributable deaths for lung cancer and for all causes in Italy, assuming both primary, i.e. tobacco control policies, and secondary prevention scenarios, i.e. spiral CT scan.
Methods: A dynamic model describing the evolution of current, former, and never smokers was developed. Quit and relapse rates were estimated by fitting the model with smoking prevalence in Italy, 1986-2009. The estimated parameters were used to predict smoking prevalence and lung cancer smoking attributable deaths under different scenarios: 1) status quo, i.e. maintaining present smoking habits; 2) increase in cigarette taxes; 3) implementation of cessation treatments (financial coverage of cessation treatments, empowering an active quitline, widespread use of counselling among general practitioners and health professionals); 4) implementation of lung cancer screening for heavy smokers and heavy former smokers; 5) implementation of lung cancer screening for all smokers and former smokers; 6) implementation of cessation treatments and screening. In the screening scenarios a 20% decrease in lung cancer mortality was assumed according to National Lung Screening Trial results.
Results: Quit rates resulted very low: 2000-2009 weighted means were 2.5% and 1.8% for males and females, respectively. Maintaining present smoking habits, prevalence will remain higher than 10% in the next three decades, however smoking attributable deaths for lung cancer will decrease by 30.4%. The increase in cigarette taxes showed a 33.2% reduction in the number of smoking attributable deaths for lung cancer. The lung cancer screening showed a big effect in reducing the smoking attributable number of deaths for lung cancer in the first decades. It's effect varied largely depending on the population involved: a decrease of 39.9% and 33.6% in the number of deaths for lung cancer, from 2009 to 2040, was observed for screening scenarios for all smokers and heavy smokers, respectively. Screening for all smokers was the scenario with the major effect until 2020, after which the cessation treatments scenario gave higher reduction of lung cancer mortality (48.7%). Screening for heavy smokers was more effective in reducing lung cancer deaths with respect to cessation treatments scenario only in the first 2-3 years.
Conclusion: The combination of lung cancer screening and cessation treatments could reach the best results in terms of lives saved for lung cancer mortality.
Keywords: population model, smoking cessation treatments, lung cancer screening, smoking attributable death

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P4.087 SMOKING BEHAVIOURAL CHANGE IN MALE SMOKERS OF A RANDOMIZED CONTROLLED LUNG CANCER SCREENING (NELSON) TRIAL: 4-YEAR FOLLOW-UP.

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Background: Lung cancer screening might be a teachable moment for smoking cessation or a possible health certificate effect. Previous analysis indicates that smokers in the screen arm of the Dutch-Belgian lung cancer screening (NELSON) trial were less likely to refrain from smoking compared with control arm participants after 2-year follow-up. Aim of the current study is to investigate whether this result persists over time.
Methods: Two random samples were selected of 50-75 years old male smokers randomized to the screen (n=641) or control arm (n=643) of the NELSON trial. Smoking behavioural change was investigated from randomization (T0) to 4 years of follow-up (T2). Differences in smoking behaviour and predictors of prolonged smoking abstinence were investigated. Data was analyzed according to the intention-to-treat in addition.
Results: Responses were 88.2% and 60.2% in the screen and control arm. Data was weighted for non-response bias in control arm participants. At T2, prolonged smoking abstinence rates were 24.3% (screen arm) and 29.3% (control arm) (p=0.09). Multivariate analysis showed that lower baseline nicotine dependency and randomization to the control arm increased the likelihood of being abstinent from smoking at follow-up (p<0.05).
Conclusion: In conclusion, male smokers who received CT screening for lung cancer who were more addicted to nicotine were less likely to refrain from smoking, although the impact is limited. Adequate treatment of nicotine addiction would be of special interest to maintain the abstinence from smoking to further eliminate tobacco related health problems in male smokers participating in a lung cancer screening trial.
Keywords: lung cancer screening, smoking cessation, teachable moment, health certificate effect

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P4.088 TOBACCO,WOMEN AND CANCER

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Background: Tobacco , Women ,and Cancer: facts and figures of tobacco related diseases that is common among women Preamble: As early as 1939, Franz Hernan Muller, a German researcher had observed a relationship between smoking and lung cancer. Dr Morton Levin also made a similar observation eleven years later and published his findings in the Journal of the American Medical Association (JAMA). Despite these findings and that of other notable researchers such as Ernst Wynder and Evarts Graham, the tobacco industry continued to raise doubts about the methodology adopted in these works until the landmark work of Doll and Hill published in the British Medical Journal in 1954 which provided the evidence of a dose-response relationship between tobacco smoking and lung cancer. This prompted the setting up of an Advisory Committee and a full-scale investigation by the Surgeon General of the United States, Dr Luther Terry which culminated in the Surgeon-General's report on smoking and health published in 1964 stating that cigarette consumption is a health hazard of sufficient importance to warrant appropriate remedial action.
Methods: Cancer Smokers are at increased risk of developing cancer. Common cancers related to smoking include cancers of the mouth, throat, pharynx, larynx (voice box), oesophagus (food pipe), lungs, pancreas, kidney and cervix. Lung disease An estimated 85 per cent to 90 per cent of lung cancer is attributable to smoking. Smoking has also been known to cause chronic obstructive pulmonary diseases such as emphysema, bronchitis and asthmatic bronchitis. Heart disease Smokers are at increased risk for both stroke and cardiovascular disease, including high blood pressure and heart

attack. Gastrointestinal disease There appears to be a link between smoking and the development of some stomach and digestive system disorders. Peptic ulcers (holes in the stomach or digestive tract) and Cohn's disease (inflammation of the digestive tract) tend to be more common among smokers than non-smokers.

Results: Effects on women's health Reproduction and fertility Smoking may have harmful effects on a woman's reproductive system and her ability to become pregnant. Women who smoke and use oral contraceptives (birth control pills) are at risk of developing serious cardiovascular side effects such as blood clots, heart attack or stroke. Smoking can lead to women having problems with becoming pregnant, and pregnant women who smoke are more likely than non-smokers to havea miscarriage or premature birth. Smoking may affect menstruation. Monthly periods can stop or be disrupted, and there is some evidence that smoking may destroy eggs in the ovaries, even in young women. Women who smoke are more likely to go through menopause early, meaning that their menstrual cycle, and therefore their ability to become pregnant, may end at an earlier age. Women who smoke are at increased risk of developing osteoporosis, a condition in which the bones become thin and weak. There is some evidence that women are more likely than men to develop lung cancer and other respiratory diseases after the same levels of exposure to cigarettes. Women who smoke are more likely to develop cervical cancer than women who do not smoke. Women who smoke are at increased risk of developing cataracts. Effects during pregnancy There is no known safe level of tobacco consumption. It is not clear whether a child's health problems are caused directly by a mother's use of tobacco during pregnancy or in combination with other factors including poor nutritional habits alcohol consumption using other drugs using more than one drug sleep problems a mother's general health prior to pregnancy genetics how much alcohol, tobacco or other drugs are consumed during pregnancy at what stage in the pregnancy a substance is consumed the length of time over which a substance is consumed The effects of tobacco use have been difficult to study because these other factors also affect pregnancy. However, it is safest to avoid alcohol, tobacco and other drugs during pregnancy. Nicotine and its metabolite, cotinine, are metabolized much more quickly by pregnant women than by non-pregnant women. This could mean that women who continue smoking into pregnancy may smoke more, thereby exposing the fetus to the dangerous health effects of tobacco more often. Effects on the fetus Carbon monoxide, nicotine and other chemicals in tobacco smoke enter the mother's bloodstream and pass into the baby's body. This affects the supply of food and oxygen a baby needs to grow. Therefore, a common effect of smoking during pregnancy is low birth weight of the infant. Having a small baby does not mean labour and delivery will be easier. On the contrary, a smaller baby is not strong enough to help in its delivery, making the labour more difficult. Low-birth-weight infants are also more likely to suffer health and developmental complications throughout life, including delayed speech, cerebral palsy, visual and hearing difficulties, learning disabilities and respiratory problems. Other increased risks for babies exposed to tobacco before birth include premature labour and delivery placenta abnormalities such as low-lying placenta or premature separation of the placenta from the wall of the uterus; each of these conditions can be serious for both mother and baby increased risk of spontaneous abortion, miscarriage, stillbirth and early infant death increased risk of sudden infant death syndrome (SIDS, or crib death) Effects on breastfeeding The nicotine in tobacco transfers into breast milk. This may affect the way breast milk smells and tastes, and may decrease the amount of milk produced by a nursing mother. Although nursing mothers who use tobacco should not be deterred from breastfeeding, quitting tobacco (and therefore eliminating nicotine from the mother's breast milk) is best for both the baby and mother. Effects on child development Effects on long-term development Children exposed to tobacco before birth may experience the negative effects of that exposure for years after theyare born. Studies show that children are at increased risk for developmental and behavioural problems such as immature, aggressive, and oppositional or defiant behaviour inattention and impulsivity reduced lung functioning poor performance at school disruptive or impulsive behaviour depression and anxiety decreased motor, memory, language, creativity or reasoning skills developing alcohol or other drug problems as they get older Evidence suggests that children of mothers who smoked during pregnancy are at increased risk of developing tobacco dependence later in their lives. Also, the transition from initial to daily use of cigarettes was more rapid for women who were exposed prenatally to tobacco.There is also growing

evidence that children whose fathers smoked before conception are at risk of developing childhood leukemia as a result of genetic damage caused by tobacco exposure.This risk is higher for children whose mothers also smoked before conception, and children who are also exposed to second-hand smoke after birth. Second-hand smoke Second-hand smoke contains higher levels of tar, nicotine and carbon monoxide than inhaled cigarette smoke. Exposure to second-hand smoke, also called passive smoking, can cause problems during and after pregnancy Effects on women Women exposed to significant amounts of secondhand smoke during pregnancy are more likely to give birth to low-birth-weight babies. Women, even if they do not smoke, are at risk of developing lung cancer and coronary heart disease when exposed to second-hand smoke. Smokeless tobacco Mothers who use smokeless tobacco during pregnancy are at risk of pre-term delivery and decreased infant birth weight, even at full gestational age. There are indications that using smokeless tobacco is just as harmful to fetal health as cigarette smoking. Nicotine replacement therapy It is not yet known whether nicotine replacement therapy (NRT) is safer for a fetus than tobacco exposure. Tobacco cessation as early as possible in a pregnancy is healthiest for both the mother and her fetus, but more research is needed to determine the effects of NRTs on an unborn child.

Conclusion: Tobacco cessation Some people think that withdrawal from tobacco may be harmful to fetal health. However, quitting tobacco is healthiest for both the mother and infant, at any stage or time during pregnancy. Withdrawal is temporary; smoking, on the other hand, even just one cigarette a day, constantly exposes the mother and child to dangerous health risks. It is never too late to quit using tobacco products. Studies show that infants of women who quit smoking in the first trimester have weight and body measurements similar to those among infants of mothers who never smoked during pregnancy. The negative health effects that may be caused by using smokeless tobacco, smoking or being exposed to second-hand smoke eventually disappear after quitting tobacco or eliminating exposure to second-hand smoke.

Keyword: Communicating effects of tobacco on women and the link to cancer

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Poster Session 4 – Tobacco Control Thursday, 7 July 2011 10:00-12:30

P4.089 NON AIRED MASS MEDIA METHODS IN TOBACCO CONTROL

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Background: World Health Organisation estimates that 1.3 million people die of lung cancer worldwide every year, 90 percent because of smoking. Tobacco is the leading cause of not only Lung Cancer but also of Oral Cancers as well as many other cancers. WHO had proposaed its first health treaty in the form of Framework Convention on Tobacco Control (FCTC) which has been ratified and implemented by many countries, however. tobacco control and its different aspects still elude many. In the FCTC & MPOWER policy of WHO -W stands to Warn about hazards of Tobacco, specially the health hazards. Many governments are working on this, however, this complex problem requires attention of all parties and hence the role of NGO. Cancer Society of M.P. has been working in the field of Cancer awareness & Tobacco control for many years. We wish to share our different methods of tobacco control with all the delegates. Although, TV media has the highest visibility, non aired mass media methods for creating awareness, has its own importance and many a times it is much cheaper and gets free coverage also.

Methods: Some of the activities conducted by us for Tobacco control and creating awareness about its health hazards are:- Posters:We have prepared, published and distributed various posters for tobacco control and self examination of oral cavity. Our posters have won international awards and have also been presented in many national & international conferences. The release of poster by eminent personalities, politicians gives us free media coverage on the topic too. One of our posters was also tested by Americans for its impact in Egypt. Pamphlets:- We have distributed nearly 100 thousand pamphlets in the holy Sinhastha Mela (fair) where nearly 10 million people participated. Hoardings/ Bill Boards:- Installed at strategic points they are a source of constant reminder to th health hazards of tobacco. Lectures/symposiums:- Myself & other members regularly give lectures on different aspects of tobacco control & its health hazards. Exhibitions:- Participation & display of banners,posters etc in various exhibitions, where many people come & see them. Public Rally:- Rally taken out through the

city draws attention of public as well as the press. Involvement of Priests:-We have taken lectures in various temples & holy places and involved priests into tobacco control. Car Stickers, pasteing of small banners behind autorickshaws, slogan contests & involvement of local service clubs in the activities helps us reach a larger population.
Results: We have not used any pre and post survey to gauze the impact of the activity as its a continuous process, which has to have effect on the public. However, it may be done in future by Govt. or other agencies.
Conclusion: The representative photographs of all the activities will be displayed and discussed in detail, in the presentation.
Keywords: Tobacco Health Hazards & Tobacco Control, Mass Media & Tobacco Control

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P4.090 WALCE (WOMEN AGAINST LUNG CANCER IN EUROPE) AND MAKE-UP PROGRAM FOR WOMEN DIAGNOSED WITH CANCER.

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Background: The diagnosis of cancer and receiving an explanation about its treatment can lead to a series of extremely stressful and frightening events that cause both patients and their relatives to suffer emotionally. Psychological distress in cancer patients has been estimated at a range between 20% and 50%, but without clear evidence showing of a prevalent sex. Depression and anxiety are related to poor quality of life in all its shapes and forms, including the physical-side. There is also a considerable amount of data that shows a correlation between the outcome of cancer treatment and suffering from diminished self-esteem. The Look Good ... Feel Better® is an worldwide free make-up workshop programme for women diagnosed with cancer and who are undergoing chemotherapy, radiotherapy or other cancer treatments. The programme is carried out in local hospitals and offers free beauty workshops which are strictly non-medical, and the ladies receive a gift-filled beauty bag containing brand-neutral products. The aim is to help women regain self-confidence and esteem, improve quality of life by using beauty techniques to enhance looks and improve appearances which may have suffered due to the related side effects of the cancer therapy. The Look Good ... Feel Better® programme is currently active in 22 countries worldwide and in 2006 arrived in Italy as "La forza e il sorriso – L.G.F.B. Italia". WALCE Association began its collaboration with La forza e il sorriso – L.G.F.B. Italia in 2009.
Methods: From March 2009 to December 2010 WALCE have organised 34 make-up workshops of "La forza e il sorriso – L.G.F.B. Italia" at the San Luigi Hospital (Orbassano, Turin-Italy) in collaboration with five local cancer centres and institutes. 248 ladies attended the free make-up workshops, guided by 7 voluntary beauticians and with support of a psycho-oncologist. 6% had a diagnosis of lung cancer and the majority were aged between 50-60 yrs old. Everyone filled-in an anonymous beauty-workshop evaluation questionnaire.
Results: 63% were enthusiastic, while 37% were greatly satisfied with the results. 98% declared to have learnt useful advice whereas 2% were a little doubtful. However, the overall response was most positive. Adjectives used to describe patients feelings at the end of the work-shop were: beautiful, happy, more positive, prettier and attractive. From the survey, 86% of the ladies had forgotten about the illness during the moment they attended the event. It was expressed by an overall 78% as being a positive experience meeting other ladies in similar situations.
Conclusion: Cancer patients tend to cope better with the illness and daily-life when self-confidence and esteem is regained. The sense of well-being shared in a relaxed atmosphere and acknowledging social, emotional and psychological needs, whilst being amongst other ladies who have the same fears or anxieties, has proven to be an incentive to fight-against cancer. In next workshops a more detailed evaluation on patients' interpersonal relationships, on their psychological aspects and the impact on disease outcomes will be planned.
Keywords: Quality of Life, Self-confidence, advocacy, Lung cancer

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P4.091 ACCESS TO CANCER CHEMOTHERAPY : ECONOMICAL CONSIDERATIONS

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Background: In resource poor situations, cancer NGO's are main source of cancer care. Cost of running Cancer NGO far less than medical institution. Cost of anti-cancer drugs is debatable at many forums. Govt, Health Depts need to workout formula to increase access to chemotherapy. In resource poor setting unaffordable cost leads to poor therapeutic compliance therefore high mortality. We suggest to establish common training program to develop of sound & sustainable cancer care programs for rural communities. National cancer registry based data demonstrated that subsidized chemotherapy & treatment-availability are major issues for Lung-cancer sufferers in resource-poor-nations. Hence our Non-Govt-Organisation analyzed & started this public health-policy recommendation.
Methods: cost of chemo-Radio therapy is beyond reach of common people in developing nations. No national program for financial help to lung cancer patients available. In Lung-cancer-sufferers Individual's sexual identity, sexual function and sexual relationship is dramatically wounded. Women suffer silently physically and emotionally. Hence we need Rx-Care programs designed towards poor communities from rural/tribal areas. Some Cancer NGO's do offer little psychosocial support & subsidized treatment options. But such efforts are not cohesive. Our NGO since one year offers guidance for Rx-funding, guidance those going to city-oncology-centers. This project is unique as we are training farmers & village leaders to develop a peer-peer model. Depending on support given by donors we need to give these poor people financial assistance to cover treatment cost. We must help these patients in getting access to governmental hospitals.
Results: We all NGO community workers will face hiccups in mobilizing volunteers/resources. Initially basic cost like food, training materials, posters etc is major hurdle. This strategy has minimum maintenance cost & high acceptability. Health policy planners & forums like IASLC should help like-minded activists to come together & form a forum to develop this concept. Lung cancer patient advocacy program must be tailor-made to suit specific communities/countries including socio-economical & political considerations.
Conclusion: What we need is a drug-care supply model.Economical factors & access to therapy changes out-come of Lung-cancer-Rx. With little training our community NGO in rural/tribal India formed a well knit volunteers group who is giving free part-time dedicated service. This would reduce difficulties faces by resource poor southern countries. We urge participants & Pharma Exhibitors at 14th WCLC Amsterdam to share views & expertise on this burning issue.
Keywords: socioeconomics, access to drugs, Chemotherapy

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P4.092 PATIENT ORIENTED EVALUATION IN LUNG CANCER CASES

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Background: Inspite of media hype & government strictures on tobacco use, incidence of lung cancer is very high in Asia. No complete cancer care module available in India. Some cancer-institutes do provide treatment in metro-cities, It is however unclear what follow up care patients want or which model of follow up is preferred. Hence our Cancer NGO team analyzed & suggested plan to include palliative care program in cancer care projects of rural health set-up. There is no follow-up center for palliative care for patients who return to rural/tribal villages after treatment in city hospitals. Finally no data is available about needs of Lung-cancer patients.
Methods: By deviating from regular methodology, qualitative interviews were undertaken on 41 Lung-cancer patients who had completed palliative treatment. Responses analyzed on pre-designed patient-response record data [PRRD] charts. But We need strong platform like WCLC-2011 conference to show our findings to researchers/activists from developed world & get their guidance on this difficult issue.
Results: Our patient-response record data [PRRD] charts how [1] Lung cancer patents attitude towards their illness and how they cope with feelings. [2] Plan to Cope with treatment finances, ADR's [3]

expectations for future [4] difficulties faced with medical team [5] Concerns about addressing issues of QOL Majority respondents in our study project [>94%] felt that Palliative care needs are neglected in developing nations. It is of vital importance and should be implemented on priority.
Conclusion: 23 patients wanted or expected to continue in hospital follow up, despite being fully aware of and accepting of their diagnosis and poor prognosis. Patients were also keen to have psychosocial & palliative support. Treatment finances & family education were given top priority by all seven patients from rural/uneducated background. Our Indian cancer NGO has taken initiative on this front by forming team to get training in palliative/psychosocial care. But in such initiatives we sincerely need support of IASLC for implementation of this policy to serve poor rural/ tribal lung cancer cases.
Keywords: patient advocacy, Lung cancer, WCLC 2011

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P4.093 EDUCATION IN LUNG CANCER PATIENTS : DOES IT INFLUENCE OUTCOMES

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Background: The essence of Lung cancer patient's education is in providing specific knowledge about disease and anticancer treatment, and in educating family on home based care. Informed and educated patients are able to save self-esteem, to establish good relationship with social environment and to achieve better social participation. The aim of this study was to investigate the impact of the education on patient's self-image and the impact of the education on lung cancer patient-social environment relationship. Especially lung cancer sufferers who return to villages in rural parts of India after taking chemotherapy/surgery in city hospitals need this assistance. Community NGO's can play key role in providing cancer care including PATIENT & family education.
Methods: 42 lung cancer patients (38 men & 4 women, age 50-60 yrs) included in Our analysis and control group (n=30), all matched regarding age and educational level. Both groups answered questionnaire specifically designed to assess self-image of Lung cancer patients and relationship with social environment, family support & community centers. Cancer educational efforts must be devised suitable to local communities. Due to lack of resources , this issue of role of education in lung cancer care has been neglected for last decade.
Results: The education significantly improved self-image in lung cancer sufferers group when compared to control group (P<0,03). There was no significant difference after education between these group with regard to social relationship (P>0,03). Due to resource constraints we limited sample size & evaluation parameters. But Our cancer NGO is seeking multi-institutional-collaborations to conduct more-scientific pilot project on this unexplored issue in lung-cancer-patients community
Conclusion: Our cancer NGO has taken initiative on this front of cancer patients education as supportive care. The education has important contribution in establishing self management approach in which patients assume responsibility for their behavior, for changing their environment, and for planning their future. For successful Lung cancer patients' psychosocial adaptation and social participation, it is necessary that the whole society provides more resources for psychosocial support. This is low cost approach to improve care outcomes in resource constrained settings. This issue is fertile ground for further studies.
Keywords: education, outcomes, Lung cancer

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P4.094 ASSOCIATION OF INSURANCE WITH CANCER CARE UTILIZATION AND OUTCOMES IN LUNG CANCER. A STUDY FROM INDIA

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Background: Although there is substantial evidence that insurance status is an important factor in access to and utilization of cancer care . To address such a need in India this study was undertaken to estimate the burden of Cancer patient taking treatment each year ,to estimate the percentage of patients under treatment for Cancer is Insured and Uninsured , to estimate the of Insurance Coverage in patients with

Lung Tumours ,to estimate the trends in Insurance Coverage and Utilization of Health Care Resources for these tumours

Methods and Materia: Information on insurance status was obtained by analysis of data from the 2008 to 2010.. The. data were gathered through a computer-assisted databased of adults aged 18 years and older taking treatment in Sri Ramachandra Medical College and Research Institute. Data from database were used to examine the relationship between insurance status at the time of diagnosis . Software Oracle was used with Acess, SQL to analyse the data.

Results: Among the patients who met these criteria a total of 4453 cases were available for .The total number of cases registered for treatment of cancer in 2008 was 1250 patients and in 2009 to 1437 and further increased to 2166 patients by 2010. Increased in number of patients covered by the Insurance almost from 35 % at 2008 , to 47 % in 2009 and 62% by 2010. The State Government of Tamil Nadu ,Kalaignar Insurance Scheme for Life Saving Treatment in 2010 under Star Health and Allied Insurance Company Limited and there were 500 new cases registered in the same year for treatment of cancer(20 %) of all overall insurance patient registered during last 3 years. Trends in Insurance Coverage shows an overall increase in In lung cancer the number of patients getting treated with own payment decreased over the years from 60 % in 2008 to 20% in 2010. Table . 1 showing increasing percentage of patients diagnosed as Lung Cancer getting benefit from Insurance from 2008 to 2010

Year	Individual Patients/ Paying	Insurance Patients/ Non paying
2008	60%	40%
2009	50%	50%
2010	20%	80%

Conclusion: The trends in Insurance Coverage shows an overall increase in lung cancer the number of patients getting treated with own payment decreased with a gradual increase in trend for insurance overage the past 3 years were noted. Then subsequently health economic assessment can be made and proper relocation of resources for screening and prevention of cancer done be done

Keywords: Insurance, lung

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P4.095 COMPARISON OF JAPANESE CURRENT PERCEPTIONS OF LUNG CANCER IN THE WORLD- ANALYSIS FROM INTERNATIONAL SURVEY BY GLOBAL LUNG CANCER COALITION (GLCC)

Toshiyuki Sawa[1], Matthew Peters[2], Jesme Fox[2], Carolyn Aldige[2], Jim Gowing[2], Yasuo Iwamoto[2], Kenji Eguchi[2], Hiroshi Semba[1], Shinichiro Nakamura[1], Yoichi Nakanishi[1]

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Background: West Japan oncology group had carried out several activities for patient's advocacy to improve affiliation rate for lung cancer in this decade. To evaluate the outcome of our mission, we have analyzed Japanese perceptions of lung cancer using an international quantitative survey.

Methods: This survey was commissioned to understand the following among adults, 1) perceptions of which cancers kill the greatest number of people, 2) attitude towards lung cancer. Nationally representative quota sample of 1,272 adults across Japan was interviewed. Also, interviews were conducted in other 14 countries.

Results: In Japan, unlike most other countries where this survey took place, lung cancer is tied with bowel or colon cancer as the cancer that adults perceive to kill the most people (65% and 67%). 2) Despite this, along with Norway, Japan is the country with the greatest proportion of adults who think lung cancer is the biggest killer (both 65%). 3) In Japan, unlike most other countries, many people are unable to say whether they have less sympathy for people with lung cancer, given its link to smoking (44%). Of those who do give an opinion one way or the other, 32% say they do not have less sympathy but 20% do, which is about average compared to other countries. The perception of lung cancer as the biggest killer is higher among certain sub-groups, in particular, men compared to women (71% compared to 59%) , those aged under 65 compared to those aged 65+ (68% compared to 55%) and graduate of college or university compared to those of high school or junior high school (73% compared to 62% and 53% respectively)

Conclusion: It was shown that Japanese has a high interest in lung cancer, while there is a little

sympathy for people with lung cancer. It was thought that a new strategy should be planned to improve sympathy for patients with lung cancer.
Keyword: Patient advocacy, lung cancer, Perceptions

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P4.096 IGNORANCE AND PREJUDICE IN RELATION TO LUNG CANCER ARE WIDESPREAD INTERNATIONALLY

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Background: Lung cancer ranks poorly on the public policy agenda. Ignorance of its impact and negativity resulting from smoking as a causative factor may cause this. Additionally, stigma associated with lung cancer is a reality for many patients and self-reported stigma and blame are associated with poorer symptom control. However generally accepted it may be that these views are prevalent, they have not been measured. The aim of this study was to conduct an international survey that would quantify these attitudes.
Methods: A representative sample of 1,000-1,200 adults was interviewed between February and May 2010 in each of 15 countries. Two questions were added to a standard, national Ipsos MORI survey. For the first question, from a list that included lung, breast, bowel or colon, prostate and skin cancer, respondents were asked to nominate which cancer kills the most people in their country. Up to two answers were allowed. For the second question, using a five point scale from 'strongly agree' to 'strongly disagree' they were asked whether they agreed with the proposition that, as lung cancer was mainly caused by smoking, they had less sympathy for patients with lung cancer than people with other types of cancers.
Results: Lung cancer is the commonest cause of lung cancer in each country surveyed. The proportion of respondents who nominated lung cancer as within the top two causes of cancer death in their own country varied from 35%, less than chance, in Australia and Bulgaria, to a high of 65% in Japan and Norway. The number of respondents who stated that they had less sympathy for patients with lung cancer than those with other cancers varied from a low of 10% and 14% in Spain and Argentina to a high of 28-29% in Brazil and Argentina. There was a trend for stigma to be greater in countries with lower smoking rates.
Conclusion: Throughout the world, there is considerable underestimation of the impact of lung cancer relative to other cancers. Negative attitudes to lung cancer patients are also widespread. Addressing ignorance and prejudice may be a necessary precondition to achieve appropriate resourcing for lung cancer research and improved clinical care.
Keywords: stigma, Lung cancer, community attitudes

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P4.097 UNUSUAL NEUROLOGICAL PRESENTATION OF THE NON-SMALL CELL LUNG CANCER (NSCLC).

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Background: Paraneoplastic neurological syndrome (PNS) affects less than 1:10,000 patients with cancer and can involve any part of the nervous system. Condition is caused by autoimmune processes and production of onco-neural antibodies, directed against antigens expressed by both the tumour and the nervous system.[1]
Methods: We report a case of patient who presented with a central cord syndrome caused by lung adenocarcinoma, to our knowledge such presentation has not been previously described.
Results: A 49 year old female presented to our hospital with acute urinary retention, weakness and altered sensation descending from umbilical level to both lower limbs. Symptoms were associated with two months history of night sweats and weight loss. Systemic examination revealed a sensory level around T10 and decreased anal tone but no significant motor deficit. The patient was a smoker with a 10 year pack history. Routine laboratory tests, hepatitis B, hepatitis C and HIV screen were negative. Antinuclear antibodies were positive to titre 1:640 but with negative antibodies to extractable nuclear antigens. Paraneoplastic anti-neuronal antibodies Hu and Ri were also negative. Chest x-ray showed widening of the right paratracheal region confirmed on enhanced computer tomography (CT)

of thorax to be an upper mediastinal mass displacing and compressing the SVC. Whole spine MRI revealed a long central cord lesion extending from the mid-cervical area down to the lower thoracic region. Transbronchial biopsies were negative and patient underwent mediastinoscopy, biopsies from this procedure showed poorly differentiated adenocarcinoma with immunostaining suggestive of lung primary. The patient received four cycles of Carboplatin and Gemcitabine. A month after completion of chemotherapy she was readmitted with worsening paraesthesia in lower limbs. Neurological examination did not reveal any new findings and repeated the whole spine MRI looked normal. The patient received further treatment with radiotherapy (55Gy) to the right lung. Follow-up CT thorax showed almost complete resolution of mediastinal changes. She remains in remission with mild lower limbs altered sensation and residual numbness. Currently no further treatment is being considered.

Conclusion: Anti-neuronal antibodies despite a high specificity of 96-98% are detectable only in 30-50% of the clinical defined PNS cases.[2,3] Use of the PNS Euronetwork diagnostic criteria can aid diagnosis if anti-neuronal antibodies are not detected. [4] Patients who receive tumour therapy are 1.5 times more likely to have stable or improved neurological disease compared with those who are not treated. [5] Treatment of lung adenocarcinoma in our patient resulted in a significant cancer regression but also in the complete resolution of radiological spine changes and improvement in central cord syndrome symptoms resulting from PND. 1.Paraneoplastic neurological syndromes.
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Keywords: Adenocarcinoma, Central cord syndrome, Non-small cell lung cancer, Paraneoplastic neurological syndrome

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P4.098 MAINTENANCE TREATMENT IN ADVANCED STAGE NON SMALL CELL LUNG CANCER RESULTING IN PROLONGED SURVIVAL; SINGLE CENTER EXPERIENCE: CASE SERIES

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Background: Advanced stage non small cell lung cancer is an aggressive and invariably fatal malignancy that carries a very poor prognosis with a median survival of less than a year. Five year survival is reported to be less than 5% in these patients. We present case reports of three patients with advanced lung cancer who have survived over three years without any detectable disease. All of them were non smokers and presented at an advanced age. They received Erlotinib (Tarceva®) maintenance therapy.

Methods: This was a retrospective case series. Data was collected from electronic health records (Agastha Healthcare). Demographics, stage and treatment details were carefully reviewed and analyzed.

Results: Case reports: NW, a 70-year-old Caucasian female presented to our office in the summer of 2007 for newly diagnosed stage III lung cancer (adenocarcinoma). During her initial consultation, she developed seizures in the office. Imaging of her brain revealed one large metastasis adjacent to the motor cortex. She underwent radiosurgery followed by resection of metastasis. She then received whole brain radition and then was started on systemic treatment with paclitaxel/cisplatin. Follow up PET imaging revealed no evidence of disease. She was placed on maintenance Tarceva®. Fifteen months later she developed ataxia and generalized weakness. Her imaging studies revealed recurrence of brain metastases in three different locations. She received additional radiotherapy. She has had no evidence

of recurrence since then. It is over three years now since her original diagnosis. There is no evidence of systemic recurrence. DM, a 67 year old Caucasian male developed headaches, audiovisual disturbances and altered mental status while driving his car in the winter of 2006. He was taken to local ER. Work up revealed evidence of parietal lobe mass. He underwent resection of the same. Pathology revealed adenocarcinoma with possible lung primary. PET scan confirmed hilar mass with precarinal lymphadenopathy. He underwent systemic treatment with paclitaxel and cisplatin. He also received whole brain radiation. After six months of systemic treatment there was no evidence of residual disease anywhere. He then was placed on maintenance treatment with Tarceva®. Due to personal reasons he discontinued Tarceva® after two years. At the time of writing this abstract, he is alive and has no evidence of disease. JP, a 78 year old Caucasian male, non smoker presented with stage IIIB non small cell lung cancer (pleural effusion). He initially received treatment with taxanes and platinum. He had partial response with resolution of effusion. Treatment then was changed over to Gemcitabine/vinorelbine. He continued to respond. After four months, he did not wish to have any further parentral chemotherapy. He then was placed on erlotinib in fall of2006. He has no evidence of disease and continues on erlotinib.

Conclusion: All of these cases demonstrate unusually long survival in the elderly patients who initially presented with advanced stage disease. All of these patients were non smokers. We feel that biology and disease progression in elderly non-smoker patient with adenocarcinoma may be different and they clearly benefit from maintenance

Keyword: lung cancer, maintenence treatment, erlotinib

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P4.099 VACUUM ASSISTED CLOSURE WITH THORACOPLASTY FOR POST PNEUMONECTOMY BRONCHOPLEURAL FISTULA AND EMPYEMA

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Background: Post-pneumonectomy bronchopleural fistula is one of the most feared, life-threatening complications following lung cancer resection. The bronchopleural fistula pollutes the only lung with fluid from the contralateral hemithorax, and leads to contamination and empyema of the post-pneumonectomy space. Historically this was treated with open window drainage, converting that hemithorax into a chronic draining wound, and/or obliteration of the empty cavity with flaps such as omentum, latissimus dorsi, and/or serratus anterior muscle. Thoracoplasty, or removal of ribs, allows intercostal muscle and soft tissues to move medially and obliterate the cavity allowing clearance of the infection. Unfortunately, even after thoracoplasty, contraction and healing of the wound is a lengthy process involving multiple frequent dressing changes. Negative pressure therapy in the form of a wound VAC system (Vacuum Assisted Closure-Kinetic Concepts Inc, San Antonio, Texas, USA) has been applied to acute and chronic wounds with the goals of facilitating wound contraction, promoting granulation tissue, and decreasing the frequency of dressing changes. Negative pressure therapy can be administered as an outpatient with dressing changes every 72 hours rather than twice or three times daily.

Methods: Two patients were transferred to our facility with bronchopleural fistulae and empyema. The first developed bronchial stump dehiscence after right pneumonectomy which was treated with open window drainage for 20 months. Multidrug resistant pseudomonas aeruginosa developed in the cavity; at that point he was referred for evaluation. Latissimus and serratus muscles were previously severed, and omentum was nearly nonexistent due to cachexia. Restaging CT/PET, and bronchoscopy revealed no recurrent disease. Nutrition was optimized and five rib thoracoplasty was performed with use of a wound VAC. The second patient developed bronchopleural fistula and empyema one month after left pneumonectomy, initially treated by serratus anterior muscle flap, but the fistula and empyema recurred within 3 weeks, accompanied by aspiration pneumonia. At that point he was referred. Surgical exploration to cleanse the cavity was performed along with closure of the bronchial stump. The preexisting muscle flap was inadequate to fill the infected cavity, thus a three rib thoracoplasty was performed along with wound VAC management.

Results: Both patients were managed with antibiotics guided by culture results, and serial changes of the wound VAC dressings every 72 to 96 hours. Initially, dressings were changed in the operating room, then on the hospital ward with

sedation, and within two weeks were stable to transition to care at home with visiting nurses. Both patients had complete resolution of the infected cavities and closure of the fistulae, with subsequent weight gain and return to normal activities of daily living.

Conclusion: Post-pneumonectomy bronchopleural fistula is a life-threatening complication requiring closure of the fistula and collapse or filling of the empyema cavity. When local flaps are inadequate to allow healing, thoracoplasty can be performed. Application of the wound VAC system to this type of wound has not been routinely used. We have demonstrated that it has been safe and allowed fewer dressing changes than traditional gauze packing, and in addition allows therapy to continue as an outpatient.

Keywords: Bronchopleural fistula, Negative Pressure Therapy, Lung cancer, Complication

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P4.101 DO MULTIDISCIPLINARY TEAM (MDT) MEETINGS MAKE A DIFFERENCE IN THE MANAGEMENT OF LUNG CANCER?

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Background: Lung cancer multidisciplinary team (MDT) meetings are recommended by many international guidelines. However there is limited evidence regarding their effectiveness. The aim of this study was to compare patterns of care and outcomes of lung cancer patients presented at a lung cancer MDT meeting with those not presented.

Methods: All patients with a new diagnosis of lung cancer in South West Sydney (SWS), NSW, Australia between 1st December 2005 and 31st December 2008 were identified from the local Clinical Cancer Registry (CCR). This included non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and those with clinical diagnosis alone. Patients who were discussed at the Lung Cancer MDT meeting were identified from an oncology database. The MDT and non-MDT populations were compared in terms of patient and tumour characteristics, treatment utilisation and survival. A logistic regression model was constructed to determine predictors for receiving treatment and survival.

Results: There were 988 patients in the study population of whom 504 were presented at a MDT meeting and 484 not. The median age was 69 and 73 years respectively ($p<0.01$). There was no pathological diagnosis for 13% of non-MDT patients compared with 4% of MDT patients ($p<0.01$). Treatment utilisation for MDT vs non-MDT patients was 12% vs 13% for surgery (p=NS), 66% vs 33% for radiotherapy ($p<0.001$), 46% vs 29% for chemotherapy ($p<0.001$), and 66% vs 53% for palliative care ($p<0.001$). In patients with good performance status (ECOG 0-2), the MDT group had significantly better radiotherapy utilisation in Stage I-IV NSCLC and chemotherapy utilisation in Stage IV NSCLC. Treatment utilisation in SCLC was similar. Regression analysis showed that MDT discussion was an independent predictor for receiving radiotherapy, chemotherapy and for referral to palliative care. MDT discussion did not influence survival.

Conclusion: Patients discussed at a Lung Cancer MDT meeting were more likely to receive non-surgical treatments and be referred to palliative care. Although this did not change survival, the increased utilisation of these modalities may have improved quality of life in these patients.

Keywords: Small cell lung cancer, Multidisciplinary Teams, Treatment utilisation, Non-small cell lung cancer

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P4.101 OVERVIEW OF PRIMARY ENDPOINTS, PROGRESSION-FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS) FOR NON-SMALL CELL LUNG CANCER (NSCLC): THEIR VALUE IN TREATMENT DECISIONS AND PATIENT CARE

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Background: NSCLC (accounting for 80% of all cases of lung cancer) causes high morbidity and

mortality. Various treatment lines are available for NSCLC, and there are ongoing discussions on the most appropriate endpoint to measure treatment efficacy for reimbursement decisions. We examined the use of two of these endpoints, progression-free survival (PFS) and overall survival (OS) in NSCLC from a payer's perspective.
Methods: Randomised controlled trials reporting the efficacy of bevacizumab-based therapies and licensed doublet-chemotherapy combinations for first-line advanced or metastatic NSCLC treatment were identified in a systematic literature review. Additional targeted literature searches to identify payer and regulatory perspectives on the use of different endpoints in NSCLC were conducted in MEDLINE® and the Cochrane Database of Reviews using clinical and health economic-related key words and limited from 2000 to 2010. The results from both searches were reviewed and formed the analysis of the outcomes and use of these endpoints in this period.
Results: OS can be measured easily and accurately in terms of both event and time and is the endpoint preferred by regulatory bodies including the FDA and EMA. Moreover, it provides a distinct clinical benefit for patients. Over the last 10 years the length of OS achieved for first-line treatment of NSCLC has risen, surpassing the historical one-year benchmark. Nevertheless it has become increasingly difficult to demonstrate statistically significant OS benefit, as the efficacy of treatments (as shown by results from clinical trials) has generally improved by modest increments over time. Demonstrating improvements in OS over best supportive care is less challenging than against an active comparator; however, this former comparison may ultimately be less clinically meaningful. In order to demonstrate OS benefit, large, adequately powered studies are required — a challenging situation, especially with a limited patient population for trials of first-line NSCLC treatments. Demonstrating a significant PFS benefit in a randomised controlled trial is also challenging, requiring frequent assessments and precise event definition. Nevertheless, PFS provides a well-accepted alternative endpoint to OS. It primarily measures the effect of the study drug (depending on the censoring rules applied to the analysis), which is important when it is expected that a significant proportion of patients will receive second- or third-line therapy after a progression event. Furthermore, it is a measure of treatment effect on tumour burden — the means through which most anticancer therapies achieve success. A significant PFS benefit therefore, may be regarded as having true clinical relevance. PFS has also been accepted by regulatory bodies as a valid measure of the clinical efficacy of cancer treatments in other disease settings, particularly in situations where it is expected that further lines of treatment may impede detection of a significant OS benefit.
Conclusion: Despite the challenges of demonstrating an OS benefit of new therapies for NSCLC, OS is generally regarded as the preferable endpoint (from a payer's perspective) for demonstrating clinical efficacy in this disease. However, PFS data may be more appropriate for use in certain situations, especially those (for example NSCLC) in which subsequent lines of therapy exist.
Keywords: Progression, survival, endpoints

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P4.102 SYNCHRONOUS PULMONARY METASTASES FROM EXTRATHORACIC MALIGNANCIES AND PRIMARY LUNG CANCER

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Background: In the management of multiple lung nodules suspecting pulmonary metastases from extrathoracic malignancies, routine biopsy of all pulmonary lesions and obtaining histological diagnosis is not practical. The exact diagnosis for such lesions before treatment is sometimes difficult despite improvement of diagnostic procedures.
Methods: We experienced two patients who underwent pulmonary metastasectomy from extrathoracic malignancies showed synchronous pulmonary metastases and primary non-small cell lung cancer.
Results: [Case 1] A 66-year old man with a history of renal cell carcinoma showed multiple pulmonary nodules bilaterally. Patient received sorafenib and subsequently underwent pulmonary metastasectomies by video-assisted thoracic surgery (VATS). Among five lesions, four lesions were diagnosed with metastatic renal cell carcinoma and one lesion was diagnosed with bronchioloalveolar carcinoma (measuring 9mm). Bone metastases and new pulmonary lesions appeared 4 months after metastasectomy. [Case 2] A 68-year old woman was diagnosed as stage IV

rectal cancer (lung metastases). Patient received 12 courses of bevacizumab in combination with FORFIRI and subsequently underwent low anterior resection for primary rectal cancer and pulmonary metastasectomies by VATS. Among five lesions, two lesions were diagnosed with metastatic rectal cancer and three lesions were diagnosed with bronchioloalveolar carcinoma (measuring 7mm, 7mm and 2mm, respectively). No recurrence was observed for 8 months postoperatively.
Conclusion: In our case, since all primary lung cancers were diagnosed as bronchioloalveolar carcinomas less than 10mm in diameter, metastasectomies with adequate surgical margin should be potentially curable resection. One should consider the possibility of coexistence of primary lung cancer at the time of pulmonary metastasectomy. In case of synchronous pulmonary metastases and primary lung cancer, additional treatment should be considered according to the tumor biology of each primary disease.
Keywords: pulmonary metastasis, primary lung cancer

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P4.103 EXTENDED LEFT PNEUMONECTOMY WITH PARTIAL RESECTION OF THE LEFT ATRIUM, FOR SUPERIOR PULMONARY VEIN AND LEFT ATRIUM TUMOR THROMBUS DISCOVERED UNEXPECTEDLY AT OPERATION FOR LUNG CANCER

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Background: There are limited reports of curative resection for bronchogenic carcinoma invadind the left atrium. There are techniques of resection that permit a complete resection in selected cases of lung cancer invading the left atrium. All these techniques entail using vascular clamps on the left atrium and closing the left atrium by running suture. Alternatively cardiopulmonary bypass can be used for that purpose. The same applies in situations, where tumor thrombi of the pulmonary veins or the left atrium exist. In most of these cases, tumor thrombi of the pulmonary veins or the left atrium are evident on preoperative CT scan.
Methods: We describe the case of a 72-year old man with a large hilar mass of the left lung, in whom thrombosis of the left superior pulmonary vein was discovered at operation, after intrapericardial ligation and division of that vein.
Results: The patient was subjected to a left intrapericardial pneumonectomy, due to invasion of the pericadium by tumor. After ligation and division of the left superior pulmonary vein, it was discovered full by thrombus. A vascular clamp was applied at the left atrium at a distance of 1.5 cm from the cut edge of the vein. Left atrium was resected flush with the clamp and a double running suture of 3-0 prolene was used to close the atrium beneath the clamp. The patient had an uneventful postoperative course with no complications and he is well and alive three months after operation.
Conclusion: Although not quite common, the thoracic surgeon must have in mind that unexpected thrombi of the pulmonary veins and left atrium may be discovered, while performing a potentially curative operation for lung cancer, especially one for a centrally placed tumor. When that happens, the surgeon must be prepared for partial resection of the left atrium.
Keywords: Lung cancer, pneumonectomy, pulmonary vein thrombus, atrial thrombus

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P4.104 TREATMENT OF INFLAMMATORY MYOFIBROBLASTIC TUMOR WITH MALIGNANT TRANSFORMATION BY RADIOTHERAPY AND STEROID.

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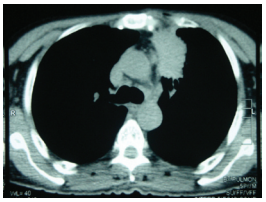
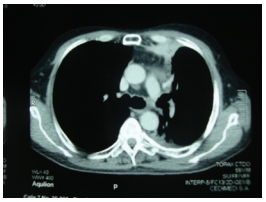
Background: Inflammatory Myofibroblastic Tumor (IMT) is a rare tumor of proliferating myofibroblasts that rarely undergoes malignant transformation, are associated with frecuent infiltration, obstruction, local recurrence and rare metastasis. IMT was initially recognized as a pulmonary lesion in adults but has been reported to ocurr in multiple anatomic locations such as the bladder, breast, colon, liver, pancreas, prostate, soft tissue and spleen. The neoplastic nature of IMT has been supported by

cytogenetic evidence of clonality and recurrent involvement of chromosomal region 2p23. The treatment of choice is radical surgical resection, but if not possible there is no standard management.
Methods: A 57-year-old man was admitted to emergency department with chest pain of 2 months. The findings in the Computed tomography (CT) of the chest incluiding the upper abdomen showed a mass in the anterior segment of left upper lobe infiltrating the chest wall, with size of 8 x 5 x 6 cm, with two anterior mediastinal lymph nodes.



Open biopsy was performed by chest surgery. The biopsy diagnosis of IMT with malignant transformation. Is presented in the oncology staff and he was considered a candidate for radiation therapy which receives lung volume of 3800 cGy and boost 1600 cGy. The patient was treated with steroids 1 mg / kg / day of prednisone for 3 months and then gradual withdrawal strategy.
Results: Follow-up CT at 1 and 3 months after radiation therapy showed partial response by RECIST criteria. Follow-up CT at 6 months after radiation therapy showed complete response and persisted only pleural thickening and bronchiectasis. (CT of the chest 2).



Follow-up CT scans 12 and 24 months off therapy with radiotherapy and steroids have shown no evidence of recurrent disease.
Conclusion: Radiation therapy and steroids for unresectable IMT can be considered as management options in highly selected patients.
Keywords: Inflammatory myofibroblastic tumor, Inflammatory pseudotumor, Spindle cell granuloma

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P4.105 PULMONER CYSTIC MESENCHYMAL HAMARTOMA: BECAUSE OF INTERESTING RADIOLOGY

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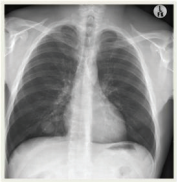
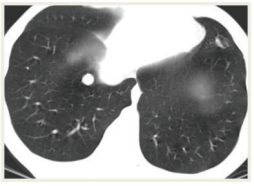
Background: 35 years old male patient with chronic renal failure being treated by peritoneal dialysis, 3 years ago and the last 1 year continuous hemoptysis (50cc) were admitted with the complaint. He had medical history of hypertension and 75 years / pack smoking. Renal failure and cirrhosis in his sister's medical history were available.
Methods: At PA (posterior-anterior) chest radiograph and thorax CT in both lungs smooth edges,homogeneous nodular and cystic-cavitary lesions were present (Figure 1, 2A, 2B). Grade 1-2 bilateral renal were seen at abdomen ultrasonography, abdominal MRI was normal.





Results: The patient's age, history, hemoptysis symptoms, physical examination and radiological findings, when considered as a priority in the differential diagnosis of benign (tuberculosis, fungal disease, hydatid cyst, sarcoidosis, Wegener's granulomatosis) and malignant (lymphoma, metastatic tumors) lung disease under consideration of further tests made. PPD test and three times negative AFB in sputum and sputum AFB cultures reproduction was not pegged. Hand-foot radiographs in the assessment for sarcoidosis and 24-hour urine calcium levels were normal. Hydatid panel

ELISA was negative. For Wegener's granulomatosis paranasal sinus computed tomography examination was normal observation, autoantibodies (ANA, p-ANCA, c-ANCA) negative pegged. Within normal limits tumor markers (CA-125, CEA, CA 19-9) was found.At bronchoscopic examination the active bleeding and endobronchial lesions weren't found, BAL cytology and bronchoscopic lavage cytology were normal.At renal biopsy Focal Segmental Glomeruloskleroz was pegged.
Conclusion: DIAGNOSIS: Mesenchymal Cystic Hamartoma. The patient's diagnosis was found especially interesting because of it's radyology and it was seen rarely.
Keywords: Hamartoma, cystic, Pulmonary

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P4.106 A CASE OF LUNG CANCER IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: Patients with chronic lymphocytic leukemia (CLL) are at increased risk of developing second primary malignancies. For patients with CLL there is a 60 % increase in the incidence of lung cancer, especially non-small cell lung cancer. Approximately 2 % of patients with CLL develop lung cancer. Prognosis of these patients is better if lung cancer is discovered at an early stage.
Methods: We describe the case of a 55-year old male, diagnosed with CLL five years before presentation, with a nodule at the superior segment of the lower lobe of the right lung, which had not been growing for about two years, but finally proved to be lung adenocarcinoma.
Results: The patient had been diagnosed with CLL five years ago. He had a smoking history of 40 pack-years. Two years ago a lung nodule about 1.5 cm in diameter was discovered at the superior segment of the right lower lobe. The patient was put under observation with chest CT scans performed at regular intervals. CT scan on December 2010 showed an increase of the size of the nodule, which reached a diameter of about 2 cm and the patient was then reffered to our department. No other diagnostic examination was performed and the patient was scheduled for surgery. At operation a wedge excision was initially performed and frozen section of the specimen revealed malignancy, but the pathology could not clarify the organ of origin . We decided to proceed to right lower lobectomy immediately. Final pathology report revealed the nodule to be lung adenocarcinoma.
Conclusion: It is appropriate to consider enrolling patients with CLL in screening programmes for lung cancer, because early diagnosis and surgical treatment appear to offer the best opportunity for cure. These patients should be informed about their increased risk of developing lung cancer and smoking cessation should be encouraged. We feel that these patients need a more agressive diagnostic and therapeutic strategy, whenever suspicious lung nodules are discovered.
Keywords: Lung cancer, lung adenocarcinoma, chronic lymphocytic leukemia, Lung nodule

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P4.107 MALIGNANT PLEURAL MESOTHELIOMA (MPM), THE BRONCHUS, TRACHEA, LYMPH NODE, TONGUE AND SUBMENTAL METASTASES (A CASE REPORT)

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Background: MPM is a very poor prognosis, in our country generally, environmental way, by inhaling asbestos and other minerals occur.However, as in developed countries can be seen with occupational exposure to asbestos.Often, local invasion but rarely do metastasize to distant organs.We wanted to present a case with metastasis at the trachea, bronchus, lymph node, tongue and submental region.
Methods: CASE: 49-year-old male, electrical technician, father died of prostate cancer, uncle died of lung cancer.History, with a diagnosis of MPM underwent pleural decortication and pleurodesis, 4 cycles of chemotherapy (cisplatin + pemetrexed) received.At the CT angiography, because of dyspnea

with bilateral lobar, segmental and subsegmental emboli, multiple lymphadenopathies and bilateral fluid was detected.
Results: Thorax CT of the lower end of tracheal stenosis and right lung upper lobe metastasis, at the bronchoscopy total occlusion of the left main bronchus, trachea and left main bronchus mucosal plaque, as a result of the trachea in the lower end of the biopsy revealed a metastasis of MPM.On the left supraclavicular LAP 2x3 cm in diameter were found, and examination of the language hyperemic, edematous and swollen mucosa lesions 0.5X0.5 cm and 1 cm in diameter mass in the right submental region and submental region, expressed as metastases evaluated.Under the mandible on the right maxillary CT 40X20X33 mm submental level, elevated language, and oral cavity with fine needle aspiration biopsy taken from the mass lesion were diagnosed with metastasis in MPM.
Conclusion: We wanted to present this rare case with metastases.
Keywords: rare metastases, malignant pleural mesothelioma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.108 HUGE MEDIASTINAL MATURE TERATOMA UNUSUAL PRESENTATION MIMICKING WITH LUNG HYDATIDE DISEASE

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Background: Benign mature teratomas are the most common type of germ cell tumors that arise in the anterior mediastinum. But its an unusual presentation with huge left intrathoracic mass mimicking lung hydatide disease.
Methods: We present an interesting clinical presentation of benign mediastinal cystic mature teratoma as unusual presentation in left intrathoracic region presenting with left free pleural effusion and huge left intrathoracic mass like a lung hydatide disease.
Benign mediastinal teratomas usually don't cause any symptoms and the diagnosis is reached accidentally. As they enlarged they may cause symptoms by compressing the nearby structures of thorax, mostly the trachea and bronchi.
The case who had giant mediastinal mature cystic teratoma, in a 25-year-old-woman with a cough and left-sided thoracic pain. Computed tomography of the chest revealed a giant cystic mass with a minimally pleural free effusion in left intrathoracic region, measuring approximately 12 by 15 by 15 cm in diameter.
Laboratory tests were normal, but clinical and X-Ray findings were suggestive of a huge hydatide disease of the lung.
Results: We performed left thoracotomy, intraoperative findings were suggestive giant benign tumor like a cystic mature teratoma which was originated from anterior mediastinum. we performed complete and radically excision of the tumor.
In the same time, additionally, we noticed there was a minimal aortic coarctation anomally in the descending aorta.
The histopathological investigation confirmed of giant mediastinal mature teratoma located into the left intrathoracic region with left free pleural effusion without evidence of pulmonary invasion.
Conclusion: In conclusion, clinical characteristics of mediastinal mature teratomas are non-specific, and the unusual presentation of the tumor makes its diagnosis difficult preoperatively.
Mature cystic teratoma is a benign tumor, but, surgical resection is recommended owing to its potential complications.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.109 PRIMARY GEFITINIB-RESISTANCE IN A PATIENT WITH METASTATIC ADENOCARCINOMA OF THE LUNG HARBORING A PR836C EGFR-MUTATION

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Background: Activating mutations of the epidermal growth factor receptor (EGFR) gene have been identified to be predictive markers for response to targeted therapy with tyrosine kinase inhibitors (TKI) such as gefitinib in patients with non-small-cell lung cancer. Primary resistance to EGFR-TKIs occurs in about 5 % and is mostly described as part of rare mutations like insertion in exon 20.
Methods: A 49-year-old female patient with a smoking history of 30 pack years and no comorbidities presented with swelling of supraclavicular lymph nodes (ECOG performance status 0-1). Specimens were taken from these lymph nodes as well as from subcutaneous skin metastases. Histopathological assessment showed a low differentiated pulmonary adenocarcinoma. Staging (UICC 7th edition) was cT3 pN3 pM1b. Further molecular analysis of the EGFR gene showed a wild-type for exons 18 and 19, but a point mutation pR836C in exon 21 (replacement of arginine by cysteine at codon 836) was detected by Sanger bidirectional sequencing. Therefore targeted therapy with gefitinib (250 mg once-daily) was started. We were aware of the fact that this mutation and its significance for response to TKI-therapy had not as yet been well described.
Results: One month after start of treatment the patient showed a clinically progressive disease with reduced overall state of health (ECOG performance status 2) and progressive and new subcutaneous metastases. CT-scans of chest and abdomen documented severe tumor progression in the lung, the right adrenal gland, the bones and the skin as well as of the lymph node metastases in different localizations. We switched treatment to a combination of cisplatin (75 mg/m^2 BSA) and pemetrexed (500 mg/m^2 BSA). Three weeks later, after one cycle of chemotherapy, the patient presented in an even worse condition (ECOG 3-4) and started to develop dyspnea. By clinical standards skin metastases as well as palpable lymph node metastases were growing. Imaging showed a progressive disease with pleural effusion and pulmonary infiltration suspected to be due to lymphangitis carcinomatosa. The patient finally died from respiratory failure two weeks later, only two months after treatment initiation.
Conclusion: EGFR-mutation is usually regarded as predictive marker for response to TKI-therapy in patients with non-small-cell lung cancer. We describe a patient with pR836C mutation at exon 21 showing primary resistance to gefitinib and cisplatin/pemetrexed. The clinical course of patients with this mutation hasn't been described yet.
Keywords: EGFR mutation, primary TKI-resistance

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P4.110 HOW TO TAGET LUNG AND RENAL CARCINOMAS?

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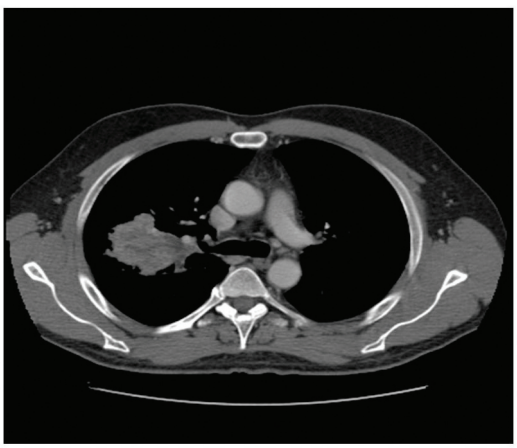
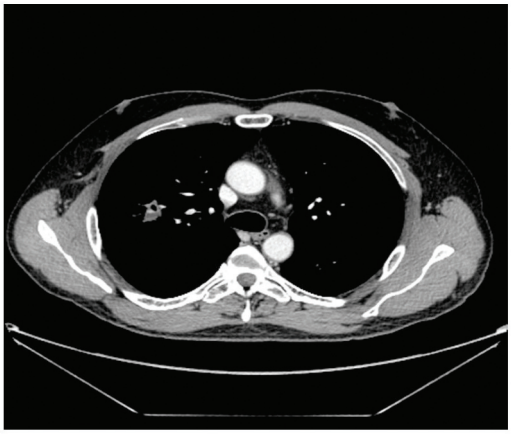
Background: Non small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) are both common and associated with smoking. Their association is not unusual. However, no data is available to guide the management of synchronous RCC and NSCLC. We report an example of concomitant treatment of RCC and NSCLC using the association of chemotherapy and targeted therapy.
Methods: A 47 year-old man, former smoker, was refered for a stage pT3bN0M1R0 polymorphic RCC with pulmonary metastases. He received adjuvant targeted therapy with sunitinib 50mg daily. A month later, a 50mm pulmonary lesion appeared and was diagnosed as a cT2N2M0 NSCLC.



The multidisciplinary team discussion (MTD) proposed to target both diseases using 4 chemotherapy cycles (carboplatin AUC6 and

paclitaxel 175mg/m²) plus sunitinib 37,5mg. The tolerance was good. The evaluation showed a complete response of the RCC pulmonary metastases and a 76% reduction of the NSCLC.



A lobectomy was performed. The pathological demonstrated a pT0N0M0R0. Sunitinib was continued without any relapse after 15 months of follow up.

Results: Previous studies showed that standard chemotherapy of NSCLC is not effective for the treatment of RCC and, in the same way, that multitarget tyrosin kinase inhibitors (TKI) such as sunitinib is poorly effective for the treatment of NSCLC. On the other hand, targeting VEGF or PDGF seems suitable for the management of NSCLC with regards to molecular patterns and results of phase III studies or meta-analyses. This case suggests that the combination of chemotherapy and antiangiogenic TKI may increase outcomes of NSCLC patients and highlights the need for predictive biomarkers in this field. It also suggests a possible strategy for patients with synchronous RCC and NSCLC in an area where data are missing. These cases always need a MTD.

Conclusion: The association of sunitinib with chemotherapy may improve the management of synchronous RCC and NSCLC but needs to be evaluated.

Keywords: Lung cancer, renal cell carcinoma, targeted therapy

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P4.111 MULTIMODAL THERAPY FOR MEDIASTINAL NONSEMINOMATOUS GERM CELL TUMOR WITH SOMATIC-TYPE MALIGNANCY WITH BRAIN METASTASIS; REPORT OF A CASE

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Background: Mediastinal nonseminomatous germ cell tumor (NSGCT) with brain metastasis is rare and has a poor prognosis. We report a clinical case of NSGCT with malignant transformation of the somatic component with brain metastasis.

Methods: Case: An 18-year-old male presented with chest pain and an anterior mediastinal mass was seen on the image exams. Chest CT and MRI revealed a large heterogeneous lesion measuring 14 x 11 cm. Histological findings of needle-biopsied specimens suspected teratoma. Although immature component was not defined, tumor markers (AFP, HCG-beta) have elevated. Four courses of BEP therapy (bleomycin, etoposide, cisplatin) made tumor markers decrease, but the tumor showed further growth. And brain MRI revealed several metastatic lesions within 5 mm in diameter. Because the huge tumor markedly compressed mediastinal structures, en bloc resection of the primary tumor was performed after gamma knife surgery for multiple brain metastases.

Results: The tumor, measuring 21 x 14.5 x 8.5 cm in size, was completely resected with partial resection of pericardium and right upper lung. Microscopic examination revealed most of the tumor was mature teratoma consisted of skin, gastrointestinal glands, bones, cartilage, neural tissues, pancreatic tissues, etc., and necrotic tissues. Partially atypical cells were detected in some areas but there were no viable tumor cells. The pathological and immunohistlogical studies showed germ cell tumor with somatic-type malignancy. The concentrations of serum AFP and HCG-beta decreased within normal limits after surgery. While stereotactic radiosurgery was performed for second brain metastases three month after surgery, then, there has been no sign of recurrence for 14 months.

Conclusion: NSGCT with somatic-type malignancy is recognized to be difficult to treat. In this case, we experienced to have good control of the disease by multimodal therapy.

Keywords: somatic-type malignancy, Brain Metastasis, multimodal therapy, mediastinal nonseminomatous germ cell tumor

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P4.112 EFFECTIVE CHEMOTHERAPY WITH CAFFEINE FOR CLEAR CELL SARCOMA OF CHEST WALL

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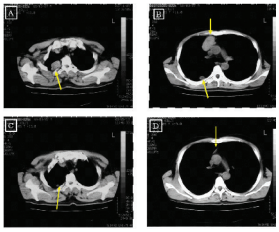
Background: Caffeine can safely enhance the cytocidal effects of anticancer drugs through its DNA repair-inhibiting effect. It has been demonstrated in several studies that caffeine-potentiated chemotherapy induces a high complete response rate in patients with osteosarcoma. We report a rare case of clear cell sarcoma in chest wall and a good effect of caffeine-potentiated chemotherapy in this case.
Methods: A 39-year old man was hospitalized with local recurrent clear cell sarcomas 3 months after surgery of his right chest wall. We applied 3 cycles of CDDP+ADM regimen with caffeine for this case (CDDP 120mg/m2 day1, ADM 60mg/m2 day1(48hrs), caffeine 2200mg day1-3).
Results: We got a very good response (figures). Sleep disturbance and palpitation are main complications.



Conclusion: Caffeine-potentiated chemotherapy has a possibility of enhancement of effects of anticancer drugs for other kinds of chest malignant tumors.
Keywords: caffeine-potentiated chemotherapy, clear cell sarcoma

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P4.113 A RARE CASE OF MIDDLE MEDIASTINAL THYMOMA COMPRESSING THE BIFURCATION OF THE TRACHEA

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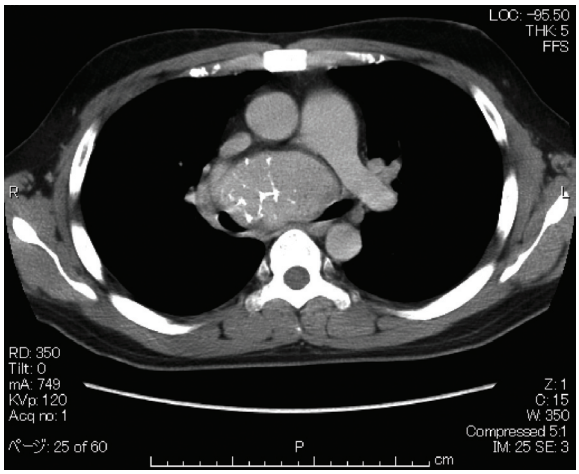
Background: Most thymomas are found in the anterior mediastinum. Occasionally, some have been found in the neck, pulmonary hilus, and posterior mediastinum. We present here a case of middle mediastinal thymoma that was markedly compressing the bifurcation of the trachea.
Methods: A 32-year-old man was referred to our hospital for further examination of an asymptomatic mediastinal mass detected on a chest X-ray at an annual checkup. Chest computed tomography (CT) revealed a well-defined and highly enhanced solid mass with multiple foci of tiny and irregular calcification, measuring 81 × 47 mm in the middle mediastinum between the superior vena cava and the bifurcation of the trachea. The tracheal bifurcation was severely compressed by the large mass, but there was no sign of invasion. With a preliminary diagnosis of benign mediastinal tumor, such as teratoma or neurogenic tumor, the patient underwent surgical intervention.



Results: The patient was operated on through the anteroaxillary thoracotomy in the 4th right intercostal space with a video-assisted procedure. The tumor was overlaid by the mediastinal pleura and located between the superior vena cava and the trachea,

extending to the inferior part of middle mediastinum. Although the tumor severely adhered to the trachea and bronchus, there were no obvious invasion of the any structures of the mediastinum, and the tumor was completely extirpated. The postoperative course was uneventful and the patient left the hospital on the 4th postoperative day. The resected specimen was a solid tumor with a fibrous capsule that measured 115 × 74 × 41 mm and weighed 150 g. The cut surface of the tumor was white or yellowish-white in color, and multiple calcifications were seen on its surface. Microscopic examination revealed that the tumor consisted of mixture of a spindle cell-predominant component and a lymphocyte-predominant component. There were many trabecular fibrous bands with marked hyalinization or calcification in the tumor. Extracapsular tumor invasion was not seen. Histopathologically, the tumor was diagnosed type AB thymoma based on the World Health Organization (WHO) classification, and stage I according to the Masaoka staging system. The patient is well, with no evidence of recurrence 15 months after the operation.

Conclusion: We present a case of middle mediastinal thymoma compressing the bifurcation of the trachea. Thymoma should be considered in the differential diagnosis of middle mediastinal tumors, although it is rarely found in this location.

Keywords: video-assisted thoracic surgery, Thymoma, middle mediastinum

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P4.114 LUNG SQUAMOUS CARCINOMA OF CLEAR CELLS – A RARE LUNG CANCER

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Background: A 70-year-old patient presents with right pulmonary nodule found at chest x-ray, with features suspicious of pulmonary neoplasm. After performing the initial examination, it was decided to perform thoracoscopic (VATS) resectiony with transoperatory biopsy. The result of intraoperatory histopathology was compatible with lung adenocarcinoma. The incision was converted to posterolateral thoracotomy and lobectomy was performed. The postoperative pathology result was initially done as clear cell adenocarcinoma, stage I, raising the possibility that the same would be a metastasis from external sources, while holding the suspected renal main origin. Was then performed a full restage of the patient, not being identified neoplastic lesions in any other location. It was also realized immunohistochemistry of the tumor removed. The imunohistochemistry was positive for low weight cytokeratin, surfactant and cytokeratin 7; and negative for valentine, HMB45, cytokeratin 20, CD10 and TTF1.

Methods: This study was performed by reviewing the medical history of the patient.

Results: The final diagnosis was lung squamous clear cell carcinoma with accumulation of glycogen, stage I which led the patient at this moment does not need another type of treatment. After six months, the patient presented hepatic metastasis and then undergoing chemotherapy treatment.

Conclusion: Lung squamous clear cell carcinoma is an rare pulmonary tumor that can lead to confusion with lung adenocarcinoma and pulmonary metastasis, mainly from kidney tumors, and with the benign clear cell tumor (sugar tumor) (1.2). Its diagnosis is done through imunohistochemistry study, wherein presents positive result for Cytokeratin, especially Cytokeratin 7 and other markers of primary pulmonary neoplasm. Concurrently there is negativity towards others lung tumors as benign clear cell tumor (HMB45) and metastatic lesions (CD10 and vimentin – kidney metastases; Cytokeratin 20 – gastro intestinal tract neoplasm and TTF1 - neoplasm of thyroid) (3). It is also possible to use electron microscopic features to establish the proper diagnosis(2). It is important to differentiate this rare tumor and distinguish it from the renal metastasis and benign clear cell tumor (4), as well from all others forms of clear cell tumours of the lung(2). The treatment as well as the prognosis is quite different in these different conditions.

Keywords: Clear Cell Carcinoma, Lung cancer

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P4.115 ATRIAL FLUTTER AS FIRST PRESENTING SIGN OF MALIGNANT MESOTHELIOMA: A CASE REPORT

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Background: Atrial flutter is the second most common tachyarrhythmia, after atrial fibrillation,the most common causes being ischaemic heart disease ,hypertension,cardiomyopathy and abnormalities of the heart valves. We present here a very rare case of primary malignant mesothelioma presenting as atrial flutter.
Methods: A 74-year-old Caucasian man was admitted to East Kent Hospital NHS Trust complaining of palpitations and exertional dyspnea. There was no history of pleuritic chest pain or hemoptysis. The patient did not have any previous significant cardiac or any other medical history and was leading a fairly healthy life. He worked in British telecom in the past and used to lay cables and was exposed to asbestos during that time.
Results: Laboratory investigations showed he was anaemic with haemoglobin of 5g/dl(13-18g/dl) and required blood transfusion. His ECG showed atrial flutter which was treated with Digoxin and Verapamil. The chest x-ray showed complete obliteration of right hemithorax simulating the appearance of a pleural effusion. Attempts were made to aspirate the chest but it was a dry tap. Subsequently, the patient underwent a CT scan of his chest, abdomen and pelvis which showed extensive lobulated pleural thickening encircling the right hemithorax and extending into the mediastinum both anteriorly and posteriorly and involving part of the pericardium with some associated fluid. Compressive atelectasis was also noted in the right lung. The left lung field was clear. Rest of the viscera including liver, spleen pancreas etc were normal. The histology of CT guided biopsy of the lesion showed appearance of an epitheliod malignant mesothelioma. Immunohistochemistry showed showed that the tumor was positive for cytokeratin 5/6 and calretinin. Ocassional asbestos bodies were identified in the lung tissue. The patient was managed symptomatically was referred to oncologist and offered radiotherapy owing to the extensive nature of the disease. After a few sessions the patient eventually died after 8 months in the due course of treatment.
Conclusion: Malignant mesothelioma is an insidious neoplasm with a dismal prognosis. Diagnosis of mesothelioma can be challenging and often requires a multimodal imaging approach including CT, biopsy and PET scans. Mesothelioma exerts its morbidity and mortality via inexorable local invasion. The median survival of patients is between 6 and 18 months, and is not significantly affected by currently available therapeutic interventions. The authors of this report have been unsuccessful in finding a similar case report upon reviewing the literature.
Keywords: Malignant mesothelioma, atrial flutter

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P4.116 PRIMARY PULMONARY LYMPHOMA: CLINICAL FEATURES, PROGNOSTIC FACTORS, AND OUTCOMES

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Background: Primary pulmonary lymphoma (PPL) is a rare neoplasm with a favorable prognosis compared with lung cancer. In order to assess clinical features, patient management, prognostic factors and outcomes, we hereby report our single-institution experience.
Methods: A retrospective review of a prospective database of patients operated on for PPL between 1998 and 2010 was performed. Univariate and multivariate analysis was performed to identify prognostic factors. Survival was calculated by Kaplan-Meier method.
Results: There were 33 patients (18 men; median age, 59 years). Twenty-one patients had marginal zone B-cell lymphoma of mucosal-associated lymphoid tissue (MALT), 4 had large B-cell lymphoma, 6 had Hodgkin's disease, and 2 had follicular lymphoma. Twelve patients (36.4%) were asymptomatic at presentation, and 21 (63.6%) had pulmonary symptoms, systemic symptoms, or both. Radiological findings at computer tomographic (CT) scan included nodules, masses infiltrates or consolidation. Bilateral pulmonary lesions were detected in 10 patients. PET scan was performed in 24 patients (72.7%): in 14 cases it was negative, in 10 it showed a median standardized uptake value of 4.3. CT-guided biopsy was diagnostic in 3 of 13 attempts. A definitive diagnosis was obtained by thoracotomy in 27 patients 81.8% - one pneumonectomy, 10 lobectomies, and 16segmentectomies and wedge resections) and thoracoscopy in 6 (18.2% - 4 pulmonary wedge resections and 2 lung biopsies).

Treatment methods included surgery only (n=13), surgery plus chemotherapy (n=17), surgery plus radiotherapy (n=2), and surgery plus chemotherapy plus radiotherapy (n=1). Median follow-up was 110 months (range, 2-322 months). Overall 5-year, 10-year, and 20-year survival rates were 69%, 42.3%, and 7.7%, respectively. Patients with MALT lymphoma had a best prognosis (p= 0.01). None of the prognostic factors studied significantly influenced survival.
Conclusion: PPL have non-specific clinical features. Surgery should be the treatment of choice in localized forms while a combination of treatment should be used for diffuse diseases.
Keywords: lymphoma, Surgery

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P4.117 FETAL ADENOCARCINOMA

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Background: Well-differentiated fetal adenocarcinoma (WDFA) also called monophasic pulmonary blastoma or pulmonary endodermal tumor resembling fetal lung tissue is classified by the World Health Organization as a variant of adenocarcinoma.
Methods: A 39 year old female presented 3 months post-partum after being referred for surgery consultation after recognition of a lobulated pulmonary mass on chest X-ray for pre-operative workup for a bilateral tubal ligation. The patient was otherwise asymptomatic and healthy, with a 20 pack year smoking history. A CT- guided needle biopsy of the mass was reported as having suspicious/ atypical architectural features. A left thoractomy for left upper lobe wedge resection was performed and frozen sections obtained. Adenocarcinoma and a subsequent left upper lobe lobectomy and mediastinal lymph node dissection was performed. The 3.7 x 3.0 x 3.5 cm tumor was later identified as fetal adenocarcinoma. All margins were free and peribronchial and mediastinal nodes were negative for metastatic disease. The patient continues to be recurrence and metastases free at 24 months post-resection.
Results: The influence of estrogen through the estrogen receptor-B (ERB) has been hypothesized in the development of a class of tumors that are comprised of biotin-rich, optically clear nuclei (BROCN). B-Catenin, a cell-adhesion molecule, is also known to be expressed in the BROCN-family which includes well-differentiated fetal adenocarcinomas. Apparently, aberrant nuclear/ cytoplasmic co-localization of ERB and B-Catenin is a feature that is common to tumors producing morules within the BRCON-family of tumors. The current case represents one of a few case reports of a fetal adenocarcinoma in the literature presenting during pregnancy or in the immediate post-partum period. Whether these cases are due to chance or whether there is in fact an association with pregnancy is not currently know. Other BROCN tumors have shown a stronger preponderance for young females while WDFA, in contrast, has been reported in equal incidence and with a slight predilection for females. Eighty percent of patients with WDFA are smokers and 40% may be asymptomatic. When symptomatic, the literature reveals that the most common presentations are hemoptysis, cough, or chest pain, but incidental findings on a chest X-ray remains the most common overall presentation.
Conclusion: Estrogen may play a role in the differentiation and possibly the proliferation of WDFA and other BROCN-family tumors but further studies are necessary.
Keyword: Fetal Adenocarcinoma

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P4.118 NON SMALL CELL LUNG CANCER (NSCLC) PRESENTING AS OBSTRUCTIVE JAUNDICE IN A YOUNG PATIENT

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Background: A 44-year-old male with a history of smoking and alcoholism and a previous episode of acute alcoholic pancreatitis presented with progressive jaundice,choluria and acholia.Physical examination revealed the presence of hepatomegaly. Blood tests showed a normocytic anemia and a cholestatic pattern.
Methods: An abdominal CT scan showed

hepatomegaly with severe dilation of bile ducts,an irregular hypodense lesion of 45 mm with heterogeneous enhancement in the pancreatic head causing biliary obstruction,and a distended gallbladder,which was confirmed by a Cholangio-MRI.CEA and CA19-9 levels were within normal levels.The patient also presented dysphonia in subsequent days,a chest radiograph showed a parahiliar mass.A bronchoscopy revealed a paralysis of the left vocal cord and an endobronchial lesion in the left anterior upper lobe.Biopsies revealed a poorly differentiated adenocarcinoma.Thorax CT scan showed a 6 cm left parahilar mass invading the aortopulmonary window and the left pulmonary artery.

Results: At this point we raised the differential diagnosis between a synchronous NSCLC and a primary pancreatic carcinoma,a NSCLC with a metastasis to pancreas and primary pancreatic carcinoma with a lung metastasis.An stent was placed in the principal bile duct using endoscopic retrograde cholangiopancreatography and cholestasis was resolved.Fine needle aspiration of the pancreatic mass revealed an infiltration of a poorly differentiated carcinoma.The immunohistochemical profile was positive for Citokeratine AE1-AE3, CK-7 and TTF-1, confirming that it was a metastasis of the lung carcinoma. The final diagnosis was an stage IV lung adenocarcinoma (T4N0M1).

Conclusion: Pancreatic metastases constitute 2-3% of malignant masses of the pancreas.Most cases occur in the context of widespread disease.Several retrospective studies have shown that the primary tumor that most commonly spreads to the pancreas is renal cell carcinoma, followed by breast, colorectal, melanoma, sarcoma and lung (predominantly small cell lung carcinoma) tumors. In a series of 234 patients, 68% of all cases corresponded to renal cell carcinoma metastasis, 6.4% were breast metastasis, 7.3% were colorectal metastasis, 7.3% were melanoma metastasis, 3.8% were sarcoma metastasis, 3.8% were lung metastasis and 1.3% were ovarian metastasis. Patients with pancreatic metastases from melanomas and lung carcinomas have worse prognosis than patients with metastasis from renal cell carcinomas.By contrary, survival does not differ significantly between patients with metastases from the breast, colon or sarcomas. However, this was a retrospective study and included patients with different stage and prognosis. Some authors have proposed resection of the pancreatic metastasis in selected cases, specially in metastasis from renal cell carcinomas, sarcomas or carcinoid tumors, with a survival rate of 35% and 17% at 2 and 4 years,respectively. Two case reports of pulmonary adenocarcinoma with solitary pancreatic metastasis have also been published. The first case described a pancreatic metastasis two years after a radical surgery for lung adenocarcinoma with a complete response of the metastasis after the third cycle of cisplatin-based chemotherapyT.he second case described a complete resection of a pancreatic mass prior to the diagnosis of lung carcinoma that was also resected; the patient was free of disease 18 months after diagnosis.These data suggest that surgical treatment of isolated pancreatic metastases in patients with NSCLC may be considered in these patients.

Keywords: Non-small cell lung cancer, pancreatic metastases

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P4.119 THYMIC CARCINOID

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Background: A 53 year-old male presented with chest pain and dyspnea on exertion, dysphagia for solids, cough for 3 months, and an unintentional weight loss of 10kg. The patient's past medical history was insignificant. On general physical exam there were decreased breath sounds in the left lung and dullness to percussion. Also noted was left cervical and supraclavicular lymphadenopathy. Chest X-ray revealed an anterior mediastinal mass. Cardiovascular and cardiopulmonary structures were displaced posteriorly. The mass displaced the trachea and esophagus to the right. Also noted on CT was significant left cervical adenopathy and evidence of thyroid nodule.

Methods: A Tru-cut CT guided needle biopsy was subsequently obtained which indicated malignancy but yielded indeterminate results. Excisional biopsy of the left cervical lymph node revealed well-formed lymphoid tissue with follicles. The cervical lymph node tissue was compared with slides from the needle core biopsy of the mediastinal mass and was found to exhibit a distinctly different morphology.

Additionally, the mediastinal mass was noted to be TTF-1 negative, while the cervical specimen is TTF-1 positive suggesting that the cervical specimens were consistent with a papillary thyroid carcinoma. There were therefore two primary neoplasms.
Results: The patient underwent an enbloc resection of the mediastinal tumor via a transverse sternotomy. The patients lungs and pulmonary vasculature re-expanded appropriately after removal of the mass. The patient had an uneventful 1 week stay in the hospital and returned 3 weeks later for an uncomplicated total thyroidectomy and left neck dissection. All margins were determined clear.
Conclusion: Thymic carcinoid is a rare malignancy of the thymus with about 200 cases reported to date. These tumors are unique in their capacity to present with a variety of clinical onsets. Patients can be asymptomatic, manifest symptoms related to endocrinopathy, particularly Cushing syndrome, or it may manifest as part of the multiple endocrine neoplasia syndrome type 1. Or, the tumor may follow a more endocrinologically silent course and present with symptoms of intrathoracic compression. Finally, there is an association with thyroid cancer (follicular, papillary, and medullary carcinoma), in patients with carcinoid tumors of the thymus. This case represents the sequelae of an endocrinologically silent tumor with a delayed presentation as a giant thymic carcinoid and symptoms of intrathoracic compression. This is an exceptionally rare case particularly because of the unique size of the tumor.
Keyword: THYMIC CARCINOID

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P4.120 UPPER AND LOWER GASTROINTESTINAL TRACT METASTASES FROM PRIMARY LUNG CANCER: CASE REPORTS AND LITERATURE REVIEW

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Background: Lung cancer remains one of the most common and malignant cancers worldwide. It most often diagnosed at Stage IV, where it has already presented distal metastases. We aim to describe the clinical presentation of gastrointestinal tract metastases from primary lung cancer.
Methods: We describe 3 synchronous and metachronous cases of upper and lower gastrointestinal tract metastases (esophagus, stomach and sigmoid colon) from primary lung cancer.
Results: Although gastrointestinal metastases have been noted in a significant percentage of autopsies, only sporadic cases of diagnosed symptomatic intestinal metastases exist in medical literature. Most common are metastases at the small bowel, rather than the stomach or the colon. Review of the literature shows that the most common clinical presentations of the metastatic sites are abdominal pain, intestinal bleeding, obstruction and perforation.
Conclusion: Despite being rare, symptoms and complications of intestinal metastases from primary lung cancer should be early indentified, as they are associated with significant morbidity and mortality, making the prognosis extremely poor.
Keywords: gastrointestinal metastases, Lung cancer, NSCLC

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P4.121 RADIATION INDUCED INJURY RESULTING IN LIFE-THREATENING HYPERCAPNIC RESPIRATORY FAILURE , PERFORATED OESOPHAGITIS AND PNEUMOMEDIASTINUM: A CASE REPORT.

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Background: Concurrent chemoradiotherapy as definitive treatment for inoperable stage III non small cell lung cancer can be complicated by dose limiting toxicities such as radiation induced oesophagitis and pneumonitis. We report a unique case of severe radiation induced tissue injury resulting in perforated oesophagitis and pneumomediastinum, together with recurrent mechanical airway obstruction from necrotic inflammatory debris leading to acute

hypercapnic respiratory arrest.
Methods: In April 2010, a 49 year old Caucasian male diagnosed with stage III B (T2N3M0) non small cell lung cancer, squamous histology, was presented at the Multidisciplinary Tumour Board meeting at our institution. Imaging including PET scan deemed our patient inoperable. Past medical history included a transient ischaemic attack at 33 years and an acute myocardial infarction at the age of 42. Curative intent chemoradiotherapy was planned. 60 Gy of radiotherapy was delivered in 30 fractions, concurrently with weekly carboplatin and paclitaxel at a dose of AUC 2 and 50mg/m^2 respectively. Carboplatin was chosen due to concerns regarding patient's tolerance of fluid load as per standard cisplatin hydration protocols. Planned chemotherapy during the 6th (last) week was not delivered due to intercurrent febrile illness. No other toxicities occurred and Computerized Tomography (CT) scan performed 6 weeks following completion of treatment showed near-complete response with significant reduction in size of a right hilar mass and almost entire resolution of mediastinal and hilar lymphadenopathy.
Results: 2 months after completing treatment our patient developed severe dysphagia and odynophagia. Upper gastrointestinal endoscopy revealed extremely fragile, "paper thin" oesophagus with multiple mucosal tears requiring insertion of percutaneous endoscopic gastrostomy (PEG) feeding tube. Despite treatment with corticosteroids, proton pump inhibitors and antifungal agents his dysphagia progressed over 4 months rendering him unable to swallow saliva. Oesophageal biopsies performed on 3 occasions revealed fibro-inflammatory ulcer slough and reactive squamous mucosa with no evidence of neoplasia. Repeat CT showed stable right hilar lesion and lymph node but extensive oesophageal wall thickening. Patient requested oesophageal dilatation for quality of life and one week after dilatation he rapidly deteriorated with hypercapnic respiratory failure requiring intubation and ventilation. Imaging revealed pneumomediastinum. Bronchoscopy performed via endotracheal tube revealed almost complete obstruction of main airways with thick, white, inflammatory debris which was mechanically removed and resulted in significant improvement of respiratory function and extubation. Histology showed peeling respiratory mucosa with mixed inflammatory infiltrate and atypical stromal cells consistent with radiation effect. High dose steroids were commenced. Two weeks later he developed stridor due to recurrent airway obstruction requiring removal of copious thick inflammatory debris through bronchoscopy. He had marked symptom relief and his current ECOG is 1.Further update on his progress will be presented.
Conclusion: We report an unusual case of severe delayed life threatening radiation toxicity. To date, no reliable predictors of individual radio-sensitivity are available for such patients. Emerging evidence suggests certain genetic variants in key inflammation-related genes might play a role and further research is warranted.
Keywords: stage III non small cell lung cancer, radiation oesophagitis, radiation pneumonitis, concurrent chemoradiotherapy

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P4.122 PRIMARY ADENOID CYSTIC CARCINOMA OF THE LEFT LUNG MIMICKING SWYER-JAMES-MACLEOD SYNDROME

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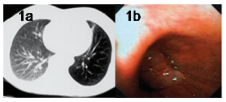
Background: Adenoid cystic carcinoma (ACC) of the lung is aggressive epithelial tumour arising from the bronchial glands and accounting for about 0.04-0.2% of all lung cancers. It is well known for its indolent course and ultimately poor prognosis. This report presents the clinical course of a patient diagnosed with suspected Swyer-James-MacLeod syndrome (SJMS), coexisting with this rare tumour entity.
Methods: A 50-year-old female patient presented with chronic dyspnea for several months before hospital admission. Chest radiography and high resolution computed tomography (HRCT) of the chest (Figure 1a) showed hyperlucent left lung with diminished vascular structures without any signs of intrathoracic mass. Radionuclid imaging with Tc99-m revealed complete absence of perfusion in the left lung while pulmonary angiography showed small left pulmonary artery due to suspected extravasculary tumor compression. A flexible fiberoptic bronchoscopy showed a tumour in the left main bronchus (Figure 1b). Histopathologic and histochemical analysis of biopsy specimens confirmed the diagnosis of ACC. The surgical

approach required total left pneumonectomy due to the extent of tumour spreading and postoperative palliation radiotherapy was also administered. Unfortunately, two years after the diagnosis of ACC, the patient died as a result of pulmonary embolism.



Results: SJMS is a rare condition characterized by unilateral hyperlucency of the lung, lobe or part of the lobe due to a decreased vascularity and air-trapping in bronchial airways. It occurs after recurrent pulmonary infection in childhood but the majority of cases are diagnosed at a later age. The condition should be differentiated from congenital anomalies of airway/pulmonary vessels and bronchial obstruction due to mucus plug or a foreign body. In our case, bronchial tumour caused air-trapping and a lung hyperlucency mimicking SJMS. Considering our patient's anamnestic data of recurrent lower respiratory tract infections in childhood, it remains unclear whether SJMS existed earlier in life or a hyperlucent lung was the consequence of a slowly growing ACC.
Conclusion: All patients with hyperlucent lung on chest radiographs should undergo full diagnostic work-up in order to distinguish SJMS and possible secondary reasons for lung hyperlucency.
Keywords: Primary adenoid cystic carcinoma, Swyer-James-MacLeod syndrome

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P4.123 β HUMAN CHORIONIC GONADOTROPIN (HCG) DOSAGE AND LUNG CANCER – A PITFALL WHEN SCREENING PATIENTS FOR CLINICAL TRIALS

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Background: β-HCG belongs to the glycoprotein hormone family and is usually assess to exclude pregnancy for patients potentially eligible to chemotherapy, especially during clinical trials.

Methods: We studied non-small-cell lung cancer (NSCLC) patients that were found with elevated serum β-HCG level during clinical trial screening. The first case is a 45-year-old woman who presented with a stage IV undifferentiated carcinoma of the lung eligible for chemotherapy. When screening the patient for a clinical trial combining platinum-based chemotherapy and targeted therapy, the plasma β-HCG level was 19 IU/L (0-5 IU/L). The second case is a 64-year-old woman presented with stage IV poorly differentiated adenocarcinoma of the lung. When screening the patient for the same clinical trial combining platinum-based chemotherapy and targeted therapy, the plasma β-HCG level was β-HCG is 13 IU/L (0-5 IU/L).
Results: The serum dosages were double checked and confirmed elevated β-HCG level. The gynecological work-up definitely rules out an improbable pregnancy. The pathological examination was also checked and confirmed in the two cases a primary lung cancer. An immuno-histochemical reassessment of the pathological specimens with additional tests was performed: for one patient 25% of tumor cells expressed β-HCG. As pregnancies were ruled out, the two cases were extensively discussed with the promoter and the patients finally treated within this clinical trial. The treatments are ongoing.
Conclusion: β-HCG is a specific marker for trophoblastic tumors of placenta and gestational tumors. Ectopic expression of β-HCG was found in 20-40% of all common epithelial carcinoma, especially for tumors of the stomach, ovary, liver and lung. Only few cases have been reported in the literature. However, in a young patient with high serum levels of Beta HCG two questions arise:
Is there a place for pregnancy? Are the pathology results accurate? All this could delay the appropriate management of these patients and also potentially prevents the participation of innovative therapeutic strategies. Therefore, knowing this rare but possible expression of β-HCG by lung tumors may speed out the gynecological work-up and the reevaluation of the histological samples in order to minimize the delay in the care of these patients and give them a chance to have new innovative drugs within clinical trial.
Keywords: Lung cancer, Clinical Trials, β-HCG

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P4.124 ULTRASOUND-GUIDED SUPRASCAPULAR BLOCK FOR POSTTHORACOTOMY IPSILATERAL SHOULDER PAIN

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Background: Pain after thoracotomy is very severe, probably the most severe pain experienced after surgery. Thoracic epidural analgesia has greatly improved the pain experience and its consequences and has been considered the standard for pain management after thoracotomy. Despite receiving thoracic epidural analgesia, severe ipsilateral shoulder pain is common in patients after thoracotomy.
Methods: We recruited 18 patients into a double-blinded randomized placebo-controlled study to investigate whether ultrasound-guided suprascapular nerve block would treat postthoracotomy pain. All patients received a standard anesthetic with a midthoracic epidural. The aim of this study is to compare the effectiveness of the thoracic epidural analgesia (TEA) and the thoracic epidural analgesia add suprascapular nerve block (SNB) methods in relieving the pain caused by a thoracotomy incision and shoulder pain. Thoracic epidural catheter placed between T4 and T8 with the C-arm scope. All operations were open thoracotomies done by the same team of surgeons and anesthesiologists. A thoracic epidural catheter was placed before induction of general anesthesia. Ultrasound-guided suprascapular block was placed one hour before operations. Postoperative period haemodynamic effects, pruritus, nausea, vomiting, sensory and motor block, pain score, additional analgesic requirement, sedation, and patient satisfaction were registered immediately after the surgical operation and on the first, second, and third postoperative days.
Results: Significantly less number of patients required rescue analgesia in SNB group ($P < 0.05$). Pain relief was better both at rest and during coughing ($P < 0.05$) in SNB group as compared to alone TEA.We have shown that infiltration of the suprascapular nerve with local anesthetic significantly and safely reduces this shoulder pain, potentially allowing the ideal goal of a pain-free thoracotomy.
Conclusion: We present 18/9 cases in which an ultrasound-guided suprascapular nerve block was immediately effective for severe postthoracotomy ipsilateral shoulder pain. The block resulted in no related complications, and it provided long-lasting relief and a high degree of patient satisfaction.
Keyword: Epidural analgesia, pain, thoracotomy

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.125 MULTIPLE SPLENIC METASTASIS FROM PRIMARY NON SMALL CELL CARCINOMA OF THE LUNG-A CASE REPORT

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Background: Metastatic disease of the spleen is uncommon and associated with widely disseminated disease. Patients are usually asyptomatic or have nonspesific symptoms such as fatigue and abdominal pain. We report a 64 year old man who presented with fatigue, weight loss, sweating and abdominal pain and was diagnosid with multiple splenic metastasis from primary non small cell carcinoma of the lung.
Methods: We report a 64 year old man.
Results: A 64 year old man who presented to the hospital with fatigue, weight loss, sweating and abdominal pain. He was an ex-smoker who quit 5 years after smoking 2 pack per day for 40 years. Computed tomograpy scan of the abdomen showed multiple metastases in the spleen. Contrast enhanced Computed tomograpy scan of the chest showed multiple bullous lesions in the lungs, and emphysematous changes, no mass selected. Right submandibular, superior mediastinal, paratracheal and subcarinal lymph nodes were enlarged. PET-CT was performed. The outer edge of a bullous lesion revealed a slight increase in activity. Increased level of activity of pathological lymph nodes were

identified. Right submandibular lymph node biopsy was positive for invasive,high grade non small cell carcinoma metastasis. PET-CT revelated normal liver and adrenals,with no bone or other side metastasis. The patient was treated with concurrent chemoradiotherapy with cisplatin and etoposide. Splenectomy was not performed. So tissue diagnosis from splenic lesion were not attempted.
Conclusion: metastatic disease involving the spleen is uncommon and mostly occurs in patient with widely disseminated metastatic disease. Lung cancer, malignant melanoma and breast cancer were the most frequent primary tumors all spleen metastases. Except for metastasis differential diagnosis of splenic masses include, lymphoma, granulomatous diseases, hemangioma and inflammatory pseudotumor. Management has to be individualized and splenectomy should be offered to patients with otherwise favorable primary tumor features and absence of dissemination.
Keywords: Non small cell lung cancer, splenic metastasis

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P4.126 REPORT A CASE OF EPITHELIOID HEMAGIOENDOTHELIOMA OF THE MEDIASTINUM

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Background: Epithelioid hemangioendothelioma is a rare epithelial-appearing vascular tumor usually presenting in soft tissues and was first described in 1982 by Weiss and Enzinger. The mediastinal localization has been identified as an exceptional event and diagnosis is most often established postoperatively.
Methods: A report of case of epitheliod hemagioendothelioma in the mediastinum is reported.
Results: We report the case of a 54-year-old patient with a superior vena cava syndrome (SVCS), mediastinal mass and large pleural effusion. Radiological findings favoured the initial diagnosis of a lymphoproliferative disease. A mediastinoscopic biopsy employed for tumor sampling. Immunohistochemically the cells were positive for keratine-cocktel, CD34 and CD 31 and negative for TTF-1, CK 7, CK 20, P63 and synaptophysin, this is consistent with an epitheliod hemagioendothelioma. He was treated with intravenous 'bolus' i.v. methylprednisolone for 3 days and then radiation therapy. The patient experienced initial significant symptomatic improve. Despite radiation therapy, our patient had progressive dissemination to the mediastinum and bone. He died 6 months after diagnosis.
Conclusion: Epithelioid hemangioendothelioma should be distinguished mainly from primary or metastatic carcinomas, angiosarcoma and lymphoproliferative disease when presenting a mediastinal tumor. Despite the different treatment strategies, there is currently no standard treatment and their prognosis in some cases is very poor.
Keywords: mediastinum, immunohistochemistry CD34, epithelioid hemangioendothelioma

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P4.127 STRESS INDUCED CARDIOMYOPATHY DURING LOBECTOMY FOR LUNG CANCER

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Background: Stress induced cardiomyopathy is caused by emotional or physical stressors and it mimic acute myocardial infarction but this disease is characterized by reversible left ventricular (LV) apical ballooning in absence of significant coronary artery disease.
Methods: 51-year-old male was admited for the left upper lobe lobectomy due to non small cell lung cancer.
Results: During the lobectomy, cardiogenic arrest occurred due to stress induced cardiomyopathy.
Conclusion: This was successfully managed by intra-aortic balloon pumping and extracorporeal membrane oxygenation and the patients was discharged without complication.
Keywords: Stress induced cardiomyopathy, lobectomy, Extracorporeal membrane oxygenation

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

P4.128 SYNCHRONOUS BILATERAL LUNG AND GASTRIC TUMORS

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Background: Patients with lung cancers have sometimes other malignancies simultaneously.
Methods: Sixty six years old man had chest pain, cough, sputum, vomiting, abdominal pain and 10% of body weight loss about eight months.
Results: In computerized tomography, 10L and 11R calcific lymphadenopathies of mediastinal region, calcification on wall of aorta, pleural thickening and fibrotic sequelae in the left lower lobe of lung were seen. In abdominal CT, calcification in 8th segment of liver, minimal perihepatic fluid, and a benign cysts in the right kidney and prostatic hyperplasia were detected. Mucosal infiltration was seen in apicoposterior segment of the left upper lobe by fiberoptic bronchoscopy. Squamous cell carcinoma (in situ) was reported as result of mucosal biopsy. Thickening small curvature of gastric wall (suvmax: 20.5) were detected in PET-CT. Gastroscopy showed an ulcerated polypoid structure on fundus-corpus junction and hyperemic antrum. The result of polypoid lesion biopsy was adenocarcinoma. Total gastrectomy + total omentectomy + esophagojejunostomy were done. Postoperative pathology was invasive adenocarcinoma (poorly differentiated). Bronchoscopy was repeated one month after abdominal surgery and the mucosal irregularity was found in the superior segment of right lower lobe. Atypical cells were seen in histology of this region. Argon laser destruction of the right lower lobe lesion was performed. Left upper lobe lobectomy was done for the treatment of squamous cell carcinoma of left upper lobe. Results of pathology were tumor size 0.8x 0.8 cm length, 1 cm surgical margin, squamous cell carcinoma (moderately differentiated), lymph node involvement was negative.
Conclusion: Surgery can be performed to selective patients who have synchronous lung and gastric tumors.
Keywords: Synchronous tumor, in situ carcinoma, gastric tumor

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P4.129 TREATMENT OF MULTIFOCAL INTRACRANIAL PROGRESSION OF ADENOCARINOMA OF THE LUNG WITH HIGH-DOSE PULSED ERLOTINIB COMPLICATED BY HEMORRHAGE AND GENERALIZED CEREBRAL EDEMA.

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Background: The development of isolated intracranial metastases is increasingly recognized as a relevant clinical problem in patients who respond well to EGFR tyrosine kinase inhibitors (TKIs). Single case reports of successful and well-tolerated treatment with high-dose, pulsed erlotinib have been published. (Hata et al, JTO 2011; Dhruva and Socinski, JCO 2009)
Methods: We analyze the course of patient who developed intracranial hemorrhage and generalized cerebral edema during treatment with high-dose erlotinib.
Results: A 44 year old Caucasian female never-smoker presented in 12/08 with left arm weakness. Computed tomography (CT) revealed several brain lesions, and a mass in the right lung. Positron emission tomography (PET) showed metastases in the liver and right kidney. Following bronchoscopic biopsy, adenocarcinoma of the lung, clinical stage IV, was diagnosed. Whole brain irradiation (35 Gy) and three cycles of chemotherapy (cisplatin 75mg/m2 and pemetrexed 500mg/m2 day 1 every 3 weeks) led to a partial response; however, during the fifth cycle a clear progression occurred. A pulmonary embolus was treated with tinzaparin (10,000 I.U. sc od). Genetic analyses showed an activating mutation in EGFR exon 19, and treatment with erlotinib was initiated. This led to regression of all tumor sites, including the kidney. After 13 months of erlotinib, magnetic resonance imaging (MRI) showed progression of the cerebral metastases. The primary tumor and intraabdominal metastases were stable, and so the intracerebral metastases were stereotactiacally irradiated. Three months later one further metastasis was irradiated, however multifocal intracranial progression soon developed. A neurosurgical biopsy showed the same mutation as in the primary tumor, with no known resistance

mutations. High dose pulsed erlotinib was added (600 mg q 4d). After 2 weeks hemorrhage into three of the metastases (before hemorrhage: 35x27mm, 11x19mm, 9x8mm) occurred. Anticoagulants were stopped, and due to 6mm midline shift the largest hematoma (35 x 23 mm) was evacuated. MRI showed a trend to partial response in the other intracerebral metastases and so the erlotinib pulses were continued with a 25% dose reduction. Unfortunately, 24 days later, cerebral edema and subdural hygroma developed and the patient died, 24 months after initial diagnosis.
Conclusion: Brain metastases despite systemic control increasingly pose a problem (Lee et al., Cancer, 2010). Inadequate dosing across the blood brain barrier is one explanation, but has not been proven. The absence of resistance mutations, as well as the multifocal nature of the intracerebral progression, support this theory in our case. The efficacy of high dose erlotinib for brain metastases has been previously reported. Previous reports describe minimal toxicity during treatment. The significant multi-focal hemorrhage and cerebral edema which developed in our patient have not been previously described in this setting. Simultaneous anticoagulation as well as previous stereotactic radiation of the brain metastases may have predisposed our patient to hemorrhage, and may prove to be relative contraindications to high-dose pulsed erlotinib. Because most centers only see a few patients in this clinical situation, cooperative efforts are needed to collect and analyze these cases, and to develop appropriate treatment strategies.
Keywords: erlotinib, Non-small cell lung cancer, brain metastases

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P4.130 COMPLET RESPONSE DESPITE A VISIBLE TUMOR MASS IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH ERLOTINIB

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Background: Non-small cell lung cancer patients with a sensitizing mutation in the EGF receptor are likely to respond to treatment with an EGFR inhibitor and some patients experiences rapid, durable, and most frequently partial responses. Often some tumor tissue can still be visualized on a Computed Tomography (CT) or a Magnetic Resonance Imaging (MRI) but may be negative on a Positron Emission Tomography(PET)
Methods: Two patients with multiple bone metastases and pathologically verified adenocarcinoma in the lung were followed after start of treatment with erlotinib by clinical parameters and CT/MRI/PET of both lung tumor and bone metastasis. Pretreatment biopsies and blood samples were examined for the presence of EGF receptor mutations and lobectomy was performed by standard procedure after 10 and 30 months of treatment respectively.
Results: Both patients responded clinically to treatment with erlotinib and both patients displayed a mutated EGF receptor. After 10 and 30 months of treatment respectively, both still displayed a mass in the lung and underwent lobectomy. No cancer cells could be identified in the resected lung tumor tissue.
Conclusion: Treatment with erlotinib may induce complet pathological responses in lung tumors in patients with metastatic NSCLC. This opens up the question if treatment with erlotinib can be discontinued in these patients.
Keywords: metastatic NSCLC, erlotinib, EGFR mutation, complet response

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P4.131 PERCUTANEOUS STENT MANAGEMENT OF SUPERIOR VENA CAVA SYNDROME WITH ADVANCED LUNG CANCER

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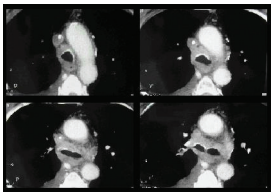
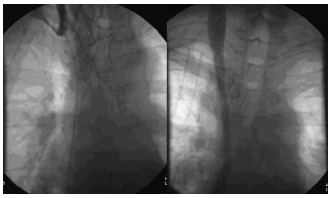
Background: The authors introduce the case of a 61-year-old male who had been experiencing acute dispnea, headache, edema and cyanosis of the face and arms. The patient had bronchial scamous cancer diagnosis two years ago, staging IIIB by mediastinal extension of the cancer. In addition, the patient had undergone first line chemotherapy with gemcitabine plus vinorelbine (PS 2) with parcial

response after three cicles of chemotherapy. There was disease progression with ocorrency of superior vena cava syndrome, which was treated by second line chemotherapy with paclitaxel plus carboplatin and total dosis radiotherapy (45Gy). This treatment determined a good response with regression of the vena cava superior syndrome. The disease remainded stable for five months. Two months ago the patient again developed vena cava superior syndrome with acute symptoms. It was submitted to angiotomography wich evidencied vena cava superior obstruction (figure 1).



Methods: The patient was submitted to a digital angiography with total obstruction of the vena cava superior (Figure 2A). It was performed a superior vena cava stent placement (Wall stent - Boston Scientific, MA) at this time.



Results: After stent placement we can observe the restoration of the blood flow through superior vena cava (figure 2B). The patient remainded withouth symptoms for a follow-up period of six months apter stent replacement. The control angiotomography performed at this time did not demonstrate vascular obstruction.

Conclusion: The standard treatment of the malignant superior vena cava syndrome is the chemotherapy and radiotherapy association. This treatment may determine several side effects besides the results may be delayed. Stent placement is a minimally invasive treatment wich determine a rapid restoration of the blood flow. Several authors have demonstrated the superiority of stent placement in patients with superior vena cava syndrome due to cancer, in particular in the patients with acute symptoms.

Keywords: superior vena cava syndrome, wall stent

Poster Session 4 - Clinical Cases Thursday, 7 July 2011 10:00-12:30

P4.132 A RARE CASE OF INFLAMMATORY PSEUDOTUMOR IN AN OCTOGENARIAN: NECESSARY PNEUMONECTOMY

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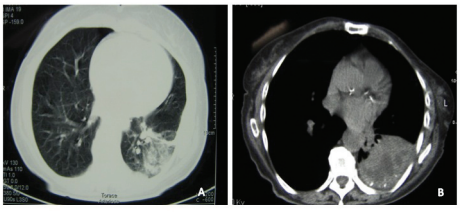
Background: Inflammatory pseudotumors are reactive lesion simulating a neoplasm characterized by a proliferation of fibroblasts and myofibroblasts mixed with varying numbers of inflammatory cells. Pseudotumors of the lung are rare disease predominantly occurring in younger patients. Diagnosis is difficult because its unspecific clinical and radiological presentation.

Methods: A 81-year-old woman was admitted to our hospital complaining astheny, fever (38°C) and nonproductive cough. The patient was a non-smoker and had a history of hypertension. Chest X-ray and CT scan showed a suspected consolidation in the left lower lobe (Fig.1A). After two weeks antibiotic therapy there was no clinical symptomatology regression; a new CT scan demonstrated significantly increased mass within abscessualized areas (Fig.1B). Bronchoscopy not revealed airways obstruction. TBNA and CT guided TTNA cytology were not diriment for malignancy. Increasing mass size combined with the onset of dyspnea, asthenia, sudden weight loss put an indication for surgery.



Results: A left pneumonectomy with lymphadenectomy was performed because of tumor involvement of left upper lobe. The resected tumor measured 58 mm × 47 mm × 35 mm and resection margins and all regional lymph nodes were free of disease. Inflammatory myofibroblastic tumor was diagnosed. At the last follow-up (12 months after operation), the patient was symptom free and there was no evidence of tumor recurrence on chest CT scan.

Conclusion: Inflammatory pseudotumors are rare in elderly, surgery is required to differentiate inflammatory pseudotumors from primary or metastatic lung cancers. Even though the elderly should be considered always an high risk patient an aggressive approach is advised to maximize the likelihood of long-term cure.
Keywords: inflammatory myofibroblastic, pseudotumor

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 - Clinical Cases Thursday, 7 July 2011 10:00-12:30

P4.133 ADENOID CYSTIC CARCINOMA:PRIMARY AND METASTATIC LOCATION TO THE LUNG.

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Background: Adenoid cystic carcinoma is the most common type of salivary gland type tumor of the upper respiratory track. It is usually centered in the major bronchi but peripheral examples are also referred. Aim: These salivary type neoplasms probably arise from the submucus bronchial glands. Metastasis to lung from an adenoid cystic carcinoma of the salivary gland has the same features with the primary neoplasm. We investigate the possibility of defining the primary or metastatic disease by the use of immunoistochemistry.
Methods: We examined five (5) cases of adenoid cystic carcinoma of the lung by performing immunoistochemistry methods of three steps(avidine-biotin-peroxidase).The antibody used were :S-100,SMA,CEA,CD-117(c-Kit),Keratin,TTF-1 and CD-56. After the conclusion of the immunoistochemistry study, we looked further back to the rest clinical and laboratory data on the purpose to define the origin of the neoplasm(primary or meta).
Results: The immunoistochemical positive expression of the antibodies:S-100,SMA,CEA,CD-117(c-Kit) and Keratin was identical to all cases(primary and metastatic to lung).The expression of the TTF-1 and CD-56 was such as to offer a novel point of view in the istological differential diagnosis between primary and metastatic to lung adenoid cystic carcinoma.
Conclusion: The immunoistochemical positive expression of the antibodies:S-100,SMA,CEA,CD-117(c-Kit) and Keratin was identical to all cases(primary and metastatic to lung).The expression of the TTF-1 and CD-56 was such as to offer a novel point of view in the istological differential diagnosis between primary and metastatic to lung adenoid cystic carcinoma.
Keyword: Adenoid cystic carcinoma, lung, TTF-1

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P4.134 ASPERGILLUS INFECTION IN LUNG CANCER PATIENTS.OUR EXPERIENCE

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Methods: To present the aspergillus infection recorded among 40 lung cancer patients with febrile neutropenia consecutively admitted in our oncology department in the prior two years.
Results: Case 1: A 72 years old lady with mesothelioma was admitted with febrile neutropenia post five days of her chemotherapy .She had persistent productive cough and worsening right pleural effusion albeit her myelotoxicity recovery. The prolonged respiratory discomfort led to imaging tests and multiple microcystic lesions with a right median lobe encapsulated cyst were documented. She underwent bronchoscopy and the diagnosis of invasive aspergillosis was histological confirmed. She was offered antifungal therapy with voriconazole and experienced rapid clinical improvement. The patient died 9 months later due to her disease progression. Case2: A 76 year old man never smoker with diabetes and cardiovascular disease presented with persistent neutropenic fever post his chemotherapy for his lung cancer. His respiratory function although his hematological

improvement was deteriorated and a computer chest tomography was performed revealing a dirty opacity of the right lower lobe whereas the cancer mass on the upper lobe was still stable. High suspicion for disease progression or opportunistic infection led to a bronchoscopy reevaluation. An intrabronchial mass with necrosis was found. Histological test confirmed its asperlillus origin .The patient although was initiated on voriconazole, he died because of respiratory shock. Case 3: A 78 years old man with extra pulmonary small cell lung cancer was admitted with febrile neutropenia and respiratory stress post his 3rd consequent chemo therapy. No specific lung imaging findings were found but blood cultures revealed aspergillus growth. The patient had severe liver failure and did not manage to recover although was initiated on caspofungin treatment. All the above stated cases were tested for antigen of aspergillus but no positive results were found. The use of the galactomannan assay was not performed All diagnoses were documented according to histological species. The imaging pictures are really interesting.
Conclusion: Among febrile neutropenic patients post chemotherapy, fungal infections of unusual appearance should be thoroughly considered.The clinical management remains a challenge in the setting of the compromised host defence system The mortality is really very critically high and all diagnostic tests should be performed , even aggressively when pulmonary aspergillosis is suspected.
Keyword: Aspergillus Infection,Febrile Neutropenia

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P4.135 PHYSIOTHERAPY IN THE POSTOPERATIVE OF LUNG CANCER

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Background: Lung cancer is a malign expansion and transformation of the lung tissue. It is the most lethal type of cancer in the whole world, responsible for 1,2 million deaths every year. Smoking habits are the main cause of the disease. The treatment depends specially on the type, "stage" and estadio (dispersion grade) of the cancer. Surgery, chemotherapy and radiotherapy are the most common treatments available. Usually after a lung surgery, patients are referred to physiotherapy practice in order to enhance the lung perfusion and ventilation ratio, conventionally with respiratory exercise support. OBJETIVE: To analyze the physiologic changes caused by respiratory exercise in patients submitted to segmentectomy for lung tumor
Methods: 10 lung cancer patients with average age of 40 years old were submitted to the protocol. PROCEDURE: Heart rate, respiratory rate and blood pressure were analyzed in all patients, before and after the application of the protocol. The protocol is based on the application of 5 sets of 10 repetitions of the following exercises: maximum inhalation held for six seconds, fractioned inhalation and exhalation. The results were statistically analyzed through test-t students.
Results: The respiratory rate after the protocol decreased in 18,8% (from 19,6 ± 1,2 to 15,9 ± 1,5 rpm) ($p < 0,05$), the heart rate had a non significative increase of 6,9% after the protocol (from 81,8 ± 5,0 to 87,5 ± 5,3 bpm) ($p>0,05$), the systolic blood pressure had a non significative increase of 1,15% (from 130,5 ± 8,7 to 132 ± 9,8 mmHg) ($p> 0,05$) and the diastolic blood pressure had a non significative decrease of 3,2% (from 76,5 ± 2,7 to 74 ± 2,6 mmHg) ($p> 0.05$).
Conclusion: The respiratory exercise when applied under a standard don't present a significant interference on the vitals readings of a lung resected patient, however can be responsible for the adequation of the respiratory rate of those patients.
Keywords: Physiotherapy, postoperative of lung cancer

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P4.136 OVARIAN METASTASIS OF PULMONARY SMALL CELL CARCINOMA

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Background: Small cell lung cancer which is an aggressive tumour, has worse prognosis and constitute 20% of lung cancers. Small cell carsinoma may originate from organs other than lung. Clinical course and treatment of extrapulmonary small cell carsinomas are smilar to the tumour of lung.
Methods: Small cell lung carsinoma has wide spectrum of distant metastases that may be confused with extrapulmonary primary tumours. So that the exact diagnosis may be difficult for clinicians and pathologists.Small cell lung cancer metastasizes to many different organ, but genital metastasis,especially ovarian metastasis is very rare. A 51 year old –woman with pulmonary small cell carsinoma was admitted to our hospital with abdominal pain during the following 18th month of lung cancer diagnosis.
Results: Left ovarian mass and gastrointestinal metastasis was found during the examinations .Bilateral ovarian ,uterus,omentum and appendix metastasis was detected by total abdominal hysterectomy and bilateral salpingo-oopherectomy.
Conclusion: In this report we presented a pulmonary small cell cancer case which metastasized to ovaries beside gastrointestinal metastasis.
Keywords: small cell carsinoma, ovarian metastaz

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P4.137 PULMONARY EPITHELOID HEMANGIOENDOTHELIOMA PRESENTING AS PANCOAST TUMOUR- A CASE REPORT.

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Background: Pulmonary epithelioid hemangioendothelioma (PEH) is a rare vascular tumor categorized into borderline or low-grade malignancy. The disease was originally reported by Dail and Liebow in 1975 as an intravascular bronchioloalveolar tumor (IVBAT). Immunohistochemical and electron microscopic studies revealed that IVBAT is of endothelial origin, and the tumor was renamed epithelioid hemangioendothelioma.These tumors are usually multifocal and more common in females.
Methods: We report a case of PEH presenting as a Pancoast tumour causing diagnostic dilemma and was managed with Radical RT.
Results: A 49 year old gentleman was referred to our hospital with complaints of dyspnea and pain radiating to the right upper arm since 1 month. On examination, patient's general condition was stable with an ECOG performance score of II.A hard immobile swelling was present in the right supraclavicular region of size 8 x 7 cm.The swelling was non tender and was non pulsatile.Auscultation revealed diminished air entry in both lung bases. Initial lab investigations revealed leucocytosis.CXR showed a heterogeneous opacity in right upper zone with bilateral moderate pleural effusion.CECT chest done to ascertain the nature of the mass revealed a irregular soft tissue mass lesion of size 5.5 x 4.3 cm in the right upper lobe in apical and anterior segments.Right subclavian vessels were engulfed by the tumor mass.The mass was seen eroding the anterior aspect of the first rib.Few mediastinal nodes were noted in the right paratracheal and subcarinal region.Bilateral moderate pleural effusion with atelectatic changes were also noted. Screening of abdomen showed a soft tissue lesion in right adrenal gland measuring 3.7 x 2.5 cm size,? Metastasis.Pleural fluid cytology was reported as Inflammatory effusion.FNAC from the mass was reported as poorly differentiated malignant tumor. Hence a CT guided Core needle biopsy was done for categorization.Histopathological examination showed fibrocollageneous tissue infiltrated by pleomorphic cells with high N:C ratio,nuclear pleomorphism and moderate eosinophilic cytoplasm. Immunohistochemistry studies showed that the tumor cells stained positive for vimentin and CD 31 and stained negative for Cytokeratin, Chromogranin,Desmin, Synaptophysin and S100. Based on the above findings , a final diagnosis of Epitheloid Hemangioendothelioma was arrived at.An USG guided FNAC of the adrenal gland lesion did not reveal any malignant cells.Patient was initially managed with analgesics.He underwent bilateral therapeutic pluerocentesis to relieve dyspnea.The case was discussed in tumor board and planned

for Radical RT.Patient received RT to the right supraclavicular region 38 GY/19#.On the 20th day ,patient complained of severe pain in the left chest radiating to left arm in the early morning and became unconscious. He was evaluated by the cardiologist and was diagnosed as acute coronary syndrome.He was started on inotropes and antiplatelet drugs. But patient's condition continued to deteriorate and had a cardiac arrest from which he could not be revived.
Conclusion: This case has been presented for its rarity and the diagnostic dilemma it posed. A strong index for suspicion should be there to rule out PEH in poorly differentiated carcinomas as their behavior is unpredictable.
Keywords: Pancoast tumor, Pulmonary epitheloid hemangioendothelioma

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P4.138 PITFALLS IN RADIOLOGIC EVALUATION OF TNM STAGING IN LUNG CANCER

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Background: Although new 7th TNM classification provides improved prognostic relevance of its descriptors, problems in radiologic staging of lung cancer have not been fully addressed. With increasing role of imaging in staging of disease, both radiologists and clinicians should recognize its limitation.
Methods: Comprehensive imaging demonstration of variable difficulties in radiologic staging of lung cancers will be presented.
Results: In terms of T descriptors, i.e., primary tumors, there are limitations in measuring size of ill-defined, irregular, or subsolid lesions, as well as tumors with postobstructive pneumopathy or peribronchial infiltration. In addition, measurement of maximal diameter of tumors either on multiplanar reconstruction images or only on axial images has not been established. Invasive nodal disease may be interpreted as the primary tumor, and whether the mediastinal invasion of primary tumor or concurrent mediastinal lymphadenopathy is sometime difficult to determine. Staging of axillary, diaphragmatic, and other unusual nodal group is also tough. Management guideline for many additional nodules which are frequently observed during CT evaluation is lacking. Lymphangitic metastasis does not have a designated T or M descriptor. Despite of wide availability of PET and its integral role in staging, there is lack of explicit reference in utilization of this newer imaging modality in staging of lung cancer.
Conclusion: It is hoped that many of these radiologic issues in staging lung cancer will be addressed in the future TNM system.
Keywords: Lung cancer, radiologic staging, CT

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P4.139 SQUAMOUS CELL LUNG CANCER IN A 17-YEAR-OLD GIRL WITH JUVENILE LARYNGEAL PAPILLOMATOSIS. A CASE REPORT. GOMEZ R., VILLALBA V., YOFFE I. ONCOLOGY DEPARTMENT. CLINICAL HOSPITAL. FCM.-UNA. PARAGUAY 2011.

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Background: Introduction: Juvenil Laryngeal Papillomatosis (JLP) is a neoplasia that generally shows a benign but recurrent behavior.
It is induced by the Human Papilloma Virus (VPH) specifically serotypes 6, 11, 16, and18. JPL can produce hoarseness because it's association with verrucous nodules on the vocal cords, and rarely can disseminate to the lungs, and produce a significant morbidity. JLP treatment is difficult because its recurrences and lung extension. It´s treatment is surgery (laser vaporization, micro-instrumental, among others) chemical, and biologic aproaches, as Alfa Interferon (AIF), none of them eradicate the disease and multiple treatments are usually required. When malignization occurs it is treated

with worldwide approved protocols. A malignant transformation could occur in the larynx and more rarely in the lungs. In Paraguay lung cancer is the second cause of cancer related death in males and the fifth in females. Squamous Cell Carcinoma (SCC) of the lungs represents between 35 to 50% of lung cancers and it's generally associated to tobacco use. There is strong, but controversial evidence regarding it´s association with Human Papilloma Virus infection (HPV) especially genotypes 16 and 18. We report a case of a 17 year old girl with JLP and SCC of lung.

Material and Methods: Case: A 17 years old girl, with JLP diagnosed at age 2, with multiples relapses leading to 140 resections during her life. She was treated with interferon when she was 3 years old, for 8 weeks, in the ENT department of the ORL service of our Hospital. For financial reason she couldn't receive the two years protocol.
Results: In January 2009 a CT-scan showed multiple areas of consolidation in the lungs with a predominant area in left low lobe. She underwent a low left lobectomy in March 2009 in which a lung carcinoma was founded, and it was staged as a T3 N0 M0, EC IIb. The histological feature was of a 7,3 cm. Squamous cell lung cancer well to moderate differentiated aroused in papilomatous lesions. She was admitted to the Oncology Department in April 2009 and treated with Carboplatin and Gencitabine. Treatment was irregularly delivered because of recurrent lung infections. She completed two cycles in august 2009. Since then she remains asymptomatic for her lung tumor but with JLP relapses. JPL relapses seemed to slow down after chemotherapy with less frequents needs of resections.
Discussions and Conclusions: JLP is an entity associated to HPV. It has a recurrent behavior and it is potentially deadly due its complications. In the other hand, some studies had related squamous cell lung cancer with HPV infection. Lung cancer is very rare at the age of our patient. In fact we were unable to found other cases of this particular histology in teenager patients. We report the case of a 17 years old girl who after 14 years of a diagnosis of JLP developed a SCC lung cancer
Keywords: dragon, lung cancer and jlp, Lung cancer, jlp

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P4.140 ENDOSCOPICAL TREATMENT OF TRACHEAL AND TRACHEOBRONCHIAL LESIONS WITH A NEW SHAPED METALLIC STENT

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Background: The use of airway stent for the treament of tracheal and tracheobronchial lesions is increasingly advocated. However the long term safety and efficacy of these devices has not yet been established because of many complications. At present silicon and covered metallic stent have been proposed by different authors as a therapeutical option. The treatment of carinal lesions remain a major challenge since the anatomical structure may require an y stent.
Methods: In this paper we present a series of 23 patients with benign and malignant tracheal and carinal lesions successfully treated with a new metallic tracheal stent system . This stent is composed of biomedical monofilament wire braided in a tubular mesh or in an Y configuration.
Results: In the last two years we endoscopically treated 18 patients with benign and malignant tracheal stricture and 5 patients with carinal lesions. All procedures were performed under general anestesia through rigid bronchoscope. In all patients the stent was delivered under direct visualization. In all patients the outcome was satisfactory without major complications
Conclusion: Our clinical results indicates that this new serie of metallic stent provide immediate and satisfactory results in patients with benign lesions . Since palliation remain the main purpose of malignant lesions the Y metallic stent proposed in this experience may represent a new therapeutical option in patients with tracheal and carinal obstruction .
Keywords: airway stenting, tracheobronchial lesions, Y stent

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P4.141 MALIGNANT PLEURAL MESOTHELIOMA WITH A CENTRAL NERVOUS SYSTEM METASTASES

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Background: We present the case of a patient of 66 years, ex- smoker, with antecedents of labor exhibition to asbestos diagnosed of Malignant pleural Mesothelioma Stage III that progress to 1º Qt line into de central nervous system
Methods: Patient of 66 years, ex- smoker, with antecedents of labor exhibition to asbestos, that consulted in March of 2010 by pleurític pain being diagnosed Malignant pleural Mesothelioma Stage III
Results: Was made irradiation on the scar of thoracotomy made for the biopsy by the high risk of dissemination in the zone, administering itself 20 a total dose of Gy (5s of 4 Gy) finalizing the 09.03.2010.

The patient received treatment of QT with CCDP+Premetrexed. 6 cycles were administered (last the 22.06.2010), being obtained Stable Disease. The patient required entrance in August of 2010 by bad control of the pain. A TC of thorax made then showed tumor plural progression level with vertebral bony commitment (D10) and bag by contiguity. It made antialgic RT on the costal zone affects. During the entrance the patient presented/displayed picture of disorientation and bradypsychia. After discarding infectious pathology, metabolic alterations and picture of poisoning by opiate, cranial TC was made that showed compatible injury with metastases in right temporary area. The patient was considered tributary of holocraneal RT that finally did not receive by deterioration of the general state.
Conclusion: This case is about a 66 years old man diagnosed to Malignant pleural Mesothelioma Stage III that progress into central nervous system after 1º line chemotherapy. The interest to present/display this patient is due to the infrequent cerebral dissemination of this tumor, being an almost anecdotal presentation. They are less than the 60 cases published in present Literature. The handling of these patients can be made with RT or surgery according to the extension of the disease at this level and systemic level.
Keyword: Malignant pleural mesothelioma , central nervous system metastases

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P4.142 AN UNUSUAL CASE OF AN UNUSUAL LUNG CANCER

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Background: Mucoepidermoid carcinoma of the lung is a rare tumour subtype comprising approximately 0.1% of lung cancers. There is no standard of care to manage this disease. We present a case of asymptomatic mucoepidermoid carcinoma of lung identified on follow-up imaging for another malignancy.
Methods: Case A 75 year old female with a significant smoking history underwent a radical cystectomy for an extensive bladder tumour which was causing bilateral hydronephrosis. Pathology revealed a grade II, 10cm superficial urothelial carcinoma of the bladder without muscle invasion (Ta N0). No adjuvant therapy was given. Three years later, a routine chest x-ray demonstrated a lesion in the upper lobe of her left lung. Pathology revealed a non-small cell carcinoma with overall features that were favouring a metastasis from the prior bladder tumour, however, clinicopathological correlation was advised.
Results: A multidisciplinary team decision recommended a trial of systemic chemotherapy and then consideration of surgery or radiation therapy. Platinum and gemcitabine chemotherapy was administered over a 2 month period and treatment was stopped early secondary to persistent grade 3 myelosuppression. Positron Emission Tomography (PET) scan confirmed no further metastatic disease and a modified lingular resection of the lung was performed. Histology confirmed a non-small cell lung carcinoma (NSCLC)/Mucoepidermoid Carcinoma with focal high grade features (pT2b, pN2), stage IIIA. Epidermal growth factor analysis was wild type. Our patient received adjuvant radiotherapy, 59.4Gy in 33 fractions. Adjuvant chemotherapy was not given and she remains well 8 months following lung resection.
Conclusion: Urothelial carcinoma can often be confused with other histologies. Mucoepidermoid carcinoma is a rare subtype of NSCLC and there

is little data on adjuvant chemotherapy after surgical resection. In fact this disease is thought to be chemotherapy insensitive unlike conventional NSCLC. EGFR gene changes are variably reported in several series and may impact prognosis. In our case the histological appearances resembling urothelial carcinoma resulted in preoperative chemotherapy being given which may not have been necessary. This case highlights the importance of consideration of other primary rare lung tumour subtypes even when there is a history of another malignancy.

Keyword: mucoepidermoid carcinoma

Poster Session 4 - Clinical Cases Thursday, 7 July 2011 10:00-12:30

P4.143 COMPLETE REMISSION OF ADVANCED NON SMALL CELL LUNG CANCER INDUCED BY ERLOTINIB INTERCALATED WITH CONVENTIONAL CHEMOTHERAPY - A CASE REPORT

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Background: In Dr. Soetomo General Hospital, Non-Small-Cell Lung Cancer (NSCLC) accounts for approximately 80% of all lung cancers, 40% of which present with distant metastases. Conventional chemotherapy usually only give a short survival, but with the advance of epidermal growth factor receptor tyrosine kinase inhibitor, the new drug can be intercalated with combined conventional chemotherapy with very surprising results. We reported a patient with liver metastatic NSCLC which achieved complete remission after treatment with Erlotinib intercalated with Gemcitabine – Carboplatin chemotherapy.
Methods: A 66 year old man was admitted to our hospital due to chronic cough for 1 month. He also complained of left sided chest pain, loss of appetite, and weight loss. Chest CT-scan confirmed the presence of a solid mass on anterior segment superior lobe of left lung (Æ 42 mm), with satellite nodule on anterior segment of right lung (Æ 17.2 mm). The mass caused atelectasis on inferior lobes of both lungs. There were infiltrations of mediastinal, peribronchial, and pretracheal lymph nodes. There were also multiple metastatic nodules on the liver. Fine needle aspiration biopsy showed adenocarcinoma pathology. The staging was thus T4, N3, M1. His physical state score was ECOG-1. Gemcitabine – Carboplatin chemotherapy was given until 5 cycles, intercalated with Erlotinib 150 mg orally on day 15-28 of each cycles. After 5 cycles, he is continuously received oral Erlotinib as maintenance therapy.
Results: Follow-up visit was scheduled for every month to evaluate clinical data, physical performance, hematology and clinical chemistry laboratory data, drug side effects and CT-scan according to RECIST criteria. After 2 months follow-up (post cycle 2) target lesion mass was disappeared. The patient also reported improvement of the symptoms and gain weight. After 9 months follow-up (maintenance phase) all non-target lesion (atelectasis, lymph node enlargement, and liver metastasis) were disappeared. The physical state improved to ECOG-0. Side effects encountered were mild anemia, mild to moderate leucopenia after cycles 3. An increased in creatinin and blood urea nitrogen were observed after cycles 5. Mild skin rash also found during maintenance therapy.
Conclusion: Erlotinib used as intercalated therapy with conventional chemotherapy may induce complete remission of advanced NSCLC on properly selected patient.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.144 ACCESSIBILITY OF BURKITT LYMPHOMA (BL) TREATMENT IN CAMEROON

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Background: A high per centage of about 60-65% of children diagnosed with the commonest form of childhood cancers in Cameroon; just like in any other African country known as Burkitt lymphoma (BL) are cured with either single cyclophosphamide (CPM) therapy or combined with methrothrexate (MTX); yet these drugs are very rare, expensive and inaccessible. Besides, there are very few professionals, care and diagnostic centres, located mainly in the capital cities and the masses, already

hit by the prevailing global economy recession are left with little or no other choice to spending the last days with a sorcerer, witch doctor or herbalist who are untrained and their practices dangerous. There is neither any national palliative nor oncology society.
Methods: Touring national BL treatment Centres, questionnaire surveys and analysis of clinic data on BL.
Results: Basic oncology and palliative care needs especially treatments like chemotherapeutic and opiods agents are very rare, expensive and afforded mainly by the very rich class whereas the disease has nothing to do with social status and about 35% of affected children die without commencing treatment or even undiagnosed.
Conclusion: Malaria-the highest killer disease; endemic in Africa, is strongly believed that the Plasmodium vivax has a major causative role to play in BL. Sadly, if as much as 50%+ of BL can be cured with single CPD regimen and as many as 35% of kids die without diagnosis or a single treatment attempt; then there is great need for support and funding of intensive research on this domain in Cameroon and Africa. This has also greatly retarded the MDG. There is also the need for funding and supporting interested professionals from Africa in international events like the upcoming as to transmit the current expertise in research, care and education.

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.145 OUTCOME OF SEQUENTIAL CHEMO RADIATION IN STAGE IIIB LUNG CANCER PATIENTS. THE NORTH WALES CANCER CENTRE EXPERIENCE.

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Background: NSCLC Stage III B represents a heterogeneous group of patients with a total of seven different designations included within the 6th edition of TNM classification. The addition of induction chemotherapy to radiotherapy in locally advanced NSCLC have demonstrated a survival benefit confirmed with several phase III trials and three meta-analysis. There is still controversy to whether the use of concurrent chemo radiation in selected locally advance lung cancer is superior to sequential
Methods: From January 2006 to march 2007 thirty-one-lung cancer patients staged as IIIB according with the 6th edition TNM classification were treated with a combination of sequential chemotherapy and radiotherapy. Eligible patients for this retrospective analysis were required to have histological proven non-small cell lung cancer, stage IIIB with no pleural or pericardial effusion and no previously treated. Patients were required to have a Karnofsky performance status of 80 to 100; adequate bone marrow reserve and renal function and no previous malignancy and tumour volume, which can be incorporated within a tolerable radiotherapy treatment field. Before initiation of treatment, all patients underwent history and physical examination, determination of performance status and fully staging with CT scan. No PET scan was available for staging. Sixteen patients were men and eight women. Patient's ages ranged from 43 to 80 years with median age 65.3 years. All patients' received four cycles of carboplatin AUC 5 and gemcitabine 1250mgs/m2 followed by a course of radiation receiving 55Gy/20 fractions or 36/12 in patients who had progressed to induction chemotherapy.
Results: Toxicity was predominantly haematological with grade 3-4 neutropenia occurring in 45% of patients during chemotherapy and no grade 3-4 thombocitopenia occurred. The overall response rate after chemotherapy was 41.5 % partial response, 45. % stable disease and 12.5% progressive disease to chemotherapy. The estimated median survival was 21.1 months (5-55). The 1-year survival probability was 50% and 2-year and 3-year survival was respectively 30% and 25%. The estimated time to progression was 14.9 months and 5 patients (16.6%) are still alive and disease free after 49 months follow-up.
Conclusion: The NWCTC results in highly selected patients with stage IIIB NSCLC are comparable with published randomised trials of induction chemotherapy followed by radiation and those using concurrent chemo radiation. Patients who can tolerate the treatment should be treated with combined radio chemotherapy modality and although there is some evidence that concurrent modality is better than sequential; however with the use of new radiotherapy techniques, new chemotherapy agents and accelerated radiotherapy schedules, how concurrent chemo radiotherapy compares with sequential treatments remains unresolved. Individualization of treatment is of paramount relevance in lung cancer patients

Keywords: sequential, Chemotherapy, Radiotherapy, survival

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.146 A TRIAL OF THE PREVENTION OF POSTOPERATIVE PNEUMONIA OF ELDERLY PATIENTS(75 YEARS OR OLDER) OF NON-SMALL LUNG CANCER, ABOUT THE ROLE OF THE NURSE TO ORAL CARE

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Background: Japan is becoming the aging society, and aging goes ahead through Onomichi in particular(75years and older 10.4% in Japan comparison to 16.3% in Onomichi). Due to the aging of the general population, non-small cell lung cancer is a typical disease of the elderly, and is becoming increasingly. The opportunity of lung surgery in the elderly is increasingly. Preoperative preparation and postoperative care are very important in chest surgery, and particulary in elderly patients. Especially elderly patients are at high risk of postoperative pneumonia after lung surgery. It is important that we prevent the onset of postoperative pneumonia. We wrestle with critical prevention of postoperative pneumonia in performing oral care before lung surgery of aged 75 years or older at our hospital. We report the role of the nurse in the oral care team at our hospital.
Methods: We make a personal prescription of elderly patients who undergo lung surgery and we teach oral care using a pamphlet. Elderly patients(aged 75 years or older) of non-small cell lung cancer and metastatic lung cancer at our hospital have a check up in dentist after having received explanation of oral care from the nurse of the oral care team and have intraoral examination. We confirm by a telephone whether elderly patients continue and perform oral care according to the schedule during before hospitalization.
Results: 21 patients aged 75 years or older who underwent surgery for non-small cell lung cancer and metastatic lung cancer at our hospital in 2010 were studied. The postoperative pneumonia did not occur in all cases.
Conclusion: Oral care is important for prevention of postoperative pneumonia in the elderly after lung surgery. We cooperate with staffs of the other type of job and will practice oral care of elderly patients before lung surgery by the oral care team.
Keyword: naechan

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.147 A TRIAL OF THE PREVENTION OF POSTOPERATIVE PNEUMONIA OF ELDERLY PATIENTS(75 YEARS OR OLDER) OF NON-SMALL LUNG CANCER, ABOUT THE ROLE OF THE NURSE TO RESPIRATORY REHABILITATION

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Background: Japan is becoming the aging society, and aging goes ahead through Onomichi in particular(75years and older 10.4% in Japan comparison to 16.3% in Onomichi). Due to the aging of the general population, non-small cell lung cancer is a typical disease of the elderly, and is becoming increasingly. The opportunity of lung surgery in the elderly is increasingly. Preoperative preparation and postoperative care are very important in chest surgery, and particulary in elderly patients. Especially elderly patients are at high risk of postoperative pneumonia after lung surgery. It is important that we prevent the onset of postoperative pneumonia. We wrestle with critical prevention of postoperative pneumonia in performing respiratory rehabilitation before lung surgery of aged 75 years or older at our hospital. We report the role of the nurse in the respiratory rehabilitation team at our hospital.
Methods: We make a personal prescription of elderly patients who undergo lung surgery and we teach respiratory rehabilitation using a pamphlet. Elderly patients(aged 75 years or older) of non-small cell lung cancer and metastatic lung cancer at our hospital have a check up in department of

rehabilitation after having received explanation of respiratory rehabilitation from the nurse of the respiratory rehabilitation team. We confirm by a telephone whether elderly patients continue and perform respiratory rehabilitation according to the schedule during before hospitalization.
Results: 21 patients aged 75 years or older who underwent surgery for non-small cell lung cancer and metastatic lung cancer at our hospital in 2010 were studied. The postoperative pneumonia did not occur in all cases.
Conclusion: Respiratory rehabilitation is important for prevention of postoperative pneumonia in the elderly after lung surgery. We cooperate with staffs of the other type of job and will practice respiratory rehabilitation of elderly patients before lung surgery by the respiratory rehabilitation team.
Keyword: chiaki

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.148 ROLE OF NUTRITION IN TREATMENT OUTCOMES OF LUNG CANCER

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Background: Lung cancer 2nd most common cancer in Asia. Lung cancer is usually associated with poor intake of food due to mechanical obstruction affecting nutritional status of patient. No study has been undertaken on this issue in Indian population till now. Our Indian cancer NGO performed this retrospective study through hospital based database search. Aim was to determine nutritional status in pre-treatment and post-treatment phase and how it affects the treatment outcome.
Methods: 23 carcinoma of Lung sufferers who would be treated by chemo-radiation were enrolled for nutritional status assessment in pre-treatment phase and categorized as normal, mild, moderate or severe under nutrition group by clinical, hematological, biochemical, anthropometrical, dietary and immunological criteria. At six week post treatment phase the nutritional status was re-assessed by same parameters and compared with pre-treatment phase. Analysis of treatment outcome done with clinical, endoscopic and radiological findings.
Results: n = 23, 21 males, 4 females. Age 45-60 years. 18 from lower middle class. 60% uneducated class from rural India. Nutritional status: At pre treatment phase on clinical and anthropometrical ground based on height, weight, body mass index and waist hip ratio were normal = 6, mild under nutrition = 3, moderate under nutrition = 4, severe under nutrition = 5 and corresponding figure at 6 week post-treatment phase were 9, 5, 7 and 4 respectively. Hematological and biochemical assessment: Done with parameters of Hb, ESR, WBC count,
Conclusion: Nutritional status is grossly affected in Lung-cancer-patients. Dysphasia to liquid and solid is the main reason for poor nutritional status. In developing nations socio-economic factors play vital role in nutrition & subsequently survival period , QOL in lung cancer sufferers. Normal and mild under-nutrition patients tolerate treatment related toxicities well; recover better in post-treatment phase. So nutritional assessment and its supplementation plays an important roll in treatment of cancer Lung. Due to resource constraints we limited sample size & evaluation parameters. But Our Indian cancer NGO seeking multi-institutional-collaborations to conduct more-scientific pilot project on this unexplored issue in Indian lung-cancer-patients community
Keywords: NGO, nutrition, lung-cancer

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.149 TRAINED NURSING CARE TO LUNG CANCER SUFFERERS : STATUS IN RESOURCE POOR COUNTRIES OF SOUTH

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Background: Patient Advocacy Issue : Trained nursing care for lung cancer sufferers is a dream by patients community. Trained nursing care facilities available only in few city hospitals in India. Especially cancer sufferers who return to villages in rural parts of India after taking chemotherapy/ surgery in city hospitals need this assistance. NGO's can play key role in providing Trained nursing care . Current status: Very little nursing research has been conducted within lung cancer patients in Asia. Even national cancer registry doenot provide scientific information on this crucial issue. Oncologists need to propose increase research activity of nurse specialists

working with patients with lung cancer. Here module of training must be devised suitable to Asian hospital care setup. Due to lack of resources for Training nurses, this issue has been neglected.
Methods: Our Indian cancer NGO palliative care team plans to mobilize training resources from local Health-centers. In phase I of our project 6 tertiary care hospitals and two NGOs will be included. Primary Training imparted to nurses by Tam-experts invited from city hospitals. This Team will have social worker & nurse trainer & oncologists. Local traditional faith-healers & community leaders involved for more community acceptance/ participation. Aim to provide physical-comfort to patient, improve relationship with family members for terminal lung cancer disease
Results: Our NGO proposed plan will present our findings/need & ways to overcome obstacles in providing nursing care. Survey questionnaire will be sent to Team members asking them to identify important areas for nursing research in lung cancer care. Trainee nurses will be asked to suggest possible research. The findings of this survey will be presented. Plan about findings may be used to generate nursing research studies will also be discussed. We present our NGO's proposed Nursing-Training-Module [NTM] project finding in printed chart-format at WCLC-2011 conference, Amsterdam. We need strong platform like IASLC-2011-conference to show our findings to researchers/activists from developed world and get their guidance on this difficult issue. Government hospitals in collaboration with NGO-clinics must carry out supportive-care-programmes with NGO-counselors to bring down incidence of frailty/ depression in thoracic cancer patients.
Conclusion: Our Indian cancer NGO has taken initiative on this front by forming education module for nurses and rural physicians. Our project has been awaiting further guidance/funding for implementation to serve poor rural/tribal geriatric lung cancer populations If resources like fellowship/ training-grants are made available to oncology nurses, then NGO's can perform good job of providing economical home based nursing care for Lung & other cancer sufferers in remote areas of India.
Keywords: nurses, NGO, Asia

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.150 OCCUPATIONAL THERAPY INTERVENTION TO IMPROVE FUNCTION AND QUALITY OF LIFE FOR PATIENTS LIVING WITH LUNG CANCER

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Background: Occupational Therapists are specialists in assessing function and intervening to improve a person's ability to engage in their occupational roles. People living with lung cancer often experience a change in their function. Breathlessness can severely limit a patient's ability to perform their daily activities across all areas of their occupational performance. These include self-maintenance, productivity, leisure and rest. Occupational Therapists are able to utilise interventions to assist patients with the management of their breathlessness. The intervention of an Occupational Therapist can have a positive impact on the function and quality of life for the person living with lung cancer and those they share their life with. This paper will outline the development of occupational therapy interventions for people living with lung cancer with the oncology and palliative care teams at the Prince of Wales Hospital. Occupational Therapists can assist individuals prioritise their goals while managing the side effects of curative treatment, also having a vital role in assisting individuals as their roles and function change with progressive non-curative disease. The involvement of the Occupational Therapist with the Lung Cancer Multidisciplinary Team has led to the development of specialist skills in the management of occupational performance dysfunction in lung cancer at Prince of Wales Hospital.
Methods: The use of task analysis, energy conservation and pulse oximetry assessment with functional activities by the occupational therapist has improved patient education and understanding of the reasoning behind task modification. Changes in pulse oximetry readings allow occupational therapists to make objective recommendations to patients on ways to manage their breathlessness and hypoxaemia with functional activity. This assists patients to achieve optimal independence and safety with their chosen human occupations.
Results: It is the Occupational Therapists unique

ability to analyse and modify functional tasks that has improved function and achievement of occupational performance goals for patients towards the end of life. The results of the occupational therapy functional assessments are a crucial factor in the medical teams decision for the prescription of palliative home oxygen.
Conclusion: This presentation will explore the role of the Occupational Therapist in the specialist setting of lung cancer. Through task analysis, task modification, energy conservation and goal setting people living with lung cancer can continue to live with increased confidence, independence and safety, while achieving their chosen goals towards the end of life.
Keywords: function, Quality of Life, Management of Breathlessness

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.151 POSTOPERATIVE REHABILITATION CONVERSATION – FOR RADICALLY OPERATED LUNG CANCER PATIENTS

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Background: Lung cancer patients feel uncertain, after being discharged, following a surgical procedure and experience physical and psychosocial problems. Patients who receive concluding conversations are less likely to feel uncertain post discharge compared to other patients. However, these concluding conversations are not conducted at a regular basis and the need for rehabilitation has not been charted. Aim: The objective of this study is to test whether systematic concluding rehabilitation conversations, combined with a follow up phone call, can help patients handle issues post discharge in order to minimise their uncertainty.
Methods: The methodology is quasi-experimental consisting of a control and intervention group. It is based on phone interviews and questionnaires with eight patients aged 54-74. The patients have assessed their level of satisfaction on issues such as information, communication, rehabilitation and support. Furthermore, the patients' understanding of rehabilitation and lifestyle has been examined.
Results: Patients in the intervention group experience that their rehabilitation needs are identified and that they receive support in getting back to everyday life, addressing symptoms and problems, and achieve a rehabilitated lifestyle. Hence, the intervention group experienced less uncertainty after discharge, as they gained greater knowledge of issues relating to their disease and emotional reactions that accompany a cancer diagnosis. Furthermore, the patients have felt that they were personally involved in their discharge process and received support afterwards.
Conclusion: The patients have, based on a concluding conversation and a follow-up phone call, gained greater insight into how issues of rehabilitation and post-surgical consequences can be handled after discharge. Thus, they have less uncertainty after returning home. Perspective: This study can be characterised as a pilot study due to the fact that the empirical material (eight patients) collected is not large enough to make statistical generalisations. A new intervention study has started on these grounds, including 120 patients.
Keywords: lung cancer surgery, discharge, Rehabilitation, conversation

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.152 DERMATOLOGIC TOXCICITIES ASSOCIATED WITH TARGETED THERAPIES: NURSING IMPLICATIONS (POSTER)

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Background: As treatment of cancer becomes more sophisticated, nurses continue to be challenged with management of multiple toxicities. The skin is assaulted from many avenues: tumour burden, radiation, chemotherapy, surgery, and now targeted therapies.The approach to cancer has changed over the last 10 years, due to improved understanding of how tumors develops and grow. Targeted therapies demonstrate significant clinical activity with manageable adverse events.
Methods: Oncology nurses with patients experiencing skin toxicities related to targeted therapies should understand the pathophysiology of the toxicity and provide ongoing assessment with consistent criteria and photo documentation.
Results: Patient education remains vital to minimize

these toxicities, maximize clinical benefit and should include the goals of therapy, the importance of compliance, assessment of response to therapy, and management of drug- and disease-related issues The management of these toxicities which include patient assessment, counselling, and education, are a critical role of the oncology nurses.
Conclusion: The best way to manage dermatologic toxicities associated with the administration of targeted therapies is through an early, proactive approach.Nursing education prior to treatment initiation is imperative, this enable patients to tolerate higher doses of cancer treatment for longer time which leads to better control of illness.
Keywords: Epidermal growth factor inhibitors, EGFRI,anti-EGFR, side effects, skin rash, dermatologic toxicity, Pro-active approach

Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.153 NATURE AND INTENSITY OF PAIN AFTER THORACOTOMY

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Background: The aim of this study is to clearly define the pain which disturbs the patients having thoracotomy in postoperative period. Because, it can be possible to manage to get pains under control according to pain characteristics without using drugs.
Methods: The study included 70 patients who underwent thoracotomy (lobectomy or segmentectomy and mean duration of surgery was 90 minutes) and were hospitalized in the intensive care unit of the Thoracic Surgery Department of Akdeniz University Hospital between 01.11.2007 and 15.11.2008. In this study, 68.6% (24) of the patients were male and mean age was 49.90 ± 11.62. The study was achieved. Considering that the patients have pain in the first 24 hours postoperatively and the effect of sedation, the Behavioral Pain Scale, which is filled out by a researcher, and the Verbal Category Scale, which allows the patient to define his/her pain with short responses, were used for pain assessment. Pain was assessed at the postoperative 4th, 8th, 16th, 24th and 48th hours, following extubation.
Results: The patients mostly reported throbbing (65.7%), stabbing (65.7%) and stinging (62.9%) pain in the incision site while 40% of them (n=28) reported a "sharp", "exhausting", and "splitting" pain. The investigation of the factors increasing pain during the postoperative period revealed that most of the patients (85.7%) reported that their pain increased due to movement in bed and/or walking while 74.3%, 68.6%, 54.3% and 37.1% of them stated that their pain increased due to breathing, coughing, and chest tube movement respectively. Each pain characteristics, throbbing, stabbing and stinging, can be specifically relief using one or more methods such as place of ice on the incision site, little press on the thoracotomy region, preoperative pain education etc.
Conclusion: In conclusion, it was determined that the patients experienced a sharp, stabbing and unbearable pain in the first 48 postoperative hours and their pain exacerbated with activities such as movement and coughing.
Keywords: pain charactheristic, Surgery, Post-thoracotomy pain

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Poster Session 4 – Nursing Thursday, 7 July 2011 10:00-12:30

P4.154 PHARMACOECONOMIC IMPACT OF DOSE ROUNDING FOR CANCER THERAPY

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Background: The past ten years have seen a significant and progressive cost rising in medical oncology, largely due to the increase in cancer prevalence and the incorporation into clinical practice of novel, highly expensive drugs. Dose rounding is increasingly used in oncology departments to improve efficiency of outpatient clinics. The purpose of this project was to determine the theoretical cost saving related to a dose rounding process for adult biological and chemotherapy agents at Riyadh Military Hospital.
Methods: Data was obtained prospectively during December 2010. All chemotherapy and targeted therapy orders prescribed in adult oncology out patient clinics as well as in-patient adult oncology wards have been collected. Prescriptions that include cancer therapy in doses that might be rounded according to study criteria were identified.

Results: Two hundred and thirty three orders of chemotherapy and targeted therapy were processed by Adult Oncology Satellite Pharmacy and adult oncology wards during the period of data collection. Forty percent of the collected prescriptions fulfilled the criteria. We considered rounding to an amount within 15% for targeted therapy and 10% for cytotoxic drugs. Chemotherapy dosing was calculated according to body surface area. The potential cost savings from dose rounding per year was US $ 192,800. Data was extrapolated from the determined monthly cost savings. The highest cost saving was for breast cancer drugs US $ 80,819 (42%), followed by colorectal cancer US $ 47,965 (25%), while in non-Hodgkin's lymphoma cost savings was US $ 45,107 (23%) and for other types of cancer that include non small cell lung cancer, prostate and ovarian cancer, in addition to head and neck cost savings was US $ 18,867 (10%).
Conclusion: Dose rounding of chemotherapy to an amount within 10% and up to 15% for targeted therapy would lead to significant cost savings. Although controversial, routine minor dose reductions might be acceptable to oncologists. Acceptance and opinion of oncologists in Saudi Arabia need to be surveyed.
Keyword: Pharmacoeconomic, Chemotherapy, Targeted therapy

Poster Session 4 - Palliative Care Thursday, 7 July 2011 10:00-12:30

P4.155 LUNG CANCER & GERIATRICS

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Background: Elderly patients of lung cancer provide challenging situation for oncologists. We undertook this one year old project targeted at geriatric cancer patients from rural/tribal india. Since geriatrics specialty is unheard of in rural india, we decided to address this burning issue of geriatric cancer patients. standardized geriatric evaluation is essential for multidisciplinary approach of cancer Rx in patients with lung cancer. In developed nations geriatric as well as an oncological evaluation are mandatory to offer to these patients the best therapeutic option and improve their prognosis as well as their quality of life. But this facility is luxury in asian/African nations. Hence our Cancer NGO team evaluated frailty & suggested plan to include it in cancer care of rural health set-up.
Methods: 11 tertiary care hospitals & two NGOs included in study. 132 healthcare providers given questionnaire on needs of geriatric cancer patients, their needs. 209 terminally ill geriatric cancer patients with life expectancy of 2 yrs were interviewed/evaluated.Geriatric Depression Scale used for geriatric evaluation. A standardized geriatric evaluation is essential for multidisciplinary discussion of elderly patients with lung cancer. oncological evaluation mandatory to offer to these patients best therapeutic option and improve their prognosis as well as their quality of life Patients were asked to mark cancer care as satisfactory or non-satisfactory & asked to rate incidence/severity of depression on diagnosis of Ca. Due to enormity of project we had initially taken frailty/depression as primary parameter for evaluation. Then responses of cancer service providers were rated against suggestions given by patients.
Results: GIT solicited for 209 patients over 2-year period. mean age 61.2 ± 4,6 years old), 61% male, 39% females. 64% subjects had symptoms of cognitive disorder [Folstein MMSE] . .The mini-GDS used to detect depression, was positive in 68% of the evaluations. we can clearly identify frailed patients (68%) who did not received any counseling/ psychotherapy. 82% patients pointed to lack of psycho-social care. counseling as major lacunas in current set-up. Inadequate patient education on nutrition, social support & absence of trained psychologist were mentioned as dominant factor in responses by 132 healthcare providers who participated in our project. these were clubbed to referred as geriatrics care.
Conclusion: Our two year on-hand experiences clearly show need & benefit of close collaboration between geriatricians and oncologist. Sadly counseling/geriatric care is virtually non existent in india. In daily management of elderly patients, alteration are nedded in 68% of patients by geriatric assessment. We need strong platform like IASLC-2011 to show our findings to researchers/ activists from developed world & get their guidance on this difficult issue. Government must carry out supportive-care-programmes with NGO-counselors to bring down incidence of frailty/depression in Lung cancer patients. Lessons learned : Our Indian cancer NGO has taken initiative on this front by forming operational module for nurses & rural physicians. Our project has been awaiting further guidance/funding from government agencies for

implementation to serve poor rural/tribal geriatric populations.
Keywords: Lung cancer, NGO, Asian population

Poster Session 4 - Palliative Care Thursday, 7 July 2011 10:00-12:30

P4.156 COUNSELING/REHABILITATION IN RESOURCE POOR NATIONS : LUNG CANCER PATIENTS ISSUES

Pramod Shankpal
Community Medicine, Health Alert Organsiation[ngo]/India

Background: Counseling/rehabilitation facilities available only in few city hospitals in India. Especially cancer sufferers who return to villages after chemotherapy need of these assistance. NGO's play key role in psychosocial-support/ Counseling/ rehabilitation . Our Project aimed to formulate policy for trained personals to give better & cost-effective rehab-services.
Methods: Our Indian cancer NGO palliative care team mobilized training resources from local Health-centres. Primary Training in Counseling & pain-management imparted to nurses. Team consisted social worker & nurse trained by physician. Local traditional faith-healers & community leaders involved for more community acceptance/ participation. Four nurses & 10 volunteers trained till now. Aim to provide physical-comfort to patient, improve relationship with family members. for terminal cancer diseases, gradually we prepared patient/family for death with dignity. counselor managed pain & broke bad news of cancer status to family. Discomfort/anxiety due to severe pain decreases overall treatment efficacy 63 Patients enrolled during community out-reach-programs. Data collected on feedback-questionnaire. Most difficult tasks is discussing end of life issues" telling diagnosis/its outcome, managing pain in terminal cases. Till today 32 lung Ca patients shifted to specialty hospital due to intractable pain.
Results: Counseling/rehabilitation must be made more accessible in rural-areas. This technique is also very cost-effective. Due to non-availability of trained-oncologists in rural areas this approach helps. We noted 94% responded favorably to counseling/ nursing care, 80% showed willingness to motivate fellow cancer-patients to facilitate supportive-care-program of NGO's. Infact 19 patients themselves became regular active facilitators in our NGO's cancer-care workshops. Our Holistic approach helped overcome hopelessness/fear depression. Pain management/supportive care emerged very serious issue affecting QOL in colorectal-patients. Cancer-NGO's need Improved access to specialized training/ CME's on Counseling/rehabilitation.
Conclusion: If resources like Lung-Cancer fellowship/training are made available to oncology workers, then NGO's can perform good job of Counseling/rehabilitation for Lung & other cancer sufferers. Restricted resource-limitations didn't permit us to analyze this issue in large-sample-size, but we can collaborate with other NGO's at IASLC-2011-conference for larger effort. Our recommendations most suitable to resource-poor-settings.
Keywords: NGO, Rehabilitation, counseling

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P4.157 LONG-TERM FOLLOW-UP OF ADVANCED NSCLC PATIENTS TREATED WITH CISPLATIN-VINORELBINE

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Background: Platinum-doublets remain the standard chemotherapy regimens for advanced/metastatic NSCLC. Here we aimed to study the long-term outcomes of NSCLC pts treated with the cisplatin-vinorelbine combination as first-line chemotherapy.
Methods: It is a retrospective study on pts diagnosed with advanced/metastatic NSCLC and consecutively treated with cisplatin (DDP) 80 mg/m^2 d1 and vinorelbine (VIN) 30 mg/m^2 d1, d8, d15, every 21 days, 4-6 cycles, in our institution, between Sep/02 and Oct/08. Overall survival (OS) was estimated by the Kaplan-Meier method and curves were compared with log-rank. A multivariable Cox proportional hazards model was used to control for prognostic factors.
Results: 142 pts were treated with DDP-VIN. Median age 63 y (34-87) and 95 pts were male (67%); 121 active smokers (86%) with a median of 45 pack-years. Histology: 58 pts were diagnosed with adenocarcinoma (42%) and 49 pts with

squamous cell carcinoma (36%). The median number of cycles was 4 (1-7). Median OS (mOS) was 7.5 mo, and 99% of all pts were dead in the most recent follow-up. Better 1-year OS was observed in those pts with better Karnofsky perfomance status (KPS ≥ 70% vs. KPS < 70%: 39% vs. 11%, HR 0.46, 95%CI 0.12-0.82, p=0.019), hemoglobin level ≥ 12 g/dL vs. < 12 g/dL (42% vs 19%, HR 0.67, 95%CI 0.39-1.01, p=0.054), and normal platelet count (< 400 K/mL) at the beginning of chemotherapy (42% vs. 20%, HR 0.61, 95%CI 0.33-0.97, p=0.040). Hemoglobin level ≥ 12 g/dL at the beginning of chemotherapy remained significant as a favorable prognostic factor in terms of OS in a multivariate analysis.
Conclusion: DDP-VIN remains a valid chemotherapy regimen in unselected pts diagnosed with advanced/metastatic NSCLC. Some pts, like those with hemoglobin level ≥ 12 g/dL, seems to present better outcomes. Supported in part by FAPESP 2010/15761-9 and 16134-8.
Keywords: Non-small cell lung cancer, Cisplatin, Vinorelbine

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P4.158 QOL IN LUNG CANCER : OPTIONS AVAILABLE

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Background: The QOL & survival rate for lung ca patients depends on relationship between the medical social worker [MSW]/Nurse and palliative care team, providing continuity of care and a smooth transition from diagnosis to death. It is essential that a good collaborative relationship exists between the Lung Nurse and Palliative care team. Aims: To determine qualities relationship between a nurse/ MSW and a Hospital-based Palliative care team. To asses needs of lung ca patients. To forward these recommendations to NGO clinics &cancer care institutes. The effort was to overall increase in quality of life in rural areas.
Methods: We evaluated roles of MSW & cancer nurse within a multidisciplinary team. Devise methodologies by which their services can be integrated together. In phase II of project it was decided to rationalize their training module & to see how MSW/nurse and palliative care team work together to enable support for patients and families. Maximum stress was to improve communication channels between cancer care multidisciplinary team and community workers.
Results: A retrospective analysis lung cancer data base from cancer care centers registry was taken as reference: We evaluated how many patients referred to lung cancer team from June 2007 till Jan 2011. how many patients diagnosed of lung cancer, and how many patients were referred to Palliative care team. On rationalized protocol, case study proforma devised to study nature of the lung nurse/ palliative care team relationship.
Conclusion: Results The Lung Cancer team saw 120 patients from june 2007. 102 were diagnosed with lung cancer. 90 patients with known lung cancer were referred to the palliative care team. : Conclusion: lung cancer incidence very high, relationship between MSW/nurse and palliative care team is crucial for survival period & Quality of QOL . This close relationship provides support for specified module for training of MSW/Nurse and continuous care for both patient and their families. Our project outlines need for developing collaborative working relationship between MSW/ Nurse and hospital-based palliative care team. Resource limitations & lack of expertise in rural area limited our project duration. But we suggest collaborative studies with IASLC on this fertile topic of lung cancer research in developing nations of the southern countries.
Keywords: palliative care, QOL, social worker

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P4.159 EVALUATION OF PAIN AS PARAMETER OF QOL IN LUNG CANCER

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Background: When assessing QOl parameters of Lung cancer, pain is very commonly observed . No uniform approach on pain management. Lung cancer patients are traditionally followed up in hospital outpatient clinics with the emphasis of care on surveillance for disease progression, recurrence, or metastatic spread. CAM-Therapy highly preferred by Asian cancer patients. Cultural/psychological/ spiritual/social factors influence quality-of-life (QOL) of Lung cancer patients Current approach : The work-up of pain in the individual with cancer

begins with a thorough pain assessment, including a comprehensive history combined with a complete physical examination. But very few institutions have specialized pain care team.
Past studies/experiences:
The management of pain due to Lung cancer requires a sound understanding of pharmacotherapy, including drug mechanisms, adverse effects, and potential drug-drug interactions. Three primary categories of analgesics include non-opioids, opioids, and adjuvant agents. opioids analgesics represent most useful agents for the treatment of pain associated with Lung cancer.
A wide variety of non-opioids medications from several pharmacological classes used additionally are anticonvulsants, antidepressants, corticosteroids, local anesthetics. Chemotherapy -with-CAM & spirituality/psycho-social-support emerging new hope pain management. Spiritual well-being prevents end-of-life-despair. Effect of spiritual/psycho-social-community support fertile ground for further investigations
Methods: Done by interviews on 23 patients who had completed Rx for Lung cancer who were having intractable pain. Score on pain perception before treatment & after treatment noted. Any optional alternative therapy treatment [complimentary medicines] taken noted. Patients receiving palliative care evaluated for overall improvement in QOL before treatment & after treatment support.
Results: This was a qualitative evalution project in phase II. all findings will be presented at WCLC Amsterdam congress in leaflet format. copies will be available to all conference participants at venue. [Masking identity of patients]
Conclusion: 21 out of 23 lung cancer cases-participants in our survey felt that pain due to Lung cancer is distressing and can be challenging to manage. In most cases, available therapies can provide relief. A comprehensive assessment is critical, along with knowledge of analgesic agents and their use. If palliative care team can co-ordinate with counselors/psycho-therapists on this issue then maybe we will get better results.
Keywords: pain, Lung cancer, QOL

P4.160 THE URINE CORTISOL LEVEL IS RELATED TO THE PERFORMANCE STATUS OF LUNG CANCER PATIENTS.

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Background: Patients with advanced cancer often experience symptoms such as pain, anorexia, and fatigue. It is well known that the cortisol plays an important role with terminal cancer who are now facing death, but it is not clear in advanced stage lung cancer when considering chemotherapy.
To examine the association between urine cortisol levels and performance status or TNM stages in pre-teratment patients with lung cancer.
Methods: A total of 14 persons, twenty-four hours urine cortisol concentrations were measured for two days, and the mean value of them was compaired with the clinical data.
Results: Twenty-four hour urine cortisol level was increased in lung cancer patients with performance status 2 or 3 compared PS 1 ($p < 0.05$), and increased proportionally to performance status ($R^2 = 0.32$, $p < 0.05$). It was increased in patients with regional lymph node metastasis status N2 or N3 compared with N1 ($p < 0.01$) , and has a tendency to increase in patients with stageIV compaired with other stages ($p = 0.088$). The urine cortisol levels were shown a positive correlation with serum potassium level ($R^2 = 0.33$, $p < 0.05$), and negatively correlated with serum sodium level ($R^2 = 0.42$, $p < 0.05$).
Conclusion: Twenty-four hour urine cortisol levels was increased not only in end stage, but also in rather earlier stage lung cancer when considering chemotherapy. The serum levels of potassium and sodium ion might indicate relative adrenal insuffiency.
Keywords: Chemotherapy, cortisol, Lung cancer

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P4.161 COMPARISON OF EXERCISE CAPACITY AND HEALTH-RELATED QUALITY OF LIFE ACCORDING TO STAGES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Non-small cell lung cancer represents approximately 80% of the total lung cancers. Surgery, chemotherapy and/or radiotherapy are planned for treatment of non-small cell lung cancer according to stages. Associated with disease and/or the treatments in lung cancer survivors, serious side effects are occurred, changes are appeared in their functional capacity and health related quality of life (HRQL). Accordingly, the success of medical treatment and pulmonary rehabilitation programmes can also negatively affected. For these reasons, HRQL and exercise capacity is important to plan treatment of patients with non small cell lung cancer and monitor patients during and after the therapy. With the reasons, the aim of our study was to compare exercise capacity and HRQL parameters in patients with non-small cell lung cancer and to discuss the results with clinical characteristics of patients.
Methods: Twenty patients with less than stage 2 (Group 1, n=8) and greater than stage 2 non-small cell lung cancer (Group 2, n=12) were included. The demographic and clinical characteristics of the patients were recorded. Exercise capacity (6 minute walking test), back and legs strength (Back-Leg Dynamometer), HRQL (European Organization for Research and Treatment of Cancer Questionnaire and Short Form-36 Health Survey), depression and anxiety (Hospital Anxiety and Depression Scale), pulmonary functions (spirometry), severity of dyspnea (Medical Research Council Scale) were evaluated.
Results: No difference was found in age, body mass index and pulmonary symptoms between 2 groups compared with patients with less than stage 2 group and greater than stage 2 group (p>0.05). When distribution of respiratory symptoms was examined, in group 1, dyspnea was fixed in 50%, cough in 50%, fatigue in 12.5% and sputum in 37.5% , in group 2, dyspnea in 16.7% , cough in 58.3%, fatigue in 50% and sputum complaint in 41.7% were founded. The distribution of symptoms were similar in both groups (p>0.05). Disease cell types were recorded squamous cell carcinoma in 62 % of group1, adenocarcinoma in 25% of group 1 and squamous cell carcinoma in 41.7 % of group 2, adenocarcinoma in 50% of group 2. In group 2, FEV_1 and FVC were lower (p=0.04), peripheral muscle strength were lower (p>0.05), dyspnea (p=0.72) and depression and anxiety levels were higher (p<0.01), and in HRQL scores especially the category of functional capacity were lower (p>0.05) according to group 1. Examining exercise capacity according to the stages, walking distance were found 402.50±82.46 m in group 1 patients and 355.58 ± 116.75 m in group 2 patients (p=0.31).
Conclusion: However in patients with less than stage 2 non-small cell lung cancer, exercise capacity and HRQL values were lower according to greater than stage 2, especially the respiratory function in these patients, as well as with increased levels of anxiety and depression is striking. Although the number of patients were insufficient, the results give rise to thought that exercise capacity and HRQL assessments for lung cancer patients should be made systematically and it is important that results should be commented according to stages and should be take into consideration for pulmonary rehabilitation programmes.
Keyword: Exercise Capacity, Health-Related Quality Of Life, Non-Small Cell Lung Cancer

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P4.162 DIAGNOSIS OF BONE METASTASIS IN PATIENTS WITH LUNG CANCER USING URINARY AND SERUM COLLAGEN TYPE I TELOPEPTIDE (NTX)

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Background: Many cancers metastasize to bone. Bone metastasis may cause an increase in bone resorption due to direct effects of the tumor itself or osteoclastic activation. This study evaluates the bone resorption biomarkers urinary NTx (uNTx) and serum NTx (sNTx) for the diagnosis of bone metastasis in patients with lung cancer.
Methods: The uNTx and sNTx were measured in 100 patients with lung cancer and 50 control patients with benign respiratory diseases using the uNTx:OSTEOMARK® and sNTx:OSTEOMARK® serum NTx assays (Inverness Medical Japan). Bone metastasis was characterized by scintigraphy. The extent of disease (EOD) was determined by the number of sites of bone metastasis. Area under the curve (AUC) for receiver operating characteristic (ROC) analysis was used to evaluate the detection of bone metastasis. Sensitivity and specificity of uNTx and sNTx to detect bone metastasis were calculated using cutpoints of 64 nM BCE/mM Cr for uNTx and 22 nM BCE/L for sNTx. All patients were required to provide written informed consent.
Results: Patients with bone metastasis had significantly higher levels of both uNTx and sNTx (uNTx; 93.2 +/- 105.1 nM BCE/mM Cr., sNTx; 24.0 +/- 14.6 nM BCE/L) vs. lung cancers without bone metastasis (uNTx; 51.6 +/- 26.8 nM BCE/mM Cr., sNTx;17.2 +/- 4.1 nM BCE/L), or benign respiratory diseases (uNTx; 42.8 +/- 21.8 nM BCE/mM Cr., sNTx; 16.8 +/- 7.9 nM BCE/L.). There was good correlation between uNTx and sNTx (R = 0.807). ROC AUC for the detection of bone metastasis was 0.743 for uNTx and 0.712 for sNTx. The sensitivity and specificity for the diagnosis of bone metastasis using uNTx was 48% and 86%, and using sNTx was 40% and 87%, respectively. Levels of uNTx and sNTx were increased in patients classified as EOD grade I compared to controls and in patients classified as EOD grade II or greater, compared to patients classified as EOD grade I.
Conclusion: Both biomarkers may have value as an aid in the diagnosis of bone metastasis in patients with lung cancer.
Keyword: serum NTx, urinary NTx, NTx, lung cancer, bone metastasis

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P4.163 ANTIBIOTIC PROPHYLAXIS IN CHEMOTHERAPY-INDUCED NEUTROPENIA IN PATIENTS WITH LUNG CANCER

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Background: Chemotheapy-induced neutropenia can potentially cause fatal bacterial infection in cancer patients. Human granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are usually recommended as prophylaxis. Alternatively, prophylactic antibiotics have been administered to prevent the development of bacterial infections.
Methods: A literature search in PubMed and Scopus was performed to identify randomized control trials and comparative cohort clinical studies that evaluated the role of antibiotic prophylaxis in chemotherapy-induced neutropenia in lung cancer patients.
Results: Five randomized controlled trials, 2 non-randomized cohort studies, 1 comparative non-randomized case control study and 1 case report were identified as eligible for inclusion in this systematic review. A total of 1175 patients with lung cancer were evaluated to receive antibiotic prophylaxis during the expected neutropenic period after widely used chemotherapy regimens and doses associated with a known risk of cyclic severe neutropenia (on days 4-13 after chemotherapy) or from the beginning of chemotherapy until the completion of 3 cycles of chemotherapy. The main histologic diagnosis was small cell lung cancer in 720/1175 (61.7%) patients. Quinolones and trimethoprime/sulfomethoxazole were the main antibiotics used as prophylaxis in these studies while G-SCF were administered in 2 studies and totally 260/1175 (22.1%) patients. Studies showed that prophylactic use of antibiotics in lung cancer patients undergoing chemotherapy reduced significantly the number of episodes of febrile neutropenia, documented infections and the duration of hospitalizations due to suspected infections.
Conclusion: Although routine antibiotic prophylaxis remains controversial due to the lack of survival advantage, and risk for antibiotic resistance, this

systematic review showed that the prophylactic use of wide spectrum antibiotics in chemotherapy-induced neutropenia in patients with lung cancer is as effective as the G-CSF and GM-CSF recommended and, thus, could be considered as therapeutic strategy.

Keywords: neutropenia, Cancer, malignancy, prophylaxis

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P4.164 TALACTOFERRIN ALFA (TLF) REDUCES MORTALITY ACROSS A BROAD RANGE OF PATIENTS WITH SEVERE SEPSIS

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Background: This randomized, placebo-controlled, double-blind study evaluated TLF, an oral agent with immunomodulatory and antibacterial properties, on 28-d all-cause mortality in patients with severe sepsis. TLF previously showed activity in NSCLC as monotherapy in the 2nd/3rd line setting and when added to a 1st line chemotherapy doublet.

Methods: Eligible pts had onset of severe sepsis (at least 1 organ dysfunction) within 24 hours prior to randomization to TLF 1.5 g or placebo enterally (oral or by feeding tube) q 8 h for a maximum of 28 d in addition to standard care including drotrecogin alfa (activated).

Results: Baseline characteristics of 190 randomized pts (97 TLF; 93 Placebo [P]) were similar. The study met the primary endpoint of reducing 28-d mortality in the modified ITT population (14.4% TLF/26.6% P; 2-tailed P = 0.052 [Guntupalli ATS 2010]). The effect on mortality was seen across a broad range of patients in the study including those with and without cardiovascular function, varying degrees of organ failure and different types of infection. Mortality decreased in patients with and without cardiovascular dysfunction (22% and 2% TLF/29% and 23% P), in patients with organ failure (1 organ – 7%TLF/13% P, 2 organs – 8% TLF/34% P, 3 organs – 28% TLF/29% P, 4 organs – 67% TLF/40% P, 5 organs 0% TLF/50% P) and in patients with various types of infection. The most common sites of infection were lung (46% TLF/52% P) and urinary tract (21% TLF/23% P). A positive culture was obtained in 66% TLF/71% P pts. Of the positive cultures, Gram + isolates were the most common (73% TLF/79% P) followed by Gram - (36% TLF/44% P) and fungal (16% TLF, 6% P). Of the positive cultures, blood was the most common site for isolation (59% TLF/49% P). Polymicrobial infection was present in 28% TLF/34% P pts. There was a consistent mortality decrease in the TLF arm by sites of infection (lung: 18% TLF/38% P p=0.04; urinary tract 5% TLF/29% P p=0.09), with the exception of intra-abdominal infection (31% TLF/14% P p=0.38). A consistent reduction in mortality also occurred in pts with a single isolate (19% TLF/29% P) and polymicrobial isolates (15% TLF/22% P). For single isolates, mortality was lower for Gram + (22% TLF/32% P) and Gram – (18% TLF/33% P) infections. The decrease in mortality was also seen across age groups in the study and men saw a greater reduction in mortality than women (11% TLF/36% P, 18% TLF/17% P).

Conclusion: The effect of TLF on mortality reduction appears consistent across a broad range of patients with severe sepsis. Further study of TLF in severe sepsis and in cancer patients with severe sepsis is warranted.

Keyword: Sepsis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.165 SYMPTOM BURDEN IN PATIENTS WITH ADVANCED LUNG CANCER ADMITTED TO HOSPITAL FOR PALLIATIVE CARE

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Background: Treatment of cancer symptoms is an integral part in lung cancer care. Patients with lung cancer in advanced stage have a high prevalence of multiple symptoms affecting their daily life at home. Lung cancer patients are frequently admitted to unscheduled hospital care due to cancer symptoms like dyspnea and pain. To assess the variety of symptoms at admission we mad a pilot study to increase our understanding and awareness of symptom burden in lung cancer patients. We asked used Edmonton Symptom Assessment Scale (ESAS) as a tool to elucidate what are teh symptoms the patient is not able to cope with at home. The following symptoms were assessed: pain at rest, pain during motion, fatigue, dyspoea, appetite, nausea, dry mouth, constipation, depression, anxiety, insomnia and well-being.
Methods: During 3 month period all lung cancer patients admitted to hospital ward due to cancer associated symptoms were asked to complete ESAS form in the beginning and at the end of hospital care. Patient demographic data and ESAS scores were summarized using descriptive statistics.
Results: ESAS was completed by 32 patients admitted to pulmonary ward at Helsinki University Central Hospital during collection period of three months in 2010 (June, July and August). 15 patients completed the second ESAS at the time of hospital discharge. 15 (47 %) were male and 17 (53 %) were female. The mean age was 65 years (range 45-87). At baseline all patients suffered from fatigue. The percentage of patients suffering from pain, dyspnoea, loss of apetite, nausea, dry mouth, constipation, depression, anxiety and insomnia were 84, 69, 81, 66, 81,53,56, 56, and 63, respectively. Those patients who completed ESAS at discharge had a little lower ESAS scores in all symptoms assessed. However, anxiety was increased during hospital stay.
Conclusion: The patients with advanced lung cancer have a high prevalence of symptoms when they are acutely admitted to hospital care. There is a variety of symptoms driving tha patient to seek help. Awareness of these symptoms is needed for planning an adequate treatment for these patients. ESAS provides a tool to symptom assessment in patients with advanced lung cancer.
Keywords: Edmonton Symptom Assessment Scale, palliative care

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P4.166 REFUSAL OF PALLIATIVE CHEMOTHERAPY TREATMENT IN ADVANCED LUNG CANCER PATIENTS –PERSPECTIVE FROM A TERTIARY CARE CENTRE IN SOUTH INDIA

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Background: Palliative chemotherapy treatment is a very important in Lung cancer Patients , as most of the patients present in an advanced stage of the disease. Palliative treatment includes symptom care, anti cancer Treatment, Psychosocial care, palliative surgeries etc. Patients refuse palliative treatment due to various reasons. We are trying to identify the reasons for declining palliative care treatment in our hospital.
Methods: A Prospective study was done on Lung cancer patients who had presented to our hospital during January 2010 and december 2010 for palliative care. 82 patients presented to our outpatient clinic for treatment, 61 patients had stage IIIB and IV disease and were eligible for palliative chemotherapy only. Questionnaire were given either to the patient or the relatives to fill up. 52 of our patients were not knowing about the disease status, due to the request of the family members, in such instances the attenders were allowed to fill the same.
Results: Sixty one patients were evaluable for the study. Thirty three patients were started on palliative treatment of which only 24 patients completed the prescribed treatment of the oncologist. Twenty eight patients had refused any kind of treatment due to various reasons of which 8 (28.57%) patients had refused due to the discouragement by the society, 15(53.57%) patients were not affording the medicines, 4(14.28%)patients were not willing in view of the poor prognostic nature of the disease, 3(10.71%)patients refused due to the lack of family support. two patients had more than 2 reasons to say. Out of 61 patients who were offered palliative chemotherapy 33 patients were initiated on the treatment. Twenty four patients completed treatment

and 9 patients discontinued treatment in between. The reasons for dropouts were, 2(22.22%) had been discouraged by their neighbours, 3(33.33%)patients had dropped due to the toxicities of treatment and 5(55.55%)patients cited financial reasons. One patient had more than two reasons to say.
Conclusion: Major reason for refusing treatment was the non-affordability of cancer drugs and some times even general drugs, which is less expensive. Lack of family support has also been a major problem because they were not ready to adjust, as they are not aware that palliative care treatment is going to give them a good Quality of life.
Keywords: Refusal, Palliatve chemotherapy, Lung cancer

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P4.167 EXPANDABLE METAL TRACHEOBRONCHIAL STENT (ULTRAFLEX®) PLACEMENT IN THE RIGHT MAIN BRONCHUS STENOSIS DUE TO BRONCHIAL CARCINOMA.

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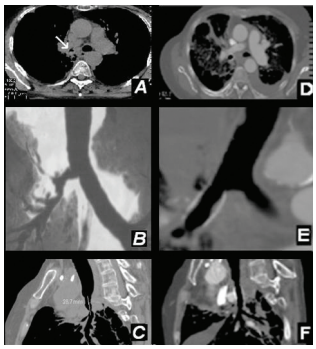
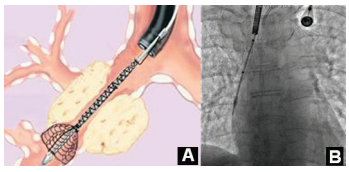
Background: CASE REPORT: The authors introduce a case of a 54 years old female, with non small cell lung cancer localized in the upper right lobe (T4N3M0 stage). Patient was receiving third line chemotherapy and received total chest radiotherapy dose. Flexible bronchoscopy detected eight percent stenosis of the right main bronchus due to recurrent bronchial carcinoma. The symptoms were dyspnea, non-productive cough and localized sibilance. PHYSICAL EXAMINATION: localized sibilance in the upper third right hemithorax and ipsilateral reduced vesicular breath sounds. THORACIC CT SCAN: endobronchial tumor determining subtotal stenosis of the right main bronchus (Figure 1 – A,B,C). Complete athelectasy of the upper right bronchus. FLEXIBLE BRONCHOSCOPY: confirm eighty percent right main bronchus stenosis due to endobronchial carcinoma and complete obstruction of upper right bronchus.



Methods: TREATMENT: It was performed endobronchial dilatation with complacent balloon following Ultraflex® expandable endobronchial stent placement (Figure 2).



Results: The results were dyspnea relief and a good permeability of the right main bronchus (Figure 1 – D,E,F).
Conclusion: The Wallstent® and Ultraflex® metalic expandable stents have a good compression resistence and a uniform radial centrifugal force, excusing the hook necessity to fix it. They easily adapt yourself to airway tortuosity, remain an effective permeability. The complications include difficulty to remove it, granulation tissue formation and secretion retention. Chhajed,et al performed the unique comparative trial analyzing three different stents. The Gianturco®, Wallstent ® and Ultraflex® were analyzed and the last one had lesser reestenosis index (60%, 27% and 0, respectively), lesser secretion retention (0, 27% and 0, respectively) and lesser migration index. They concluded that Ultraflex® have less long time complications than Gianturco® and Wallstent® prosthesis.
Keywords: ultraflex, bronchial stent

Poster Session 4 - Palliative Care Thursday, 7 July 2011 10:00-12:30

P4.168 RENEWED HOPE THROUGH THEIR JOURNEY: LUNG CANCER CHALLENGES AND THE CLINICAL TRIALS

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Background: The number of lung cancer patients in the world is steadily increasing. In 2010, in Canada alone, there were approximately 24,000 new cases (Canadian Cancer Society). Many of these survivors have advanced disease with a poor prognosis. Clinical trials offer patients renewed hope for prolongation of life, improved quality of life (QOL), and effective symptom control. Being able to offer all patients best possible care coordinated and monitored by a specialized team, should be an ultimate goal.
Methods: In spite of the fact that trials have been part of Oncology care for a long time and their outcomes help to demonstrate safer and more effective treatments, less than 5% of all patients with cancer will take part in clinical trials. At our McGill University health centers, the number of patients with a lung cancer diagnosis has increased over the past several years and many are enrolled to clinical trials.
Results: The challenges due to the increasing numbers cannot be underestimated. Issues related to new, often complex treatment options, the aging population, emphasis on quality of life, and most importantly the need for earlier and improved palliation, are just a few. Can access to enhanced knowledge and possible participation through the rigorous clinical trials program help prepare lung cancer patients for this difficult journey? Would a database expand our knowledge and understanding in this therapeutic area? Through our clinical trials based approach, can we offer improved symptom management, end of life care and better outcomes?
Conclusion: This presentation will describe the initiatives of our Clinical Trial Team, and the potential benefits of clinical trials for lung cancer patients as they move through their journey.

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.169 T-CELL CD38 EXPRESSION IN B-CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: -cell chronic lymphocytic leukemia (B-CLL) is a heterogeneous disease with some patients having an indolent course never needs treatment, while others having rapidly progressive one requires intensive treatment. In recent decades, numerous prognostic markers, such as IgVH mutational status, ZAP-70 and the expression of CD38 on leukemic cells were introduced to screen for patients likely to have progressive course of B-CLL bearing the potential to facilitate risk-adapted treatment strategies. In B-CLL, T cell function is shown to be dysregulated. CD38 has been demonstrated to be an important transmembrane signaling molecule of T cell with a direct effect on its function.
Methods: By using flow cytometry, CD38 expression on T cells were analysed in 88 unselected B-CLL patients.
Results: CD38 expression level on T cells was shown to predict the clinical course of B-CLL in male patients but not in female patients. Male patients showed CD38 expression on T cells in a stage-dependent manner, in contrast to female patients who showed higher expression irrespective to clinical staging. CD38 expression on T cells negatively interacted with treatment-free survival in male patients. Multivariate analysis revealed that CD38 expression level on T cells is an independent prognostic factor in B-CLL male patients.
Conclusion: A simultaneous evaluation of CD38 expression on both B-CLL cells and T cells allowed predicting male patient groups with the most favorable prognosis as well as those with the worst.
Keyword: B-CLL • T cell • CD38 • prognostic factors

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.170 IMAGING CHANGE OF EGFR-MUTATED LUNG ADENOCARCINOMA DURING THE TRANSITION FROM AIS TO MIA AND ADC. CORRELATION WITH STROMAL ELASTOSIS

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Background: In the early development peripheral adenocarcinoma, there is preservation of the elastotic framework of the stroma due to contraction and thickening of the alveolar septa by approximately three to nine-fold (Eto et al. Cancer 1996). EGFR-mutated non-mucinous adenocarcinoma shows moderate stromal elastosis during the transition from in situ (AIS) to minimally invasive (MIA) and invasive adenocarcinoma (ADC). Therefore, contraction of EGFR-mutated adenocarcinoma should be expressed on imaging analysis. We investigated the characteristic imaging changes in EGFR-mutated non-mucinous lung adenocarcinoma during the transition from AIS to MIA and ADC.
Methods: EGFR-mutated non-mucinous adenocarcinoma measuring less than 7 cm in diameter were obtained from patients who underwent resection at our institute between April 2007 and March 2010 and these specimens were studied. Seventy-eight patients were enrolled and divided in four groups 1.AIS (n=8), 2. MIA (n=10), 3. Negative for ADC-related factors (absence of any lymphatic, vascular, pleural or nodal invasion) (n=21), 4. Positive for ADC-related factors (the remaining adenocarcinomas) (n=39). Imaging was evaluated with regard to internal veins, arteries and bronchi in the nonsolid component, as well as external veins and arteries. Retrospective CT history could be analyzed in 20 patients (AIS 4, MIA 4, negative for ADC-related factors 3 and positive for ADC-related factors 9) who were followed for more than 90 days, ranging from 97 to 2017 days.
Results: In all of AIS and 90% of MIA, imaging studies showed that small arteries and veins were visualized at close intervals in the nonsolid component, seen as vascular reticulum. In the CT history of patients with MIA and those negative for ADC-related factors, external neighboring vessels gradually approached or were captured by the nodule, while the nodule size grew along the major axis but hardly grew or shrank along the minor axis. The internal vascular reticulum developed into a dense solid component. As the tumor progressed, dominance of the solid component increased from 13% in AIS to 89% in patients who were positive for ADC-related factors. In the solid component of ADC, external arteries and veins appeared to bend and converge into the nodule. Contraction differences between the major axis and minor axis were emphasized on 3D images. In patients who were positive for ADC-related factors, nodule growth was seen in 60% on CT history and the diameter of the external draining veins and the internal bronchi were increased.
Conclusion: Imaging of EGFR-mutated non-mucinous lung adenocarcinoma demonstrated that contraction and thickening of the lepidic septa originated in AIS. During minimal invasion, vascular reticulum was visualized as a nonsolid component. During early progression, dense vascular reticulum became a solid component, often demonstrating a long elliptical nodule, suggesting contraction along the bronchovascular trees, while nodule growth was restricted by the contraction and the external neighboring vessels became closer to the internal nodule component. During late stage of progression, nodule growth was advanced and draining veins developed.
Keyword: vascular reticulum

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.171 PROGNOSTIC IMPACT OF THE PRIMARY TUMOR LOCATION BASED ON THE HILAR STRUCTURES IN NON-SMALL CELL LUNG CANCER WITH MEDIASTINAL LYMPH NODE METASTASIS

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Background: The status of lymph node metastasis is an important factor determining the treatment strategy and predicting the prognosis in lung cancer. By the typical nodal metastatic process

that lymphatic drainage develops from interlobe to mediastinum through the hilum, metastatic lymph nodes located in the intrapulmonary, ipsilateral, and contralateral mediastinum are defined as N1, N2, and N3, respectively. Namely, the farther the metastatic lymph node from the primary tumor, the worse is the prognosis. On the other hand, little attention has been paid to location of the T descriptor in lung cancer. Our hypothesis is that if mediastinal lymph node metastasis comes from further located tumor, it might be unfavorable result reflecting wider spread metastasis. The aim of this study was to estimate the prognostic value of the primary tumor location on the basis of the hilar structures in NSCLC with mediastinal lymph node metastasis.
Methods: Among 337 patients with NSCLC who underwent mediastinal lymph node dissection between January 1995 and December 2004, 40 patients with pathological T1a-2bN2M0 NSCLC were retrospectively analyzed. All the pN2 patients were preoperatively regarded not to have metastatic mediastinal lymph nodes. To determine the primary tumor location anatomically, we divided the cases into two groups on the basis of the primary tumor proximity to the hilar and bronchial structures: tumors located close to the first branch of the extrapulmonary bronchus were defined as central-type tumors, and those not meeting this criterion were defined as peripheral-type tumors. We analyzed only small size tumors (pT1a-T2b) and excluded advanced cases with pleural invasion (PL3) not to include unusual metastasis such as subpleural lymphatic pathway metastasis. The overall survival time was estimated by the Kaplan–Meier method and the influence of variables on survival was analyzed by using the log-rank test for discrete variables. The Cox proportional hazards model was employed for multivariate analysis.
Results: Of the 40 patients with N2 NSCLC, 18 and 22 had central- and peripheral-type tumors, respectively. There was no significant difference between the tumor groups with regard to age, gender, tumor side, primary lobe, histological type, pathological stage, surgical procedure, pleural invasion, lymphatic invasion, and vascular invasion. The five-year survival rate was significantly higher with the central-type tumors than the peripheral-type tumors (51.5% vs. 21.2%, P =0.034). The multivariate analysis showed that the primary tumor location (hazard ratio = 2.760, 95% CI = 1.132–6.326; P = 0.026) was a significant prognostic factor for overall survival. The 40 analyzed patients included 13 patients with skip metastasis (32.5%). However, lobe-specific tendency for metastatic lymph nodes was noted regardless of the skip or non-skip metastatic cases and the prognostic significance between the two tumor groups did not change after excluding the skip metastatic cases (51.3% vs. 12.5%, P = 0.034).
Conclusion: Our study indicates that evaluation of the primary tumor location based on the hilar and bronchial structures is useful to predict the tumor extended status in N2 NSCLC. Furthermore, it is suggested that this assessment might be valid even to unusual case with skip metastasis.
Keyword: extrapulmonary bronchus, mediastinum, non-small cell lung cancer, prognosis, skip metastasis, TNM cl

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.172 EGFR AND K-RAS MUTATIONS IN JAPANESE PATIENTS WITH RESECTED NSCLC

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Background: The theory that existence of somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene is corresponded with therapeutic sensitivity of tyrosine kinase inhibitors (TKIs) in patients with non-small cell lung cancer (NSCLC), has been recognized widespread. The response of EGFR-TKIs is expected 70-80% in patient with EGFR mutation, but is estimated around 10% to a wild-type EGFR. On the other hand, the presence of the V-Ki-ras2 Kirsten rat sarcoma (K-RAS) mutation is shown oppositely to the EGFR mutation. EGFR-TKIs would not be responded in the NSCLC patients with K-RAS mutation. We examined whether the presence of EGFR or K-RAS mutation became a prognostic factor in NSCLC patients who had received lung resection.
Methods: We intended consecutive 126 cases of

the NSCLC for this study. All of these cases were performed lung resections in Shinshu University Hospital form December 2000 to August 2008. We evaluated retrospectively whether the gene mutation could be detected using the lung specimen; EGFR mutation was analyzed by the PCR-invader method and K-RAS was by the PCR-clamp method. The relationships between the presence of EGFR or K-RAS mutation and the clinicopathological features of the NSCLC were also analyzed.
Results: All patient characteristics in the study were displayed as following: the ages varied between 35 and 87 years (mean 69.3 years), the genders were 72 men and 54 women, and smoking history had in 68 cases. Histological findings included 93 cases of adenocarcinoma (AD), 22 cases of squamous cell carcinoma (SCC) and 11 cases of the other histological types. The EGFR mutations were found in 52 cases (41.3%), and the K-RAS mutations were found in 12 cases (9.5%). The presence of these gene mutations were recognized exclusively each other. The EGFR mutation was detected in the following characteristics: histological types were 52 ADs, the genders were 15 men and 37 women, and 39 cases were non-smoker. The K-RAS mutation was detected in the following characteristics: histological types were 9 ADs, 2 SCCs and one of pleomorphic carcinoma, the genders were 8 men and 4 women, and 10 cases were heavy smoker. The EGFR-TKIs treatment was enforced in 23 cases (18.3%). 16 cases of them were detected the EGFR mutation; 14 cases were good response and 2 cases were progression disease. The EGFR-TKIs treatment for patients with wild-type EGFR was shown in 7 cases, and was invalid in all cases. We did not administer EGFR-TKI to a KRAS mutation patient. The median overall survival time (MST) was 78.6 months of all patients. The MST according to the EGFR mutation, the K-RAS mutation, and the double wild-type were 90.1 months, 31.5 months, and 65.6 months, respectively. The overall survival of EGFR mutation was significantly longer than K-RAS mutation.
Conclusion: The EGFR mutation was accepted a lot by AD and a woman. On the other hand, the K-RAS mutation was recognized a lot by a man and heavy smoker. The EGFR mutation extended overall survival than wild-type EGFR and K-RAS mutation.
Keywords: EGFR, Kras, NSCLC

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.173 THE PROGNOSTIC VALUE OF LYMPHANGIOGENESIS ON NON-SMALL CELL LUNG CANCER

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Background: Lymph nodes invasion is common and one of the most important prognostic factor during the progress of cancer. Until now, some papers indicated that lymphangiogenesis promoted the metastasis of primary tumor cells to surround tissue and lymph nodes on breast and gastric carcinoma. Also, the research of lymphangiogenesis on non-small lung cancer had been involved recently, but the relationship of the lymphangiogensesis and the clinicopathological parameters on non-small lung cancer was not clear. The prognostic value of lymphangiogensis still need to explore. We study the relationship of the patients' clinicopathological parameters and peritumoral/ introtumoral lymphatic vessel density, lymphatic vessels invasion and the lymph nodes metastasis. And the prognostic value of lymphangiogensesis on non-small lung cancer was analyzed.
Methods: The introtumoral lymphatic vessel density (79 cases) and the peritumoral lymphatic vessel density (45 cases) of paraffin-embed tissues were tested with the D2-40 marker (Immunohistochemistry method), respectively. And, the relevance of lymphangiogenesis-related clincopathological parameters was evaluated.
Results: The average number of introtumoral and peritumoral lymphatic vessel density was 11.32 and 7.80, respectively. The number of introtumoral lymphatic vessel density were high in those patients who suffer from mediastinal lymph nodes metastasis (p=0.015), lymphangiogenesis tumor invasion (p=0.022) and tumor cell poorly differentiation grade(p=0.005). The lymphangiogenesis was the independent prognostic factor of patients (p=0.000). Lymphangiogenesis tumor invasion obvious affect the survival rate of patients (p=0.006). But there was no significant statistical difference between the tumor diameter and lymphangiogenesis (p=0.436) or lymphangiogenesis tumor invasion (p=0.269). Peritumoral lymphatic vessel density was no relation to the prognosis of patients (p=0.278).
Conclusion: D2-40 was the special marker of lymphatic endothelia. The lymphangiogenesis and lymphangiogenesis tumor invasion might play an

important roles during the procedure of enhanced the mediastium lymphatic nodes metastasis on non-small lung cancer. The lymphangiogenesis was a valuable prognostic factor of non-small lung cancer.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.174 CORRELATION OF BRONCHOSCOPIC FINDINGS WITH OTHER DATA IN 429 LUNG CANCER PATIENTS.

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Background: Lung cancer remains to be the big health problem in the Czech republic. The diagnostic process is unprecise and slow. We intend to evaluate the contribution of bronchoscopy (BS) for morphological verification of LC and find out correlations of BS findings with other data of the patients (pts) with LC
Methods: Prospective study on 429 pts with LC examined in 2004-2009. The BS findings were divided into the four categories: visible direct tumor masses, extramural or intramural compression of the bronchi and/or widening of the carina as indirect tumor changes, normal findings and BS not done.
Results: 151 pts (35%) had direct tumor changes and were verified during BS in 95,3%. Most of them (36%) suffered from small cell LC. In 110 pts (25%) indirect tumor changes were verified by BS in 55%. Most of them (33%) suffered by adenocarcinoma. In 93 pts were found normal findings. These pts were verified by BS in 22,8%. Most of them (38%) had adenocarcinoma. BS was not done in 75 pts. Only 30% from these pts were verified by other methods then BS. Groups of pts with smoking history, weight loss, alcohol overuse, cough and haemoptysis had significantly more frequently direct tumor changes. Pts with direct BS tumor changes had lower FEV1. The indirect BS tumor changes were more frequently found in pts with adenocarcinoma. The BS findings did not correlate with number of smoked cigarettes, fever in the time of diagnosis and the grade of dyspnoe.
Conclusion: BS is the principle examination for verification of LC. From history of illness we may, with some probability, suppose which type of BS findings pts with LC probably will have. In the opposite, definite BS findings significantly correlate with definite types of LC. Knowledge of coherence of BS findings with other pts data may contribute to precise and more rapid diagnosis in LC pts.
Keywords: lung cancer, bronchoscopy, morphology, diagnostics

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P4.175 INVASION OF THE INNER AND OUTER LAYERS OF THE VISCERAL PLEURA IN PT1 LUNG ADENOCARCINOMA: CORRELATION WITH MALIGNANT AGGRESSIVENESS AND PROGNOSIS

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Background: The visceral pleura consists of five layers including two elastic layers. Visceral pleural invasion (VPI) is defined as penetration by tumor cells of the elastic layers of the pleura. However, there is no mention in the literature which elastic layer is more important for the diagnosis of pleural invasion even in the tumor-node-metastasis (TNM) classification of malignant tumors (7th ed., International Union Against Cancer, UICC). The purpose of this study was to investigate whether the invasion of the inner or outer elastic layer is more critical in terms of patient survival.
Methods: We reviewed 120 pT1 lung adenocarcinomas that had been surgically resected at the Department of Thoracic Surgery, Fukuoka University Hospital, between January 1993 and

December 2001. We classified the tumors into three groups according to invasion of the inner and outer elastic layer, which was determined by EvG staining: group A, no invasion; group B, invasion of the inner layer but not the outer one; group C, invasion of both layers. The relashionship between VPI and the endpoint (death) was analyzed by univariate and multivariate analyses.
Results: The invasion of the inner and outer elastic layer was recognized in 22.8% (21/92) and 21.7% (20/92), respectively. The 5-year survival rate was 82% (51/92, 55.4%), 59% (21/92, 22.8%) and 38% (20/92, 21.7%) in patients of groups A, B and C, respectively. Invasion of the outer elastic layer (HR 5.92, 95% CI 2.197-15.957, P=0.0004) correlated more significantly with shorter survival than that of the inner layer (HR 3.56, 95% CI 1.151-10.992, P=0.0275). Invasion of the outer elastic layer was also significantly associated with lymph node metastasis and frequent lymphatic involvement, higher stromal invasion grade and presence of small cluster invasion within tumors. Univariate analysis showed that invasion of the outer elastic layer correlated significantly with poor prognosis. However, multivariate analysis identified lymph node metastasis as the most significant predictor of poor prognosis.
Conclusion: VPI is a significant pathological predictor of poor prognosis in pT1 lung adenocarcinoma.
Keywords: lung adenocarcinoma, Pleura, Elastic layers, Pleural invasion

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.176 STUDY OF THE MUTATIONAL STATE OF EGFR IN DIAGNOSTIC SAMPLES OF NSCLC - NEW APPROACH METHODS

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Background: Sequencing EGFR is important in all NSCLC diagnostic samples, in a quick and effective manner, in order to allow a better therapeutic strategy. Aim:Presentation of the technology developed in our service in 2010 aimed at researching EGFR mutations in diagnostic samples of NSCLC obtained by:CT guided transthoracic needle aspiration biopsy (FNAB); broncho-alveolar lavage(BAL); endobronchial ultrasound guied transbronchial needle aspiration (EBUS-TBNA) and the classic methodology used in brushing(EB) and bronchial biopsy(BB); surgical samples; pleural biopsy and fluid. Comparison between the average times for result acquisition in the various samples.
Methods: In EB, BB, pleural fluid and biopsy and surgical samples, EGFR sequencing made with DNA from cytological or histological slides or paraffin block by classical techniques described in literature. In FNAB and EBUS-TNBA, cellular debris in needle were recovered by saline solution washing and preserved in buffer at -20ºC.The extemporaneous cytological confirmation of NSCLC was followed by DNA extraction of those cellular debris and EGFR sequencing. In samples containing clots a paraffin block was used with posterior histological analysis and sequencing. In NSCLC diagnosed by BAL, performed centrifugation of BAL with separation of suspension cells and supernatant, which was preserved in 400µl of buffer at -20ºC.The supernatant was purified and subject to DNA concentration and EGFR sequencing. Linear regression analysis for comparison of average times for result acquisition, statistical significance for $p<0.05$.
Results: Sequenced 126 patients:24 BAL; 2 EB; 5 EBUS-TBNA; 43 BB; 27 FNAB; 8 pleural biopsy; 3 pleural fluid; 13 surgical samples; 1 hepatic metastasis biopsy.

	Average waiting time (days)	Time difference (days)	p
Paraffin block	8.32	-	
Cytological slides	14	5.6721	0.0255
Histological slides	20.42	12.0888	7.11e-08
Cellular debris	6.5556	-1.7723	0.1789

Table1 – Average time for sequencing result acquisition.

Diagnostic method	Type of material	Average waiting time (days)	Time difference (days)	p
BAL	Cellular debris	5.714	-12.286	0.000286
	Cytological slides	18.000		
FNAB	Cellular debris	6.05	-10.807	0.0188
	Paraffin block	16.857		
EBUS-TBNA	Cellular debris	6.144	-10.856	9.63e-05
	Paraffin block	17.000		
BB	Histological slides	19.000	11.812	1.03e-05
	Paraffin block	7.188		
Surgical samples	Histological slides	26.00	18.833	3.68e-05
	Paraffin block	7.167		

Table2 – Average acquisition time for each type of sample depending on the diagnostic method.

Conclusion: EGFR sequencing is possible in all NSCLC diagnostic samples. DNA sequencing made from cellular debris is quicker than from microscopic slides or paraffin block.This difference is statistically significant and has impact in treatment beginning.
Keywords: EGFR, Diagnostic sample

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P4.177 MODERATE DIAGNOSTIC ACCURACY OF INITIAL CYTOLOGIC DIAGNOSIS IN RESECTED NON-SMALL CELL LUNG CARCINOMA (NSCLC): IMPLICATIONS FOR THERAPEUTIC DECISION-MAKING IN ADVANCED/ METASTATIC DISEASE

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Background: The medical management of NSCLC has evolved with the emergence of targeted biological agents targeting specific activating gene mutations, the increasing recognition of a treatment-by-histology interaction (different chemotherapy regimens show differential activity for adenocarcinoma (adenoCa) v Squamous cell (SCC)). The majority of NSCLC cases are metastatic, so accurate initial cytologic diagnosis for histo-type is extremely important in guiding chemotherapy options and for selecting patients for mutational testing for targeted agents. We aimed to evaluate the accuracy of initial diagnostic cytology in predicting final histology in resected NSCLC.
Methods: The primary objective was to determine the diagnostic agreement (concordance-by kappa (k) score) between cytologic diagnosis and the gold standard of histology in resected NSCLC specimens. Secondary objectives included examining concordance by method of obtaining cytology, determining the sensitivity and specificity of community cytology for final histology subtype and examining the diagnostic accuracy of the original cytologic diagnosis, the impact of immunohistochemistry and inter-observer agreement using two blinded lung cancer pathologists. The design was a retrospective cross-sectional analytic study of patients with resected NSCLC. Cases from a metropolitan hospital campus were identified using surgical log books in the period 2009 – 10. The initial analysis was undertaken using the original cytologic and histologic reports. Other information was obtained by chart review.
Results: Fifty seven cases were identified: 23 male, 34 female. Median age was 69 years (range 44-87). Cytologic diagnosis was obtained by CT-FNA (fine needle aspiration) in 46 (81%), bronchoscopy in 9 (16%) and endobronchial ultrasound (EBUS) in 2 (3%). NSCLC subtypes by cytology were: 20 (35%) adenoCa, 9 (16%) SCC, 23 (40%) large cell, 3 (5%) mixed, 1 sarcomatoid and 1 bronchoalveolar carcinoma (BAC). By histology, final subtypes were: 30 (55%) adenoCa, 11 (19%) SCC, 5 (9%) large cell and 7 (12%) mixed. Pathologic staging included Stages: IA 11 (19%), IB 15 (26%), IIA 9 (16%), IIB 9 (16%), IIIA 12 (21%) and IIIB 1 (2%). In the primary analysis of cytology v final histopathology, concordance was moderate at 58%, k = 0.43 (95% CI 0.26-0.61). For cytology obtained by CT-FNA, concordance was 61% (k = 0.44, 95% CI 0.24-0.64), but for bronchoscopic cytologic diagnosis concordance was poorer at 44% (k = 0.15, 95% CI -0.35 – 0.65). Applying the results from the reports to 2x2 tables, for adenoCa, the sensitivity of cytologic diagnosis was 60%, specificity 78% with positive predictive value (PPV) of 78% and negative predictive value (NPV) of 61%; for SCC the sensitivity of cytologic diagnosis was 64%, specificity 95%, PPV 75% and NPV 92%; and for large cell carcinoma, the sensitivity of cytologic diagnosis was 80%, specificity 60%, PPV 17% and NPV 97%.
Conclusion: Routine cytologic diagnosis is associated with moderate agreement for histo-subtype, with CT-FNA superior to bronchoscopy in our setting. The PPVs of cytology for adenoCA and SCC were comparable and reasonable, but poor for large cell carcinoma. The NPV of cytology for SCC was very high. These findings may have implications for therapeutic decision-making. Results from blinded pathology review will be presented at the meeting.

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.178 DUTCH OBSERVATIONAL STUDY ON CHEMOTHERAPY-INDUCED ANAEMIA MANAGEMENT WITH EPOETIN ALFA (EPREX®) – SUB-ANALYSIS ON LUNG CANCER PATIENTS

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Background: The medical practice with Epoetin alfa (Eprex®) treatment (ET) for chemotherapy-induced anaemia (CIA) in the Netherlands was evaluated in an observational study; a pre-specified sub-analysis on 943 lung cancer patients (pts) enrolled from 2005-2009 is presented here. Objectives were safety and efficacy of ET.
Methods: Eligible pts were ≥18 years and diagnosed with a solid tumour, Multiple Myeloma or (non-) Hodgkin's disease for which chemotherapy (CT) was initiated. Data on haemoglobin level (Hb), blood transfusion (BT), CT, ET, iron status & supplementation and treatment-emergent adverse events (TEAE) (attribution upon investigator's assessment) were collected. Hb response to ET, not influenced by a transfusion within 28 days prior to reaching response, was defined in the protocol as ³1 g/dl Hb rise within first 4 weeks ET or ³2 g/dl Hb-rise from baseline or Hb within range 11–13 g/dl after 4 weeks of ET until end of study.
Results: Average age was 63.4±9.4 years, 57.8% were male and all pts started with 40.000IU ET once-weekly. Pts had NSCLC (71.7%), SCLC (24.6%) or mesothelioma (3.6%). The majority of pts had metastatic disease (58.1%) and received 3-weekly (98.6%), platinum-containing (91.3%) CT. ET predominantly started during the first 2 cycles of CT (74.5%). The mean duration of ET was 9.4 weeks (95% CI: 9.1-9.8). During CT, 21.1% of pts received iron supplementation (mostly oral). Transfusion-independent response to ET was reached in 51.8% of pts. ET started at an Hb of 10.84±1.14 g/dl (n=562) and resulted in a transfusion-independent Hb-rise of 0.01±1.61 g/dl after 28–35 days (n=478, NS) and 0.68±2.03 g/dl after 56–63 days (n=245, p<0.0001). Results for NSCLC and SCLC pts are shown in Table 1. TEAEs were causally related to ET in 1.3% of events. Thrombovascular TEAE's (TVE) occurred in 65 pts (6.9%); 12 events were assessed as having at least a possible causal relation to ET. On study 100 pts died, of which 66 were attributed to disease progression. Five reported TVE's resulted in death: cerebrovascular accident (3) and pulmonary embolism (2); none assessed to be causally related to ET.
Table 1. Results for NSCLC and SCLC sub-groups.

	NSCLC (n=676)		SCLC (n=232)	
BT independent response (%)	51.7%		50.2%	
Hb at ET start (g/dl)	10.83 ± 1.16	(n=395)	10.83 ± 1.02	(n=147)
Hb increase after 28-35 days (g/dl)	0.01 ± 1.59	(n=334, NS)	-0.04 ± 1.65	(n=127, NS)
Hb increase after 56-63 days (g/dl)	0.77 ± 2.05	(n=169, p<.0001)	0.31 ± 1.97	(n=65, NS)
ET duration (wks)	9.4 (95% CI: 8.9-9.8)		9.6 (95% CI: 9.0-10.1)	
BT beyond 4 wks of ET (%)	15.4%		22.4%	

Conclusion: Results show that ET generally started according to CIA treatment guidelines and is an effective treatment of CIA in lung cancer patients. Differences seen between NSCL and SCLC patients in terms of Hb-response and BT could be caused by differences in disease characteristics and treatment for SCLC and NSCL. TEAEs seem in line with current label for epoetin alfa.
Keywords: anemia management, epoetin alfa, Lung cancer

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P4.179 MDM2 SNP309 IS ASSOCIATED WITH THE CIGARETTE SMOKING QUANTITY IN EGFR WILD-TYPE ADENOCARCINOMA OF THE LUNG

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Background: Cigarette smoking is a well-known risk factor of lung cancer, inducing DNA damage and oncogene activation. The tumor suppressor protein p53 plays a crucial role in the prevention of cancer formation through DNA repair, cell cycle arrest and apoptosis. The murine double minute-2 protein

(MDM2) is a central node in the p53 pathway and a direct negative regulator of p53. A functional single nucleotide polymorphism (SNP309, T to G change at the 309th nucleotide in the first intron, rs2279744) in the promoter region of MDM2 has been shown to increase the affinity of the transcriptional activator Sp1, resulting in the subsequent attenuation of the p53 pathway. This SNP was reported to be associated with carcinogenesis of non-small-cell lung cancer (NSCLC) and G/G genotype was reported to be a higher risk of NSCLC, especially in smoker. Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that plays a crucial role in cell proliferation. EGFR mutations are less frequent in adenocarcinomas associated with smoking, unlike p53 mutations, suggesting distinct molecular genetic pathways underlying lung carcinogenesis in patients with different tobacco exposures. However, little has been studied about the relation for MDM2 SNP309 and EGFR mutations. In this study, we analyzed the association of genetic polymorphisms of MDM2, cumulative cigarette smoking and EGFR mutations in patients with adenocarcinoma of the lung.
Methods: Among the adenocarcinoma of the lung resected at Gunma university hospital in the period between June 2003 and May 2008, 146 cases were registered. Genomic DNA was extracted from peripheral blood lymphocytes according to standard procedures. PCR and RFLP analysis were used to genotype the T/G MDM2 SNP309 polymorphism. Mutations of EGFR in exon 19 and 21 were detected using a smart-amplification process (Smart Amp) method.
Results: There were 83 females and 63 males and the mean age was 66 years. There were 67 ever smokers (35 current and 32 former smokers) and 79 never smokers. The average values of pack-years are 19.6 among all cases and 42.7 among ever smokers. The genotype distributions of the MDM2 polymorphisms are as follows; T/T: 28 cases (19.2 %), T/G: 73 (50%), G/G: 45 (30.8%). No significant associations were found between MDM2 genotypes and clinical factors including age, gender, smoking status, pack-year, and EGFR mutational status. In the cases with wild-type EGFR, pack-year was significantly lower in G/G and T/G than T/T genotype (G/G vs T/T: p = 0.019, T/G vs T/T: p=0.015), while in the cases with EGFR mutation no significant difference was detected.
Conclusion: In summary, our findings indicate that the cases with G/G or T/G type of MDM2 SNP309 will easily develop wild-type EGFR adenocarcinoma by less amount of cigarettes than the cases with T/T type in Japanese population. This is the first report to analyze the association between genotypes of MDM2 SNP309 and EGFR mutational status in lung adenocarcinoma.
Keywords: MDM2, Adenocarcinoma, EGFR, cigarette smoking

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Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.180 DIAGNOSTIC VALUE OF CAIX PROTEIN LEVEL IN MALIGNANT PLEURAL EFFUSIONS BY ENZYME-LINKED IMMUNOSORBENT ASSAY

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Background: Conventional cytology for the detection of malignant cells in pleural effusion is the most specific routine diagnostic method, however its sensitivity of 50-60% is insufficient. Most cancer cells produce energy by aerobic glycolysis, which gives rise to increased acid production. Carbonic anhydrase IX (CAIX), a transmembrane glycoprotein, catalyzes the reversible hydration of carbonic dioxide to carbonic acid and functions in regulating pH and eliminating the acid load in cancer cells. CAIX is undetectable in most normal epithelial tissues and benign epithelial tumors but is overexpressed in many cancers, including lung, breast, stomach and colon. The aim of the present study was to evaluate the utility of CAIX protein level for differentiating benign and malignant pleural effusions.
Methods: A total of 131 pleural effusions including 56 benign effusions, 42 probable malignant effusions and 33 malignant effusions according to the cytological diagnosis and etiology, were subjected to detect CAIX protein level by enzyme-linked immunosorbent assay (ELISA).
Results: The mean level of CAIX was significantly higher in malignant effusions (18019.2 pg/dL) than probable effusion (1712.7 pg/dL) and benign effusion (555.7 pg/dL) (p0.05). Using cutoff values of 2000 pg/dL, the sensitivity and specificity were 63.6% and 94.6% in differentiating malignant and

benign effusions. The area under Receiver Operating Characteristic (ROC) curve was 0.775.
Conclusion: Detection of CAIX protein level by ELISA might be a complementary tool for the detection of malignant pleural effusions.
Keywords: Carbonic anhydrase IX, Pleural effusion, ELISA, cytology

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P4.181 THE ROLE OF EGFR AND KRAS MUTATION IN THE PROGRESSION OF NON-MUCINOUS LUNG ADENOCARCINOMA FROM AIS TO MIA AND ADC

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Background: Progression of non-mucinous lung adenocarcinoma from in situ (AIS) to minimally invasive (MIA) and then invasive adenocarcinoma (ADC) is associated with molecular genetic alteration. EGFR is a smoking-independent form of carcinogenesis, whereas KRAS is a smoking-dependent form of carcinogenesis. Smoking history, gender and ethnicity affect the EGFR and KRAS mutations. This study investigated the different roles of EGFR and KRAS mutations in the progression of non-mucinous lung adenocarcinoma from AIS to MIA and ADC.
Methods: Between April 2007 and March 2010, 147 patients with non-mucinous lung adenocarcinoma underwent resection at our institute. These patients were divided into four histologic grades: 1. AIS (n=13); 2. MIA (n=16); 3. Negative for ADC-related factors (absence of any lymphatic, vascular, pleural or nodal invasion, n=29); 4. Positive for ADC-related factors (the remaining adenocarcinomas, n=89). The EGFR mutational status and differences in smoking history, gender and elastosis in the lepidic septa during the progression from AIS to MIA and ADC were evaluated.
Results: EGFR mutations became increasingly pronounced in the progression from AIS to ADC in females (59/83, 71%), and were especially high in those who had never smoked or were light smokers (50/66, 76%). The mutational status of exon 21 point mutation was dominant over exon 19 deletion and both mutational spots increased proportionally from AIS to ADC. In males, EGFR mutations were found in 38% (25/65). Among males with EGFR mutations, there were fewer subjects who had never smoked or were light smokers (7/64) compared to the number of smokers (18/64). EGFR wild type was strongly represented in the group that was positive for ADC-related factors (44/63, 70%), and was especially high among male smokers (36/43, 84%), but was apparently limited during progression from AIS to lesions that were negative for ADC-related factors. Moderate stromal elastosis was detected in 94% of those showing EGFR mutations, and 49% of those showing EGFR wild type. Compared to the group that was positive for ADC-related factors, the prevalence of moderate stromal elastosis was high in the group showing EGFR mutations (89%), but limited in those showing EGFR wild type (34%), and severely limited in smokers (25%). KRAS mutation was detected in 14% (9/63) of those with EGFR wild type and these patients were male dominant (8/9) and were all smokers showing codon 12 mutational status. In patients with KRAS mutation, 78% were positive for ADC-related factors and 67% showed no or mild stromal elastosis.
Conclusion: EGFR mutation-related adenocarcinoma progressed from AIS to ADC in specific mutational-status order and was accompanied by moderate stromal elastosis. EGFR wild type adenocarcinoma mostly showed progression of stromal invasion with no or mild elastosis, especially in male smokers. KRAS mutation may play a limited role in EGFR-wild type non-mucinous adenocarcinoma in East Asia.
Keywords: stromal elastosis, EGFR mutation, KRAS mutation

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P4.182 DETECTION OF HUMAN PAPILLOMAVIRUS (HPV) GENOTYPES IN BRONCHIAL CANCER USING SENSITIVE MULTIMETRIX HPV-GENOTYPING TECHNIQUE

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Background: Bronchial carcinoma consists a major disease burden worldwide, showing increasing trends particularly among women in many societies. Epidemiological and experimental data suggest that cigarette smoke, radiation, and asbestos exposure are the prime etiological agents of this malignancy. Following the primary report in 1979 (by the senior author), evidence for the involvement of human papillomavirus (HPV) in bronchial carcinogenesis has accumulated through several lines of research: 1) HPV DNA has been detected in around 50% of benign bronchial squamous cell papillomas (SCP); 2) detection of morphological changes suggesting HPV in bronchial cancer and its precursors on light microscopy; 3) expression of HPV structural proteins by immunohistochemistry; 4) detection of HPV DNA by different hybridization assays and PCR in around 20% of bronchial carcinomas analyzed in almost 100 published studies; and 5) in vitro studies, i.e., transformation of bronchial epithelial cells by oncogenic HPV types. The causal role of HPV in bronchial carcinogenesis still remains controversial, however, and more data are needed particularly on the genotype distribution and cofactors of HPV in this process.
Methods: The present series consists of 93 consecutive non-small cell lung cancer patients treated with chemotherapy at the Department of Respiratory Medicine, Turku University Hospital, (Finland) during 2008-2010. Diagnosis of bronchial cancer was confirmed using cytology, bronchoscopic biopsy or operative biopsy. All available histological samples (n=77) were subjected to HPV genotyping with Luminex-based Multimetrix kit (Progen Biotechnik GmbH, Heidelberg, Germany), detecting 24 LR- (low-risk) and HR- (high-risk) HPV-types. HPV data were correlated with clinico-pathological variables in univariate and multivariate regression models to disclose eventual cofactors of HPV in bronchial carcinogenesis
Results: Of the 77 histological samples analysed, 4 (5.2%) were shown to contain HPV DNA. Of these 4, three represented single-type infections by HPV16, while one was double-infection by HPV6 and HPV16. All 4 patients were males, all were smokers (30 pack years by all), and all but one reported asbestos exposure in his occupation. Patients with HPV-positive tumors were significantly (>11 years) older than their HPV-negative counterparts (p=0.012, Mann-Whitney). In univariate analysis, none of the other clinical variables were significant predictors of HPV. When analysed in multivariate logistic regression model (with following variables entered: age, gender, smoking history, pack years, asbestos exposure), the only significant determinant of HPV-positivity was pack year, with OR=0.94, 95%CI 0.88-0.99, p=0.045.
Conclusion: Less pack years (30.0 vs. 37.3) being associated with HPV, despite the older age of the patients, it is tempting to speculate that oncogenic HPV can substitute a part of the smoking exposure in bronchial carcinogenesis. HPV prevalence of 5.2% reported in the present series closely parallels the data from a recent meta-analysis, where HPV prevalence levelled off at 5% (C.Peters, unpublished). This is a substantially lower figure than directly counted from the published world literature in 2002; i.e., 21.7% , 536/2468 (J. Clin. Pathol. 2002;55:885-891). In the era of prophylactic HPV vaccination, there is an urgent need to provide more data on the role of HPV in these implicated HPV-associated neoplasia at non-genital sites, bronchial cancer in particular.
Keywords: Lung cancer, human papillomavirus

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P4.183 PROGNOSTIC VALUE OF VISCERAL PLEURAL INVASION IN THE NEW TNM CLASSIFICATION OF NON-SMALL CELL LUNG CANCER

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Background: Visceral pleural invasion (VPI) is a poor prognostic factor in lung cancer. Possible VPI tumor cell pathways include the subpleural lymphatics and hilar lymph nodes into the mediastinal lymph nodes. Tumors ≤ 3 cm with P1 were classified as T1 in the previous Japan Lung Cancer Society classification, but in the new TNM classification (7th Edition) tumors with PL1 or PL2 are upgraded to T2a.
Methods: We retrospectively reviewed 1023 patients (617 men, 406 women, mean age 64.8,

median follow-up 47.1 months) with pathologically confirmed T1a-T3 non-small cell lung cancer (NSCLC) who underwent complete resection of a minimum of lobectomy with lymphadenectomy between 2000 and 2007. There were 736 patients with adenocarcinoma, 212 with squamous cell carcinoma, 54 with large cell carcinoma and 21 with other cancer types. We assessed their prognostic factors based on the new classification and examined their suitability.

Results: Patients at various stages determined using the new staging system comprised IA, 432; IB, 283; IIA, 126; IIB, 56; IIIA, 126. Patients in the T classification using the new staging system comprised T1, 562; T2, 408; T3, 46; T4, 7; T1a, 291; T1b, 207; T2a, 403; T2b, 56; T3, 66. Patients in the N category in the previous system comprised N0, 787; N1, 123; N2, 113. Those in the PL category using the new system comprised PL0, 751; PL1, 145; PL2, 75; PL3, 52. The 5-year survival rate according to the degree of VPI (tumor size ≤ 3 cm) was 82.9% in PL0 (n = 498), 68.4% in PL1 (n = 76), and 62.6% in PL2 (n = 28; PL0 vs. PL1/2, p = 0.01). The 5-year survival rate (tumor size 3-5 cm) was 73.4% in PL0 (n = 217), 68.4% in PL1 (n = 49), and 49.3% in PL0 vs. PL1/2 (n = 31; p = 0.001). The 5-year survival rate was 66.7% in tumors ≤ 3 cm in PL1-2, and 69.5% in tumors between 3 and 5 cm in PL0-2 (p = 0.42). The 5-year survival rate (tumor size 5-7 cm) was 44.7% in PL0 (n = 31), 36.6% in PL1 (n = 16), and 20.8% (n = 9; PL0 vs. PL1 vs. PL2, p = not significant). Tumor size, vascular invasion, lymph node involvement and VPI were significant prognostic factors on multivariate analysis.

	Univariate P value	Multivariate P value	Hazard Ratio	95 % CI
Sex (Women vs. Men)	<0.0001	0.052	0.75	0.55-1.00
Tumor size (≤ 3cm vs. > 3cm)	<0.0001	0.01	0.70	0.53-0.93
Vascular invasion (v- vs. v+)	<0.0001	<0.0001	0.48	0.34-0.68
Lymphatic invasion (ly- vs. ly+)	<0.0001	0.92	0.98	0.69-1.39
Histological type (Non-SCC vs. SCC) SCC: Squamous cell carcinoma	<0.0001	0.23	0.83	0.62-1.12
Pathologic N status (N0 vs. N1-2)	<0.0001	<0.0001	0.47	0.36-0.64
Visceral pleural invasion (pl0 vs. pl1-3)	<0.0001	0.02	0.71	0.54-0.95

Conclusion: Tumors ≤ 3 cm with PL1 are correctly classified as T2a. VPI is an independent prognostic factor in NSCLC.

Keywords: Visceral Pleural Invasion, Non-small cell lung cancer, TNM classification

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P4.184 CORRELATION BETWEEN ENVIRONMENTAL TOBACCO SMOKE (ETS) EXPOSURE AND ANAPLASTIC LYMPHOMA KINASE (ALK) RE-ARRANGEMENT POSITIVE NSCLC PATIENTS WHO ARE NEVER-SMOKERS

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Background: Anaplastic lymphoma kinase (ALK) re-arrangement positive NSCLC patients are generally never-smokers similar to patients with epidermal growth factor receptor (EGFR) activation mutations. However, the correlation between environmental tobacco smoke (ETS) exposure and the occurrence of ALK re-arrangement in NSCLC patients who are never-smokers is unknown.

Methods: ALK re-arrangement positive NSCLC patients who screened positive (FISH, RT-PCR) on one of the 3 crizotinib trials (A8081001, A8081005, A8081007) and who are never-smokers (< 100 cigarettes lifetime) were given detailed questionnaire about ETS. Cumulative ETS were tabulated and divided into childhood, adult, home, and work exposure.

Results: 29 ALK re-arrangement positive NSCLC patients were identified through screening. 26 were never-smokers and detailed ETS were available from 25 patients (14 females, 11 males) (18 US-born, 7 foreign-born). All 25 ALK re-arrangement positive NSCLC patients have wildtype EGFR. The mean age of all patients was 49.6 years (range; 31-80). 8 patients (32%) had no cETS. The mean cETS (total years exposed) were: 16.5 years (total), 6.9 years (childhood), 9.6 years (adult), 11.3 years (home), and 5.2 years (work) respectively. ALK positive patients with no cETS were generally younger than ALK positive patients with any cETS. The mean age of patients who had no cETS was 45.3 years compared to mean age of 51.6 years for patients with any cETS (p = 0.1367) and is independent of source of exposure: childhood ETS (45.9 yo [no] versus 53.6 yo [yes], p = 0.0965); adult ETS (46.3 yo [no] versus 53.2 yo [yes], p = 0.1646), home ETS (45.3

yo [no] versus 53.0 yo [yes], p = 0.0999); and work ETS (48.3 yo [no] versus 51.9 yo [yes], p = 0.3493). Foreign-born ALK positive patients were generally younger than US-born ALK positive patients (45.9 years vs. 51.1 years; p = 0.6276). The mean cETS for foreign-born ALK psoitive patients was lower than US-born ALK positive patients (11 years vs. 18.6 years; p = 0.4599) and is independent of source of exposure except work exposure where US-born ALK positive patients had lower exposure: childhood (5.0 years vs. 7.6 years; p = 0.3266), adult (6.0 years vs. 11 years; p = 0.6477), home (5.0 years vs. 13.8 years; p = 0.2052), and work (6.0 years vs. 4.8 years; p = 0.7513).

Conclusion: ALK re-arrangement positive NSCLC patients who were never-smokers had low cETS. 32% of the ALK re-arrangement positive NSCLC patients who are never-smokers in our series at the University of California Irvine had no cETS. ALK re-arrangement positive NSCLC patients who had no ETS tend to be younger than their counterparts who had any ETS regardless of source of exposure. Foreign-born *ALK* positive patients had lower cETS than US-born *ALK* positive patients and is independent of exposure source except work exposure where US-born *ALK* positive patients had lower cETS exposure at work. Comparison of cETS between ALK positive NSCLC patients and cumulative cETS in activating EGFR mutations positive patients is ongoing.

Keywords: environmental tobacco exposure, ALK re-arranged NSCLC

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P4.185 DIFFERENT EXPRESSION OF EZH2 BMI-1 AND KI67 IN LOW AND HIGH GRADE NEUROENDOCRINE TUMORS OF THE LUNG

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Background: The polycomb group genes Enhancer of Zeste homolog 2 (EZH2) and B lymphoma Mo-MLV insertion region 1 polycomb ring finger (BMI1) function as transcriptional repressors and are involved in the malignant transformation and biologic aggressiveness of many human carcinomas. However, the expression pattern and biological role of these genes in neuroendocrine tumours of the lung (NELT) is largely unknown. In the current study, expression levels of EZH2 and BMI1 were evaluated in a large panel of NELT, and data were correlated to Ki67-expression and clinical features including survival.

Methods: A tissue panel comprising 96 resected NELT (50 typical carcinoids (TC), 13 atypical carcinoids (AC), 23 large cell neuroendocrine carcinomas (LCNEC) and 10 small cell lung carcinomas (SCLC)) was assessed by immunohistochemisty using monoclonal antibodies against EZH2 and BMI1 and scored semi quantitatively for the percentage and intensity of tumour cells stained on whole tumour slides. The correlation of the scores to clinical data was analysed.

Results: High expression of EZH2 was found in high grade NELT (LCNEC + SCLC), whereas high expression of BMI1 was observed in low grade NELT (TC + AC) ($p < 0.0001$ for EZH2, $p = 0.02$ for BMI1). TC fell into two groups of either high expression of BMI1 or no expression. A correlation between the expression of EZH2 and Ki67 was observed ($R^2 = 0.49$, $p< 0.001$)). In univariate analyses EZH2 and BMI1 were predictors for survival in all patients ($p < 0.0001$ for EZH2, $p = 0.02$ for BMI1, whereas multivariate analyses revealed TNM stage ($p < 0.001$) and diagnosis ($p < 0.001$) as the only independent predictors of overall survival.

Conclusion: The EZH2 and BMI1 expression pattern as measured by immunohistochemistry is significantly different in low versus high grade NELT. This difference might relate to NELT tumourigenesis. The markers have no independent prognostic impact in NELT. Whether EZH2 and BMI1 could be target molecules for the development of new treatments strategies against NELT remains to be elucidated.

Keywords: EZH2, BMI1, pulmonary neuroendocrine tumours, immunohistochemistry

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.186 REPRODUCIBILITY OF CYTOPATHOLOGIC DIAGNOSES WITH MGG STAINED SMEAR AND CYTOSCRAPE FROM FINE NEEDLE ASPIRATES WITH EMPHASIS ON SUB TYPING OF NON-SMALL CELL LUNG CANCER.

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Background: Cytologic examination of fine-needle aspiration (FNA) material is being increasingly used in the diagnosis of non-small cell lung cancer (NSCLC). New treatment modalities make a reproducible subdivision of NSCLC necessary. A high interobserver agreement in the distinction between small-cell lung cancer and NSCLC on cytologic material has been demonstrated, but the distinction between subgroups of NSCLC is difficult based on cytological criteria only. A clot made directly from the aspirated material has been shown efficient for immunohistochemical staining. However, sometimes the aspirated material is too sparse to make a clot and in these cases a new method called cytoscrape makes it possible to convert cytological material into tissue fragment useful for immunohistochemistry.
Methods: A consecutive series of MGG stained smears and cytoscrape from FNA from 79 patients with a possible malignant pulmonary infiltrate or metastasis to lymph nodes or liver seen on CT or PET of the chest/abdomen were included. Cytoscrape material was obtained by gently scraping cells from one slide pr case. Cytoscrape clots were made and the sections were stained with H&E and a relevant panel of immunohistochemical antibodies. These clots are often tiny, and the panel of immunohistochemical staining must be carefully selected with respect to the morphological changes on the smear and the clinical history. This was done by an experienced cytopathologist not included in the reproducibility part of the study. One smear together with the immunohistochemical stained cytoscrape slides were circulated 2 times (with minimally 2 months between the rounds) to a panel of 4 pathologists (3 of the observers were experienced cyto/histopathologists and one was inexperienced). . The inexperienced observer was chosen to assess the influence of experience and to evaluate the learning curve between the two rounds. The cytopathologists were asked to make a diagnosis on each case based on the MGG stained slide and the cytoscrape. For statistical purposes the diagnoses were categorized in 5 groups: squamous cell carcinoma, adenocarcinoma of the lung, non-squamous cell carcinoma, benign lesion and malignancy other than the former including metastases from other organs. Kappa statistics was applied to test the intra- and inter observer reproducibility.
Results: The reproducibility of the diagnoses in the first round was good to very good (kappa 0.57 - 0.71). One value was under 0.60 and involved the inexperienced observer. We are waiting for the results of round two where the intraobserver-reproducibility and the effect of the teaching session will also be presented.
Conclusion: The reproducibility of cytopathologic diagnoses with only one MGG stained smear and immunohistochemistry on cytoscrape from FNA was very good among experienced cytopathologists. When only sparse material from FNA is available without the possibility to make a clot directly from the aspirate, cytoscrape is a new method to achieve material for immunohistochemistry, useful for making clinical relevant diagnoses, including sub typing of non-small cell lung cancer.
Keywords: cytology, Fine needle aspiration, reproducibility, immunohistochemistry

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P4.187 THE ASSOCIATION OF TOPOISOMERASE 2α EXPRESSION WITH CLINICAL, PATHOLOGICAL PARAMETERS AND PROGOSIS IN SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: Topoisomerase 2α is a nuclear enzyme that alters the topology of DNA. It's essential for normal chromosome segregation during cellular division. It's also a molecular target for some antineoplastic drugs. In this study, we aimed to investigate the association of topoisomerase 2α expression with clinical, pathological parameters and prognosis in surgically resected non-small cell lung cancer (NSCLC) patients.
Methods: The study comprised of 100 NSCLC patients (91 male/ 9 female) with a mean age of 59.7±10.5 years (range 37-78). Patients underwent lobectomy (82%) or pneumonectomy (18%) with hilar and mediastinal lymph node sampling. Histopathological diagnosis was squamous cell carcinoma and adenocarcinoma in 50 patients each. There were 5 patients with stage 1a, 28 patients with stage 1b, 21 patients with stage 2a, 21 patients with stage 2b, 25 patients with stage 3a. The paraffin embedded tumor sections of these pateints were retrieved for expression of topoisomerase 2α. Nuclear (positive/ negative) and cytoplasmic (weak/ moderate/ intense) expression of topoisomerase 2α were determined by immunohistochemistry. Clinical, pathological data and survival of patients were determined from the hospital files. Median follow-up time was 35 (range:4-120) months.
Results: Nuclear expression of topoisomerase 2α was positive in 41 (41%) patients. Cytoplasmic expression of topoisomerase 2α positive in 66 (66%) patients. There were not any significant association between nuclear or cytoplasmic expression of topoisomerase 2α and age, gender, smoking history (p>0.05). While cytoplasmic expression of topoisomerase 2α was not different, nuclear expression was significantly increased in squamous cell carcinoma (p=0.008), OR (95%CI): 3.01 (1.31-6.92). Both nuclear and cytoplasmic expression of topoisomerase 2α did not show any association with tumor diameter, pathological stage, tumor differentiation and presence of relapse. There wasn't any significant association between nuclear or cytoplasmic expression of topoisomerase 2α and survival (p>0.05). Tumor diameter (p=0.031) and involvement of N2 lymph nodes (p=0.005) were independent prognostic factors.
Conclusion: In conclusion there was no association between topoisomerase 2α expression and survival in surgically resected NSCLC patients. Nuclear expression of topoisomerase 2α was significantly higher in patients with squamous cell carcinoma.
Keywords: Non-small cell lung cancer, topoisomerase 2α, Prognosis

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P4.188 THE STATE OF PATHOLOGY EXAMINATIONS AFTER RESECTION OF LUNG CANCER: A TREND ANALYSIS BEFORE AND AFTER QUALITY IMPROVEMENT INTERVENTIONS AND SUMMARY OF ONGOING PROBLEMS.

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Background: Pathology findings after lung resection guides post-operative management of lung cancer. The College of American Pathologists (CAP) developed a checklist of mandatory report items as a quality improvement effort. Our previous analysis of a 2004-2007 Memphis lung resection cohort revealed major reporting problems: <5% contained all the mandatory CAP items; 34% failed to report 6 crucial items, including pT and pN category; when reported, we found inaccuracies in nodal staging, for example 15% of reported pN1 cases were actually pN2; 12% of reports had no information on lymph nodes (pNx). We have shown that patients with pNx have a significantly inferior long-term survival than T-category matched patients with pN0. Because examination of N1 nodes is primarily the pathologist's responsibility, the proportion of lung resection cases with no N1 lymph nodes is a pathology quality measure. We discussed our findings with regional pathologists and hospital Cancer Committees in 2008. Quality improvement efforts were recommended, including the use of report templates and synoptic reports. Here we report a preliminary analysis of the early impact of these interventions.

Methods: Retrospective study of pathology reports for all lung cancer resections in the Memphis Metropolitan Area from January 1, 2004 to December 31, 2009. We compared the comprehensiveness of pathology reports in two eras, pre-intervention (2004-2008) and post-intervention (2009), by the chi-squared test.
Results: There were pathology reports from 9 hospitals. Reportage on specific mandatory CAP items was highly variable (Table). Reportage on all CAP items increased significantly from 5.4% in the pre-intervention era to 15.4% in the post-intervention era ($p<0.0001$); reportage on the six crucial items (denoted by * in table) also increased from 61% to 83.2% ($p<0.0001$). When reported, the overall error rate in TNM staging was 7.6%. Under-staging errors were four times more common than over-staging errors, for example 8.1% of pN1 cases were more correctly staged as pN2. Nineteen percent of resections had no examined N1 lymph nodes; after elimination of sub-lobar resections (because submitted material may have had no intrapulmonary lymph nodes) the N1 lymph node examination failure rate was still 11%.

CAP Checklist Item	Reported, N (%)	Not Reported, N (%)
Reported at high frequency		
Specimen type (extent of resection)*	1346 (100)	0 (0)
Laterality	1344 (99.9)	2 (0.2)
Histologic type*	1344 (99.9)	2 (0.2)
Margin status*	1316 (97.8)	30 (2.2)
Tumor site (ie lobe)	1310 (97.3)	36 (2.7)
Tumor size*	1309 (97.3)	37 (2.8)
Direct extension	1277 (94.9)	69 (5.1)
Reported at intermediate frequency		
Histologic grade	1115 (82.8)	231 (17.2)
pM-category	1040 (77.3)	306 (22.7)
Margin distance	945 (70.2)	401 (29.8)
pT-category*	923 (68.6)	423 (31.4)
pN-category*	904 (67.2)	442 (32.8)
Reported at low frequency		
Lymphatic invasion	602 (44.7)	744 (55.3)
Large vessel invasion	382 (28.4)	964 (71.6)

Conclusion: Corrective interventions are producing early improvement in the completeness of pathology reports. Major problems remain, including a relatively high rate of failure to examine intrapulmonary lymph nodes. Wider adoption of the template reporting system should improve the quality and accuracy of reports. The need for continuing quality improvement measures remains.
Keywords: quality of care, Pathology reports, Staging, CAP checklist items

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P4.189 PATHOLOGICAL PROGNOSTIC FACTORS OF NON-SMALL CELL LUNG CANCER PATIENTS WITH MULTIPLE LUNG TUMORS

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Background: In patients with multiple lung cancers, distinction of intrapulmonary metastasis and independent primary tumors is clinically important because it determines staging, prognosis and potentially treatment plan. However, the distinction is difficult on routine histopathologic practice, and often requires a series of molecular test for clonality analysis. We studied histopathologic prognostic factors of multiple lung cancer patients, which potentially substitute Martini and Melamed criteria and the complex process of the differential diagnosis of intrapulmonary metastasis and independent primary tumors.
Methods: With 65 patients having multiple lung cancers, we analyzed patients' survival according to clinicopathologic parameters, including histologic subtypes, size difference between paired tumors, location of paired tumors, presence of lymphovascular tumor invasion, size of the largest tumor, lymph node status, and morphology of tumor margin, and immunohistochemical stainings profile of each tumor.
Results: The mean survivals of the 18 multiple primary lung cancer patients and the 47 intrapulmonary metastasis patients based on Martini and Melamed criteria were 53.0±7.4 and 91.0±11.1 months, respectively ($p=0.654$), suggesting Martini-Melamed criteria alone is insufficient to predict the prognosis. There were no significant associations between the each clinicopathologic parameter and the mean survival, except for the size of the largest tumor. We evaluated 5 clinicopathologic parameters (presence of lymphovascular invasion, presence of pushing margin, size difference between paired tumors, lobar location of paired tumors, and size of the largest tumor over 5cm in diameter) and devided into two groups, having at least three of five parameters and less than three parameters and the mean survivals were 49.5±10.9 and 111.5±9.3 months, respectively ($p=0.010$). Also we evaluated 4 histologic parameters, excluding size of the largest tumor, known independent prognostic factor, and

devided into two groups, having at least three of four parameters and less than three parameters and the mean survivals were 49.7±12.4 and 104.0±10.6 months, respectively (p=0.017). And this grouped 4 parameter was identified as an independent prognostic factor in the patients with 5cm and less in size of the largest mass (p=0.022). The differences of immunohistochemical staining results of the paired tumor were not relevant with the mean survivals (p=0.174).
Conclusion: Having at least three parameters among the presence of LVI, pushing margin without peripheral lepidic pattern, size differences over 80% between paired tumors, and different lobar location of the paired tumors could be considered as an independent prognostic factor of multiple lung cancer patients with 5cm and less in diameter (size of the T2a stage) of the largest mass.
Keywords: multiple lung cancers, Martini-Melamed criteria, clinicopathologic parameters, prognostic factors

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P4.190 DIAGNOSIS ON FINE NEEDLE ASPIRATION WITH SPARSE MATERIAL: HIGH DIAGNOSTIC INFORMATION OF CK5/6 AND TTF1 ON CYTOSCRAPE IN THE DIAGNOSIS OF SMALL CELL LUNG CANCER AND SQUAMOUS CELL CARCINOMA

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Background: Cytologic examination of fine-needle aspirations (FNA) from the lung and lymph nodes in the mediastinum is used increasingly for the diagnosis of pulmonary lesions. Correct distinction between small cell lung carcinomas (SCLC) and non small cell lung cancer is of great therapeutic importance. SCLC and squamous cell carcinomas (SQCC) are often necrotic tumours and it may be difficult to separate these tumours on cytologic material. FNA often provides insufficient material to make a clot and is not always diagnostic on conventional smears. We describe a method, called cytoscrape (CS), which can be used for ancillary methods including immunohistochemistry. The aim of this study was 1) to assess the sensitivity and the specificity of thyroid transcription factor-1 (TTF1) and CK5/6 on CS as measured by immunohistochemistry in SCLC and SQCC and 2) to see if improved diagnostic information from FNA could be achieved when these markers were applied to CS and added to May-Grunwald-Giemsa (MGG) stained slides.
Methods: 78 tumours (63 SCLC and 15 (SQCC) from which FNA as well as histologic biopsies were available were randomly collected from archives. From each aspirate one MGG stained smear was processed to obtain a CS by scraping cells of the slides. Clots were made and sections were immunostained with TTF-1 and CK5/6 together with staining of the corresponding biopsies ("gold standard") with the same antibodies. No further immunohistochemical reactions were applied, as we wanted to see if only two well-tested antibodies applied to this scanty material could improve the diagnostic information. The utility of the CS technique was evaluated by assessing the sensitivity and specificity of the method and by quantifying improved diagnostic information relative to smear alone.
Results: SCLC: Sensitivity of TTF-1: 0.78 (95% CI 0.65-0.88). Specificity of TTF1: 0.80 (95% CI 0.28-1.00). Sensitivity of CK5/6: 0 (95% CI 0.00-0.71). Specificity of CK5/6: 0.97 (95% CI 0.88-1.00). SQCC: Sensitivity of TTF-1: 0 (95% CI 0.00-0.71). Specificity of TTF1: 1 (95% CI 0.74-1.00). Sensitivity of CK5/6: 0.71 (95% CI 0.42-0.92).). Specificity of CK5/6: 0 (95% CI 0.00-0.98). The diagnoses made on smears were improved by CS in 4 cases (5.1%), which could be classified as either SCLC or SQCC in contrast to "malignant tumor NOS" on MGG stained smear.
Conclusion: Even if only spare material is available, immunohistochemical staining with TTF1 and CK5/6 on CS allows distinction between SCLC and SQCC. For experienced pathologists, the improved diagnostic information from these markers is modest compared to MGG stained slides only. However, the immunohistochemistry on CS can confirm the diagnosis made on MGG stained smear in difficult cases. Whether the markers could improve diagnostic information in a clinically relevant way for less trained pathologists remains to be solved. If enough material is available from CS, a panel including more antibodies might further improve the diagnostic information.
Keywords: cytoscrape, immunohistochemistry, Fine needle aspiration, classification

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P4.191 CLINICOPATHOLOGICAL SIGNIFICANCE OF THE CIRCADIAN PROTEINS EXPRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: Most life on this planet has biological rhythms corresponding to cycle of the earth's rotation. In particular, physiological variables that occur in an approximately 24 hour cycle are called circadian rhythms. Circadian rhythms are controlled by the circadian clock mechanism. The molecular mechanism of circadian clock is based on the transcriptional feedback loops of core circadian genes, Clock, Bmal1, Period (Per1, 2, 3), Cryptochrome (Cry1, 2), and casein kinase I ε (CKIε). Recently, it has been reported that the circadian clock is related to oncogenesis. Bmal1 was shown to be a positive regulator of tumor growth and metastasis in cancer. Furthermore, because c-Myc expression was increased, the morbidity rate of cancer had risen in the Per2 knockout mouse. This study examined the relationship of circadian related protein, especially in Bmal1 and Per2, to clinicopathological factors and postoperative outcomes in patients with lung cancer.
Methods: A total of 78 consecutive patients with pathological stage I to III non-small cell lung cancer (NSCLC) were examined, retrospectively. The patients underwent complete tumor resection and nodal dissection without any pre-operative therapy. We evaluated the expression of the Bmal1 protein and the Per2 protein by immunohistochemistry. The staining intensity was evaluated as follows: grade 1, weak staining; grade 2, moderate stainig and grade 3, strong staining. We classified the samples categorized into grade1 intensity as the low expression group, irrespectively of the cell distribution. The others were classified as the high expression group.
Results: Of all the samples, 12 samples were classified as Bmal1-low, and the other 66 were classified as Bmal1-high. In like manner, 19 samples were classified as Per2-low, and the other 59 were classified as Per2-high. Expression of both proteins was not correlated with any clinicopathological factors. The 5-years overall survival of patients with low and high Bmal1 expression was 75% and 43%, respectively. On analysis of the relations between outcomes and circadian related proteins expression, high expression of Bmal1 protein was associated with significant worse outcomes than low expression of Bmal1 in stage I (p=0.024). Nevertheless, there was no significant differences between patients with Per2-high and low.
Conclusion: Circadian related protein Bmal1 expression was associated with outcomes of surgically resected stage I NSCLC patients.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.192 THE ROLE OF ELASTIC STAINS FOR PERIPHERAL LUNG CANCER: IS IT MANDATORY?

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Background: The 7th edition of the TNM classification for lung cancer has been adopted since 2009, and some revision including visceral pleural invasion (VPI) was made. VPI has been defined as invasion beyond the elastic layer and upstaged to T2, so the use of elastic stains is recommended to distinguish between pl0 and pl1. However, because elastic stains to assess VPI are not so commonly used by pathologists including our institution's, we investigated the role of elastic stains to evaluate VPI in comparison with conventional hematoxylin and eosin (H&E) stains.
Methods: From March 2010 to January 2011, 126 patients underwent pulmonary surgical resection for primary lung cancer at our institution. Of them, 69 tumors which were abut on the visceral pleura

or showed pleural indentations on preoperative computed tomography (CT) were re-evaluated using Elastic van Gieson stains after the judgement on H&E stains by pathologists.
Results: There were 51 adenocarcinomas, 11 squamous cell carcinomas, 5 adenosquamous carcinomas, and 2 large cell carcinomas. Our pathologists assessed 27 tumors at pl0, 28 at pl1, 10 at pl2, and 4 at pl3 by H&E stains, respectively. Under re-evaluations using EVG stains, 12 specimens were re-classified from pl1 to pl0 (false-pl1 group) and 1 from pl2 to pl1, whereas 12 tumors reconfirmed pl1 (true-pl1 group). Four specimens assessed as pl1 on H&E stains could not be evaluated for VPI because of inflammation. There were 11 adenocarcinomas (92%) and 1 adenosquamous carcinoma in false-pl1 group. In comparison between true- and false- pl1 groups, tumor size less than 2cm, ground glass opacity ratio more than 50% on preoperative CT, or well differentiation on pathological findings were preferable factors in false-pl1 group, whereas the finding of pleural indentation was not reliable to differentiate pl0 from pl1 (Table 1). Table 1. Relationship between pl0 and pl1 according to some factors

Factors		False-pl1 (pl0)	True-pl1	p value
Tumor size	0-2 cm	6	1	0.079
	2-3 cm	2	4	
	3- cm	4	7	
GGO ratio	100-75%	2	0	0.055
	75-50%	3	0	
	50-25%	2	1	
	25- 0%	5	11	
Pleural indentation	yes	7	5	0.414
	no	5	7	
Histology	AD	11	9	0.333
	AS	1	1	
	SQ	0	2	
Differentiation	well	2	0	0.144
	moderate	7	6	
	poor	1	4	

Conclusion: We conclude it is difficult to evaluate VPI and distinguish between pl0 and pl1 with H&E stains alone, especially in adenocarcinoma. Elastic stains and some factors might help the correct assessment for visceral pleural invasion in lung cancer.
Keyword: Visceral Pleural Invasion

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P4.193 ADEQUACY OF TISSUE OBTAINED BY SEMIRIGID PLEUROSCOPY

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Background: For investigation of undiagnosed exudative pleural effusion, the use of semirigid pleuroscopy is getting more popular among pulmonologists as the technique is similar to that of a flexible bronchoscope. Concerns have been raised for the smaller size biopsy samples obtained by semirigid pleuroscopy when compared with the rigid counterpart. However, it is unknown if the smaller biopsy size will affect the diagnostic performance.
Methods: From Dec 2008 to Oct 2010, all consecutive cases with undiagnosed exudative pleural effusion after nondiagnostic thoracentesis (with or without closed pleural biopsy) and referred for pleuroscopy were recruited. After obtaining written informed consent from the patients, semirigid pleuroscopy was performed in a bronchoscopy suite under local anaesthesia +/- conscious sedation. Efficacy was measured by diagnostic yield – tissue adequacy for immunohistochemical (IHC) staining including cytokeratin, CDX2, TTF-1, calretinin, EGFR and EBV-encoded RNA (EBER) analysis where appropriate in addition to microbiology. Talc poudrage was also performed in the same sitting if malignancy was suggested during the procedure. Complications would be recorded if there were any bleeding, postoperative fever, desaturation, re-expansion pulmonary oedema, infection related to the procedure, persistent air leak and mortality. All the procedures were performed by the same operator with initial experience in pleuroscopy.
Results: Fifteen patients (12 men) aged 63.9 (range 35-89) had pleuroscopy performed. Malignancy was confirmed in 11 patients (73.3%). Among those confirmed with malignancy, IHC was performed in all specimens. The results showed that there were 7 cases (46.7%) of adenocarcinoma with lung as primary origin; 2 cases (13.3%) of adenocarinoma with gastrointerestinal origin (13.3%); and 1 case each (6.7%) with metastasis from nasopharyngeal carcinoma or malignant mesothelioma. For those

specimens confirmed with lung cancer, tissues were all adequate (100%) for EGFR assessment. Mutations were found in Exon 19 or 21 in five patients and wild type in the remaining two patients. Talc poudrage was performed in nine patients during the same sitting of pleuroscopic examination and all of them were confirmed malignancy subsequently. All except two patients had complete control (no reaccumulation of fluid on X-ray) three months afterwards. Three patients were confirmed to have tuberculosis pleurisy. Only one patient received non-specific diagnosis after pleuroscopy. He remained asymptomatic with no recurrence of pleural effusion after a year of follow-up. The overall diagnostic yield was 93.3%, with the assumption that patient with no specific diagnosis was false negative. No complications were detected.
Conclusion: Semirigid pleuroscopy was found to have high diagnostic yield with adequate tissue showing the origin of malignancy and for EGFR analysis. It is a safe procedure and even suitable for operator with initial experience.
Keywords: Semirigid pleuroscopy, Lung cancer

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P4.194 COMPARISON BETWEEN EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS IN CYTOLOGY AND HISTOLOGY SAMPLES OF ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Somatic mutations in the epidermal growth factor receptor (EGFR) occur in ~10% of non-small cell lung cancer and are correlated with increased response to treatment with EGFR tyrosine kinase inhibitors (TKIs). Until now, most the studies required tumor tissue for mutation screening, because testing cytological samples can pose some problems, such as sparse cellularity or interference from non-malignant cells within the sample. The aim of this study was to determine whether or not cytology specimen obtained by bronchial lavage is suitable for EGFR mutation, in comparison with histology obtained by bronchial biopsy.
Methods: Over a period of 8 months, we performed diagnostic fiberoptic bronchoscopy in 61 consecutive patients with suspected lung cancer (based on clinical data, chest CT-scan and evidence of endobronchial lesion) and screened for EGFR mutations simultaneously in bronchial biopsy specimens and the corresponding bronchial lavage, performed right after the biopsy. Exons 18, 19, 20 and 21 of EGFR gene were analyzed using automated sequencing of tumor DNA. Patients with early stage disease (IIA and IIB, n=2), small cell lung cancer histology (n=8) and those with bronchial biopsy not conclusive for malignancy (n=18) were excluded. Four cases were also excluded for technical procedures reasons.
Results: A total of 29 non-Asian patients (24 male, 5 female) with advanced non-small cell lung cancer (24,1% on stage IIIB; 75,9% on stage IV) were included. Adenocarcinoma was the most frequent histological type (65,5%), followed by squamous cell carcinoma (27,6%). Twenty-five patients were current or past-smokers (median 40 pack-year) and 4 were non-smokers (all female patients). EGFR mutation was detected in 5 patients (17,2%), both in the bronchial biopsy specimens and the corresponding bronchial lavage. All these 5 patients with positive EGFR mutations (Table 1) had adenocarcinoma, being 4 female and 1 male and 40% were smokers. These five patients presented EGFR mutation predictive of response to EGFR TKIs. In the remaining 24 patients, EGFR mutation detection was negative in both bronchial biopsy and bronchial lavage. Table 1- Patients with EGFR mutations, in both bronchial lavage and bronchial biopsy

Patient	Age (years)	Gender	Smoking habits	Tumor Stage	Tumor Histology	Exon	EGFR Mutation
1	53	Male	15 PY	IIIB	Adenocarcinoma	20	Asn771_His773dup
2	77	Female	Nonsmoking	IV	Adenocarcinoma	21	Leu858Arg
3	77	Female	Nonsmoking	IV	Adenocarcinoma	19	Glu746_Ala750del
4	66	Female	30 PY	IV	Adenocarcinoma	21	Leu861Gln
5	70	Female	Nonsmoking	IV	Adenocarcinoma	19	Glu746_ala750del

PY: pack-year

Conclusion: This study suggests that both cytological sample from bronchial lavage and histological sample from bronchial biopsy seem to have a comparable sensitivity for EGFR mutation detection.
Keywords: Epidermal growth factor receptor, cytology, Non-small cell lung cancer

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P4.195 EBUS IN PRIMARY LUNG CANCER

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Background: EBUS is becoming standard practice in the workup of lung cancer. In expert hands, multiple passes can yield precise and adequate material for diagnosis and staging, including sufficient material for molecular analysis. In this analysis of three years single-institutional experience with EBUS the number of passes, nodes sampled and cytological yield are reviewed.
Methods: EBUS-TBNA was performed under sedation using a curved linear scanning ultrasound endoscope (BF-UC160F-0L8, Olympus Corporation, Japan). Ultrasound-guided transbronchial needle aspirations were undertaken using a 22-gauge fine needle (EBUS-needle; NA-201SX-40122, Olympus) with on site cytological assessment. Data for analysis was retrieved from a dedicated EBUS procedural database, anatomical pathology records and the institutional thoracic oncology multidisciplinary team (MDT) database.
Results: EBUS was introduced into our institution in 2007. This analysis included cases from 2008 to 2010. The total number of cases of lung cancer confirmed by EBUS was 69 from 207 procedures in total. There was an almost 3-fold increase in the number of lung cancers diagnosed using EBUS over this period. By 2010 the majority of new lung cancer cases discussed at our thoracic oncology MDT had a positive diagnosis made by EBUS. The average number of passes in total increased substantially and the more difficult hilar sampling increased five-fold. Recent false negative rates were less than 3%. Review of pathology records indicates sufficient material is available for molecular analysis in the majority of cases. Table 1. Results from cases of lung cancer confirmed with EBUS lymph node sampling.

Year	No. of cases	Cases per nodal group			Average passes/case
		PT*	SC*	H*	
2008	12	9	4	2	4.5
2009	24	14	12	5	4.3
2010	33	21	16	10	5.6

*PT = paratracheal, SC = subcarinal, H = hilar lymph node groups.

Conclusion: This analysis demonstrates that in our institution EBUS has become an important part of locoregional diagnosis and staging of lung cancer. Over the four years since its introduction the uptake, precision and scope of EBUS lymph node biopsy has expanded and is set to provide the material for the molecular analysis now regarded as fundamental in lung cancer management.
Keyword: EBUS, lymph node, molecular

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P4.196 A PILOT EXTERNAL QUALITY ASSURANCE SCHEME FOR SOMATIC EGFR MUTATION TESTING IN NON-SMALL CELL LUNG CANCER

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Background: The clinical significance of somatic epidermal growth factor receptor (EGFR) gene mutations in non-small cell lung cancer (NSCLC) is now established. Testing for EGFR gene mutations is routine for the diagnosis and treatment of lung cancer. External Quality Assurance (EQA) is defined by the WHO as 'a system of objectively checking laboratory results by an external agency'. The main objective is to establish inter-laboratory consistency. The process establishes, harmonises and standardises best practice in correctly identifying mutation(s), interpretation of the results and clerical accuracy.

The European Molecular Genetics Quality Network (EMQN; www.emqn.org) is an independent, not-for-profit EQA scheme organiser that runs 28 EQA schemes for 850 laboratories around the world. The EQA process can identify systematic errors in methodology that may not be revealed by internal QA processes. The European Society for Pathology (ESP), The European Thoracic Oncology Platform (ETOP) and the European Society of Medical Oncology (ESMO) with other leading European groups are collaborating with the EMQN in a pilot EQA scheme for EGFR.

Methods: The EQA process does not specify the methodology to be used for genotyping. Samples generated from cell lines are validated by 5 laboratories and then provided to 30 laboratories participating in the pilot. Each sample is supplied with a mock clinical case. Participating laboratories register with the EMQN, perform DNA extraction and analysis using their usual method, and are requested to submit their results within a 4 week timeframe. The anonymised results are assessed and made available to all participants in order to enable comparisons between laboratories and assess individual laboratory performance.

Results: Following two meetings in 2010 a consensus was reached for the pilot phase and for the preparation of EQA materials using cell lines embedded in paraffin. It was agreed that the EQA would also include a pathology review component to allow assessment of the tumour cell content in each test sample.

Conclusion: The pilot EQA scheme brings together the expertise of pathology (ESP) with genetics (EMQN) and lung cancer clinicians and scientists (ETOP, ESMO, AIOM). It is envisaged that the pilot will expand in Q4 2011 to a scheme that will be open to laboratories worldwide. There will be no restriction on the type of participant laboratory. The scheme and the lessons learned from it will serve as a paradigm for schemes of other clinically relevant somatic gene mutations. The collaborators are also integrated with ESP and UKNEQAS providers of EQA for K-RAS, C-KIT and EGFR. Robust EQA will harmonize reporting and analytical practices which should ultimately benefit patients diagnosed with NSCLC, and be transferrable to future mutational testing. The results of the first pilot scheme will be discussed.

Keywords: EGFR, Quality Assurance, Genetic testing

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.197 UTILITY OF NON-SURGICAL DIAGNOSTIC SPECIMENS IN CELLULAR DIFFERENTIATION AND GENETIC PROFILING OF NON-SMALL CELL LUNG CANCER

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Background: Until recently, the management of lung cancer was based predominantly on the classification of small vs. non-small cell lung cancer (NSCLC). However as treatments for NSCLC become increasingly personalized, the cellular differentiation and genetic profile of the tumor is becoming essential for the selection of appropriate treatment regimens. The utility of different non-surgical specimens for the accurate determination of molecular and histologic subtypes of NSCLC has yet to be established. Our objective is to determine and compare the yield of non-surgical specimens for the accurate cellular differentiation of NSCLC and analysis of epidermal growth factor receptor (EGFR) mutation.

Methods: This retrospective cohort study included all patients with a histologic diagnosis of NSCLC from January 2004 to September 2010. Information including histologic subtypes and EGFR mutation analysis was extracted from the pulmonary oncology database. Diagnostic specimens were divided into pathology specimens (PS) and cytology specimens (CS). PS included surgical and non-surgical biopsies. CS included fine needle aspirate (FNA) (i.e. transbronchial (TBNA) and transthoracic needle aspirates (TTNA)) and body fluid samples. These groups were compared using c^2 analyses. Yield of histologic analysis was compared in a subgroup of patients who underwent both surgical and non-surgical procedures.

Results: Among the 715 included patients, 270 were investigated for EGFR mutation status. The yield of CS, when compared with PS, was lower for cellular differentiation (76% vs. 91%, $p < 0.0001$), immunohistochemistry (IHC) (70% vs. 89%, p

<0.0001), and EGFR mutation status (74% vs. 93% $p < 0.0001$). Among the CS, TTNA provided better yield than TBNA for cellular differentiation (89% vs. 67%, $p < 0.0001$), IHC (85% vs. 72%, $p = 0.023$), and EGFR mutation analysis (90% vs. 70%, $p = 0.045$). Body fluid samples were least likely (59%) to provide EGFR mutation status. 94 patients underwent both surgical and non-surgical procedures. As compared to surgical biopsies, the yield of non-surgical procedures for cellular classification was 81% in body fluid samples, 68% in FNA, and 88% in non-surgical biopsies.
Conclusion: TTNA provided high yield for both molecular and histologic analyses. Cellular differentiation of NSCLC is satisfactory with cytology specimens, however body fluid samples had poor yield for EGFR mutation analysis in our patient population. Further prospective studies are needed to confirm our findings.
Keywords: Lung cancer, cytology, cellular differentiation, EGFR

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P4.198 IMMUNOGLOBLIN BINDING PROTEIN 1 (IGBP1) IS A KEY PROTEIN RELATED TO ANTI-APOPTOTIC ACTIVITY IN LUNG ADENOCARCINOMA

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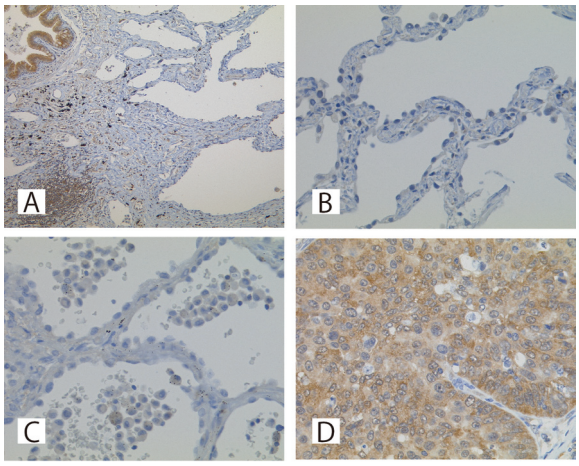
Background: Lactoferrin (Lf) is an iron-binding protein that plays an important role in cancer prevention by inducing apoptosis. After exposure to bovine Lf (bLf), several lung adenocarcinoma cell lines, including PC-14, show apoptotic change. To investigate the molecular mechanism of apoptosis induced by bLf, a major Lf-binding protein was screened using a protein microarray with bLf protein as the probe. This yielded immunoglobulin (CD79a) binding protein 1 (IGBP1), which binds specifically with bLf. IGBP1 is a 36-kDa protein that interacts with protein phosphatase 2A, thus exerting an anti-apoptotic effect in various human carcinomas. The aim of the present study was to confirm the functional activity of IGBP1 in lung adenocarcinoma cell lines, and to clarify the clinicopathological characteristics of IGBP1 expression in human lung adenocarcinoma.
Methods: We obtained 22 specimens of atypical adenomatous hyperplasia (AAH), 96 specimens of small adenocarcinomas less than 2 cm in diameter, and 10 specimens of organizing pneumonia. Using these specimens, we examined the expression levels of IGBP1 and PP2Ac by immunohistochemistry, and compared the results with the clinicopathological data for each case.
Results: No immunostaining for IGBP1 was evident in organizing pneumonia and AAH (0/32; 0%), but IGBP1 immunostaining was evident in 26.7% (8/30) of non-invasive carcinomas with lepidic growth and in 80.4% (37/46) of invasive adenocarcinomas with lepidic growth. All of the small adenocarcinomas showing a non-lepidic growth pattern were positive for IGBP1 (20/20, 100%). The IGBP1 positivity rate increased during the course of sequential cancer progression. All of the cases showing lymphatic permeation, vascular invasion, pleural invasion or lymph node metastasis were positive for anti-IGBP1. Furthermore, all cancers that proved ultimately fatal were positive for anti-IGBP1.Log-rank analysis showed that IGBP1 positivity was significantly correlated with a poor outcome. In contrast, organizing pneumonia, AAH and all lung adenocarcinomas were uniformly positive for anti-PP2Ac.



Conclusion: We have demonstrated that IGBP1 is expressed universally in advanced lung adenocarcinomas, and that its overexpression is significantly related to outcome.
Keywords: IGBP1, PP2Ac, small lung adenocarcinoma

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.199 IMPLEMENTATION OF A NATIONAL EGFR TESTING STRATEGY IN A PUBLICLY FUNDED HEALTH SYSTEM

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Background: Data from five recent randomized clinical trials have demonstrated that EGFR mutation status is predictive of improved PFS and quality of life from first-line EGFR TKI therapy compared with platinum-based chemotherapy. However, the preferred strategy in patients who are EGFR wildtype would be platinum-based chemotherapy. These results have had a significant impact on clinical practice making testing for the presence of EGFR mutations standard of care for patients with advanced non-small cell lung cancer. When gefitinib received regulatory approval in Canada in January 2010, no mechanism for EGFR mutation testing was in place. A national EGFR mutation testing program supported by AstraZeneca Canada was launched in March 2010. This study reports on the uptake of EGFR mutation testing in the initial 10 months of this program.
Methods: Five laboratories across Canada underwent a validation and quality control exercise for EGFR mutation testing using RT-PCR. Subsequently samples were sent to these 5 laboratories for testing. Oncologists registered patients for EGFR mutation testing using a web based platform. Basic demographics were collected including age, histology, sex, smoking status, and ethnicity. The decision to prescribe gefitinib was subsequently registered on the system.
Results: We estimate there were 5600 cases of NSCLC that were potentially suitable for EGFR mutation testing diagnosed in Canada in 2010 (assuming 85% of all cases had NSCLC histology, 40% presented with metastatic disease and 25% had squamous histology). Between March and December 2010, 2104 requests were received for EGFR mutation testing. All patients had non-squamous histology. Demographic details are as follows: adenocarcinoma (91.6%); Asian ethnicity (13.9%); female (58%); light/never smoker (41.3%); stage IV disease (87.1%). In the first 2 months 225 tests were requested. The number of tests requested in each subsequent 2 month period increased from 439 – 496. 1998 samples were received by the labs and results were pending in 82 patients. Mutation testing was conducted in 1771 patients. The median time to get samples to the reference laboratories was 7 days (sd 9.6 d), median time to complete testing 11 days (sd 5.5 d) and median total test time 18 days (sd 9.7 d). Some variability was observed across provinces, primarily in the time taken to get samples to the reference laboratories. Gefitinib was prescribed in 302 (17.1%) patients. Mutation rates were highest in those of Asian ethnicity (45.3%), followed by light/never smoker (27.9%), female sex (20.3%) and adenocarcinoma histology (17.5%). There was significant variation across the provinces in EGFR mutation rate: BC (20.1%); AB (18.7%); ON (16.7%); QC-Jewish General Hospital (12%): and QC- Centre de Lutte Contre le Cancer du CHUM (13.8%, $p<0.001$).
Conclusion: There was rapid uptake of EGFR mutation status into routine clinical practice in Canada. Patient demographics suggest that oncologists are adopting a selective approach to testing using clinical characteristics to select patients. However, the time to receive test results was nearly 3 weeks which might limit uptake in certain patient groups. Expansion in the number of testing centres might further increase uptake.
Keywords: Non small cell lung cancer, EGFR mutation testing, gefitinib, first line therapy

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P4.200 CARCINOEMBRYONIC ANTIGEN STAINING PATTERN RELATE WITH SUBTYPES OF PATHOLOGICAL STAGE IA PULMONARY ADENOCARCINOMA

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Background: Carcinoembryonic antigen (CEA) is a prognostic indicator for various carcinomas. Several studies about colon cancer have reported that the CEA immunohistopathological staining pattern of tumors was strongly related with patient prognosis, with similar findings reported for clinical stage I (c-stage I) pulmonary adenocarcinoma. Recently, lepidic pattern tumor in histopathological analysis has been reported to be useful in diagnosis of adenocarcinoma in situ. In addition, some gene mutations, such as K-ras and epidermal growth factor receptor (EGFR), have been the focus of interest as a prognostic factor and a pathogenesis of lung cancer. We conducted an observational study of CEA staining patterns in patients with pathological stage IA pulmonary adenocarcinoma, to investigate a significant relation with lepidic component and the gene mutations.
Methods: We assessed 103 patients, who were completely resected for pathological stage IA (p-stage IA) lung adenocarcinoma at Osaka University from January 1993 to December 2002. CEA staining patterns were classified as apico-luminal (AL) or diffuse-cytoplasmic (DC), and patient survival of the groups. Morphological classifications based on lepidic component and gene mutations were compared with the CEA staining pattern.
Results: AL was observed in 33 patients and DC in 70 patients with 5-year survival rates of 96.7 and 86.4%, respectively (p=0.022). adenocarcinoma in situ and minimally invasive adenocarcinoma (AIS) was observed in 8 patients, lepidic predominant invasive adenocarcinoma (LPIA) was observed in 12 patients, and non-lepidic predominant invasive adenocarcinoma (non-LPIA) was observed in 83 patients, with 5-year survival rates of 100, 66.7, and 92.3%, respectively (p=0.0011; LPIA vs. non-LPIA). The relation between CEA staining pattern and lepidic component was significant on χ^2 test (p=0.0085). There was no significant relation between CEA staining pattern and gene mutations on χ^2 test (p=0.761). Cox proportional hazard model revealed that the morphological classification and the CEA staining pattern had a statistical independence and significance in this cohort on multivariate analysis (p=0.0006, p=0.0363, respectively).
Conclusion: CEA staining pattern related with morphological appearance, and that is an independent and significant prognostic factor for p-stage IA pulmonary adenocarcinoma.
Keywords: CEA, immunohistochemical pattern, stage IA, lepidic component in adenocarcinoma

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Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.201 ASSOCIATION OF KRAS MUTATION IN NON SMALL CELL LUNG CANCER AND 18F-FDG UPTAKE IN PET/CT

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Background: Mutation of the KRAS gene is one of the most important events in carcinogenesis of the lung. We hypothesize that there exists relation between KRAS mutation status and 18F-FDG uptake in non-small cell lung cancer (NSCLC). This retrospective study was performed to evaluate a possible association between the presence of KRAS mutation and 18F-FDG uptake in these patients.
Methods: We included 52 NSCLC (35 M, 17 F, mean age 60.46±10,67) at the time of diagnosis who were tested for KRAS mutations by direct sequencing using DNA obtained from cytological samples, and who underwent staging PET/CT. The association of KRAS mutation status with patient characteristics, maximum standardized uptake value (SUVmax) by the primary tumor, lymph nodes and metastasis from the 18F-FDG PET was evaluated.
Results: KRAS mutations were identified in 22 (42%) smoker patients, 16 male and 6 female. Seven never smoker and 23 ever smoker patients had no mutation (23% versus 77%). There was a statistically significant association between smoking and KRAS mutation (p = 0.01). The SUVmax ranged from

1.35 to 31.02 (9.67±5.42). The 18F-FDG uptake was higher in KRAS-mutated primary tumors (SUVmax=11,55±6,72) than in wild-type tumors (SUVmax =8,29±3,78) and the differences were statistically significant (p=0.03). Nodal metastases were observed in 42 patients. 18F-FDG uptake in the lymph nodes was higher in KRAS-mutated primary tumors (SUVmax=9,15±5,78) than in wild-type tumors (SUVmax=6,19±3,12) and differences were statistically significant (p=0.04). Distant metastases were observed in 33 patients and SUVmax was higher in patients with KRAS-mutated primary tumors (SUVmax=8,90±4,95) than in those with wild-type tumors (SUVmax=6,96±2,49) but without statistically significant differences.
Conclusion: Among western patients with advanced lung cancer, those smokers, men and with higher SUVmax on primary and nodal metastases in 18F-FDG PET/CT are more likely to carry KRAS mutations. 18F-FDG uptake might be helpful to discriminate patients who harbor KRAS mutations.
Keywords: KRAS mutation, Non small cell lung cancer, 18F-FDG PET/CT

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P4.202 NON SMALL CELL LUNG CANCER(NSCLC) WITH ACTIVATING EGFR MUTATION IN CHILE

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Background: The presence of activating EGFR mutations is a well recognized prognostic factor with therapeutic implications in NSCLC. Several trials have shown the incidence of this mutation to be geographically variable. In this context, it is interesting to determine the incidence of EGFR mutations in NSCLC in the Chilean population.
Methods: We conducted a descriptive, prospective exploratory trial to determine the incidence of activating EGFR mutations in the NSCLC population in 3 cancer centers in Santiago de Chile. The centers were: Instituto Nacional del Cáncer, Clínica Alemana and Clinica Santa María. The presence of EGFR mutation was determined in the histologic sample of the primary tumour of all the patients with advanced NSCLC with diagnosed at the three centers from July 2009 to December 2010. The mutation detection methods were: direct sequencing (39,5%) and PCR with Thera Screen kit®(60,5%).
Results: A total of 118 patients were included in this trial with a median age of 67 (35-76) years. All patients were Chilean. The distribution of histology was: adenocarcinoma 80,5%, NOS carcinoma 9,3%, large cell carcinoma 7,6% and other histologies 2,6%. In 8,4 % of patients the sample was insufficient for DNA analysis. The EGFR mutation was determined in the remaining 91,6% samples, a total of 108. In 24 patients (22,2%) the EGFR mutation was positive. Fourteen patients (58,4%) had exon 19 deletion, and ten patients (41,6%) had 21 exon L858R mutations. Fifteen patients (62,5%) were female and 9 (37,5%) were men. In females, the exon 21 L858R mutation was more frequent (53,3% vs 46,7% exon 19 deletion). In men, the 19 exon deletion was more frequent (77,8% vs 22,2% exon 21 L858R mutation).
Conclusion: In this sample of the Chilean NSCLC population the detected incidence of activating EGFR mutation (22,2%) was superior to the reported incidence for Europe and USA. Further studies in larger samples accross Chile would be needed to confirm this difference which could be due to geographic variability in NSCLC biologic behaviour. The knowledge of the molecular profile of NSCLC in Chile would be useful to guide the design and implementation of therapeutic guidelines and rationalize the use of expensive therapeutic resources such as tirosine-kinase inhibitors.
Keywords: NSCLC, exon 19 deletion and exon 21 L858R mutation, EGFR mutation, Chile

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P4.203 CHARACTERISATION OF TRANSCRIPTION FACTORS IN ASIAN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: The transcription factors CCATT/enhancer binding protein alpha (C/EBPα), hepatocyte nuclear factor3β (HNF3β, FOXA2) and thyroid transcription factor-1 (TTF-1) are involved in lung morphogenesis and also have a putative role in non-small cell lung cancer (NSCLC) with C/EBPα and HNF3β acting as tumor suppressors and TTF-1 as an oncogene. The epidemal growth factor receptor (EGFR) is frequently overexpressed in NSCLC and EGFR mutations are more frequent in East Asian patients. The relationship between C/EBPα and the other transcription factors and EGFR mutations has not been previously described.
Methods: A tissue microarray (n=164) was constructed from patients with resected NSCLC and slides were stained by immunohistochemistry (IHC) with antibodies against CEBPα, HNF3b, TTF-1, and the two most common EGFR mutations (exon19 deletion and exon 21 L858R). IHC staining intensity was independently scored by two pathologists blinded to patient factors. A categorical value of positive vs negative was used for statistical analyses of marker expression. The association between CEBPα intensity and clinicopathologic factors, survival and with HNF3b, TTF-1 expression, and EGFR mutation status was analysed. The likelihood ratio test and Fisher's exact test was used where appropriate. Kaplan-Meier curves and log-rank test was used to compare the overall survival between groups.
Results: The median age was 64 years with the majority of patients being male (69%) and Chinese (85%). The commonest histologic subtype was adenocarcinoma (68%) and most were AJCC stage I disease (54%). Loss of CEBPα expression was seen in 63% of cases and was associated with advanced stage disease (p=0.023). No significant association was seen between CEBPα expression and any other clinicopathological features or with overall survival. CEBPα was associated with the TTF-1 (p<0.001) and HNF3ß expression (p<0.001) and was possibly associated with EGFR mutation status (p=0.07).
Conclusion: Absent CEBPα expression was similar to previous reports and was associated with late stage disease. Unlike previous reports, we found no association with histological subtype or tumor differentiation. The possible association between CEBPα expression and EGFR mutations is intriguing and further studies are needed to confirm this relationship.
Keywords: CEBP alpha, transcription factors, tissue array, Non small cell lung cancer

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P4.204 SOX2 OVEREXPRESSION IN PULMONARY SQUAMOUS CELL CARCINOMA ASSOCIATED WITH INTERSTITIAL PNEUMONIA

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Background: Sex determining region Y-box 2 (SOX2) is a transcription factor gene located at chromosome 3q26, the most often amplified segment in squamous cell carcinomas, and is considered to be a potential cell-lineage gene highly expressed in the pathogenesis of squamous cell carcinomas of the lung.
Methods: We examined SOX2 expression by immunohistochemistry in 46 non-small cell carcinomas surgically resected from patients with interstitial pneumonia. The patients were 38 men and eight women, ranging from 38 to 83 (median 72) years old. Anti-SOX2 (D6D9) XP rabbit monoclonal antibody (Cell Signaling Technology, Danvers, MA) was used at 1:50 for immunohistochemistry, which was performed on an automated Ventana BenchMark XT system using an iView DAB detection kit after a heat-mediated antigen retrieval procedure.
Results: We observed an abnormal nuclear accumulation of SOX2 protein in six cases (22.2%) of 27 squamous cell carcinomas, but not in non-squamous lung carcinomas (16 adenocarcinomas, 1 adenosquamous, 2 large-cell neuroendocrine carcinomas) or non-neoplastic various tissues. SOX2 overexpression tends to be observed in heavy smokers (SOX2+: 750-3660 (mean 1536) cigarette-years; SOX2-: 0-2400 (mean 953) including five non-smokers). The presence or absence of SOX2 amplification is currently being evaluated by fluorescent or chromogenic in situ hybridization using BAC DNA probes.
Conclusion: SOX2 overexpression was observed

in some squamous cell carcinomas of the lung in patients (especially heavy smokers) with interstitial pneumonia.
Keywords: interstitial pneumonia, squamous cell carcinoma, SOX2

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P4.205 ELECTRON AND IMMUNOELECTRON MICROSCOPIC ANALYSIS OF STROMAL CELLS CULTURED FROM ADENOCARCINOMAS AND SQUAMOUS CELLS CARCINOMAS OF THE LUNG

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Background: In addition to cancer cells, lung tumours contain stromal cells i.e. fibroblasts and myofibroblasts, which may have a role in the growth of lung cancer. The aim of the study was to standardize the process for culturing cells from lung cancer tissues and to characterize the ultrastructural features of stromal cells isolated from lung cancer tissue of the patients with various types of lung cancers with special interests on the fibronexus-structure of myofibroblast.
Methods: Lung tissue material from 6 patients with adenocarcinoma, 3 patients with squamous cell carcinoma and 1 patient with adenosquamous carcinoma was obtained from surgical operations (2 female, 8 male; 2 nonsmokers, 8 smokers). Tissue samples were disrupted mechanically and digested by collagenase treatment in order to obtain single cell suspensions. The cells were visualized by electron and immunoelectron microscopic methods using specific antibodies for alpha-smooth muscle actin (a-SMA), fibronectin and ED-A-fibronectin as previously described (Kaarteenaho-Wiik et al. Ultrastructural Pathol 2009;33:6-15). Electron microscopic features of myofibroblasts were quantified systematically.
Results: The cells cultured from lung cancer tissue were mixture of fibroblasts and myofibroblasts. The amount of fibroblasts and myofibroblasts varied highly in different patients. Typical features of myofibroblasts were detectable in the cells by electron and immunoelectron microscopy, such as a-SMA positive strands in the cell cytoplasm and extracellular fibronectin-containing structures on the surface of the myofibroblast. Many cases exhibited adherens-junction like cell junctions between cells.
Conclusion: Stromal cells of lung cancers comprised of fibroblasts and myofibroblasts the amount of which varied highly between different patients. The ultrastructural analyses of cultured cells revealed typical features of myofibroblasts with fibronexus, dilated rough endoplasmic reticulum (rER) and cell junctions. Using the cell culture method of tumour cells and the electron and immunoelectron microscopy may help one to achieve a new information of the structure of stromal cells of lung cancers. In the future, invasion and differentiation properties as well as cell junctions of intratumoural myofibroblasts of lung cancers will be characterized.
Keywords: myofibroblast, alpha-smooth muscle actin, fibronectin, Lung cancer

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P4.206 EGFR DIAGNOSIS IN THE CLINICAL PRACTICE

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Background: Since the approval of Gefitinib as first- and second-line treatment for lung cancer patients with advanced disease harbouring activating EGFR mutations in June 2009, evaluation of EGFR mutational status is developing into a routine diagnostic procedure.
Methods: Point mutations in exon 18 were assessed by direct sequencing, deletion in exon 19 by gene scan analysis and the L858R mutation in exon 21 by a HybProbe assay in 205 patients of european

origin with disease stage IIIb and IV or at relapse after surgery. For 99 patients this was part of the diagnostic procedure.
Results: We found 1 G719A mutation in exon 18 (0.5%), 19 inframe deletions and 2 inframe insertions in exon 19 (10.2%) and 13 L858R mutation (6.3%), resulting in an overall mutational frequency of 17 %. Tissue from the original tumor and from a metastasis or at relapse after standard chemotherapy was available in 1 not mutated and 2 mutated cases, with stable mutational status. Of 99 patients diagnostically analysed, 19 harboured one of the activating mutations. Patients were chemonaiv or had recieved 1 or 2 chemotherapies before. Of 14 patients with follow-up, 4 recieved a standard chemotherapy, with planned maintenance TKI therapy in 2 cases. 8 were treated with Gefitinib or Erlotinib, 6 of those in first line. While 1 patient discontinued the therapy, clinical response was seen in the 5 (1 stable disease, 4 remissions) and 2 patients are not yet available. 2 patients had been successfully treated with Erlotinib for 1 and 3 years respectively before relaps and tumor progression.
Conclusion: Routine EGFR mutational analysis in patients with lung adenocarcinoma helps to identify patients likely to respond to EGFR-TK inhibitor therapy in clinical daily routine with marked benefit for as much as 20 % of all lung adenocarcinoma patients. The mutational status was stable in the original tumor and metastasis or at relapse in 3 of 3 cases, which, after confirmation in a larger number of cases, will facilitate reliable EGFR diagnostic in the original operated tumor for patients at relapse even if no recent biopsy is available.
Keywords: EGFR, TKI, activating mutation, clinical routine

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P4.207 CONCOMITANT EGFR MUTATION AND EML4-ALK GENE FUSION IN NON-SMALL CELL LUNG CANCER

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Background: The fusion of the anaplastic lymphoma kinase (ALK) with the echinoderm microtubule-associated protein-like 4 (EML4) and epidermal growth factor receptor (EGFR) mutations are considered mutually exclusive. Advanced non-small cell lung cancer (NSCLC) patients with EML4-ALK did not benefit from EGFR tyrosine kinase inhibitors (TKIs).
Methods: Multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) followed by sequencing was performed for EML4-ALK fusion status detection. EGFR and KRAS mutations were determined by direct DNA sequencing. Positive results of EML4-ALK fusion were also confirmed by RACE-coupled PCR sequencing.
Results: From April 2010 to January 2011, 412 patients (398 with NSCLC; 14 with SCLC) were tested for mutation status of EGFR, KRAS and EML4-ALK respectively. Frequency of EML4-ALK fusion was 10.6% (42/398) in NSCLC patients. No patients with SCLC were found to have positive EML4-ALK fusion. Frequency of concomitant EGFR and EML4-ALK gene mutations was 1.0% (4/398) in NSCLC patients, and their variants of EML4-ALK gene mutations were Variant 1 (3 patients) and Variant 6 (1 patient); being never smokers, all of them were diagnosed with advanced (3 with stage and 1 with stage B) adenocarcinoma harbouring wild type KRAS. Two female stage patients with double gene mutations (1 with L858R and Variant 1; 1 with exon19 deletion and Variant 6) received first-line gefitinib which is one kind of EGFR TKIs and achieved partial response.
Conclusion: Though being rare events, NSCLC patients harbouring concomitant EGFR mutation and EML4-ALK gene fusion are sensitive to first-line EGFR TKIs. Whether they could also benefit from ALK inhibition after failure to EGFR TKIs warranted further investigation.

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P4.208 RT-PCR VERSUS IMMUNOHISTOCHEMISTRY FOR CORRELATION AND QUANTIFICATION OF ERCC1, BRCA1, TUBB3 & RRM1 IN NSCLC

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Background: Customized chemotherapy is increasingly used in the management of patients with advanced non-small cell lung cancer (NSCLC). However, the most reliable methodology to determine biomarker status is neither fully elucidated nor agreed upon. Accordingly, we evaluated the pedictive information of quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) and immunohistochemical analysis (IHC) on excision cross complementation group 1 (ERCC1), breast cancer susceptibility gene 1 (BRCA1), ribonucleotide reductase subunit M1 (RRM1) and class III b-tubulin (TUBB3). Furthermore, we correlated mRNA and protein expression.
Methods: IHC and qRT-PCR on ERCC1, BRCA1, RRM1 and TUBB3 were performed on surgically resected tissue samples from patients with advanced NSCLC included in a randomized phase III trial. The median values of the biomarker expression dichotomized the population into negative and positive subgroups and were correlated to response rates (RR), median progression free survival (PFS) and median overall survival (OS).
Results: Representative tissue samples from 33 patients were explored and no significant correlations were found between mRNA and protein expression. Predictive impact was demonstrated for all four biomarkers, when assesed by IHC, and reached significance for OS in ERCC1 negative (14,3 vs. 8,5 months, P = 0,018) and TUBB3 negative (18,5 vs. 11.10, P = 0,027) tumors, while this was not the case for qRT-PCR.
Conclusion: IHC discriminated more effectively than qRT-PCR across four different biomarkers in a subgroup of patients with advanced NSCLC having representative tissue samples. These findings are further supported by the demonstrated lack of correlation between transcript and protein.
Keyword: NSCLC, predictive markers, methodology, qRT-PCR, immunohistochemical evaluation

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.209 SYSTEMATIC QUANTIFICATION OF TUMOUR CONTENT IN CRYOPRESERVED SAMPLES STORED IN A LUNG TUMOUR BANK

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Background: The success of molecular characterisation of carcinomas depends upon the presence of a sufficient amount of tumour in submitted samples. Few studies on the volume of tumour represented in pathology specimens have been published, mainly focussing on bronchoscopic biopsies1. We analysed tumour cell content and percentage of necrosis in snap frozen tumour pieces harvested from resected lung cancers to assess suitability for genomic studies.
Methods: Patients gave informed consent to donate part of their resected tumour tissue for research, and data is based on 272 adenocarcinomas (AC) and 191 squamous cell carcinomas (SCC). Portions of surgical lung cancer specimens were harvested fresh by macroscopic dissection between 1992 and 2011 (one to fourteen portions per case), snap frozen in liquid nitrogen, and stored at -80oC for up to 18 years as a resource of The Prince Charles Hospital lung tumour bank. Two pathologists independently recorded percentage of tumour cell nuclei and percentage of necrosis in a single four micron H and E section from each portion (3.98±3.92 sections per AC case and 4.48± 2.93 sections per SCC case). Tumours with fewer than 30% tumour cell nuclei were reviewed to determine the reason for the low tumour content.
Results: The mean percentage of tumour cells in each section of adenocarcinoma (n=493) was 33.6±24.7% for Reader 1, and 30.5±24.9% for Reader 2, and in SCC (n=545) 35.2±26.1% (Reader 1) and 32.9±26.7% (Reader 2). The percentage of tumour cells recorded by both readers was slightly higher in SCC than AC (statistically significant for Reader 2, p=0.027). Mean percentage necrosis for adenocarcinoma was 7.5±19.1% (Reader 1) and 8.6±20.8% (Reader 2), and for SCC 15.2±24.1% (Reader 1) and 18.4±27.2 (Reader 2). The two

readers' independent scores for both tumour content and necrosis were highly correlated (Pearson > 0.90, n=989 sections, p<0.01). Percentage necrosis scored by both readers was significantly higher in SCC than AC (p<0.001). There was no strong relationship between the area of the tissue section on the slide and percentage of tumour cell content or necrosis (all correlation coefficients <0.25). Review of samples with tumour content below 30% revealed inclusion of adjacent normal alveolated lung, fibrosis, inflammation, elastotic scarring, bronchial wall, organising pneumonia, blood vessel wall and lymph node in samples harvested as "tumour".
Conclusion: In this study there was good agreement between the two pathologists, but only approximately one third of cell nuclei in both AC and SCC were tumour. Necrosis was greater in SCC than AC. Whether specimens are obtained at surgical resection or by small biopsy, all should be assessed for tumour volume prior to molecular testing.

1. Coghlin CL, Smith LJ, Bakar S, et al. Quantitative analysis of tumor in bronchial biopsy specimens. J Thorac Oncol 2010; 5: 448-452.
Keywords: tumour content, lung cancer resctions

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P4.210 DIAGNOSTIC PATTERNS OF NON-SMALL CELL LUNG CANCER AT PRINCESS MARGARET HOSPITAL.

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Background: Pathologic subtypes of non-small cell cancer (NSCLC) may have differential benefit with selected systemic treatments. Hence, NSCLC subtyping is becoming increasingly important in therapeutic decision-making. We reviewed the methods of diagnosing NSCLC at our institution and how often a specific pathologic subtype is provided.
Methods: Retrospective chart review was undertaken at a major cancer center, identifying patients with advanced stage NSCLC diagnosed between January 2007 and January 2009.
Results: A total of 238 patients were diagnosed with advanced (stage IV) NSCLC and had 274 diagnostic samples. 42 patients (17%) required a second procedure to confirm the diagnosis of malignancy. Bronchoscopy (26%) and CT-guided procedures (25%) were the most common first methods of procuring a sample. 150/274 (55%) of the samples were from the primary tumour. Among the samples, 37% were core biopsies, 42% were fine-needle aspirate biopsies (FNAB). The rest were variable and included cytologic assessment of bronchial washings and pleural effusions. Successful diagnosis of malignancy was associated with sample type (p<0.001): 61% for exfoliative cytology (effusion, bronchial washings), 89% for FNA, and 90% for core biopsy. The method of procuring the sample was also associated with success of the initial attempt (p=0.0001). CT-guided sampling with an on-site cytopathologist yielded a diagnosis in all cases. Site of initial sample was also an important predictor of diagnostic success of the initial sample with metastatic site (96%) and primary tumour (84%) having the highest rate of success. Pleural effusion had the lowest yield at 70%. Pathologic subtypes were determined in majority of cases: 61% adenocarcinoma, 13% squamous cell carcinoma (SCC), however, large cell and NSCLC not otherwise specified (NOS) comprised 6% and19% of cases. 40% of all samples had immunohistochemistry (IHC) studies performed. IHC was performed more frequently in adenocarcinoma cases (73%) to confirm site of origin. Only 28% of SCC cases had IHC performed. IHC was more commonly performed in cases of NSCLC NOS, 64% (29/45) versus 36% (70/193) in other pathologic subtypes (p=0.0006). Type of sample was significantly associated with NOS and Large cell diagnosis (p=0.008): 34% of those with FNA biopsies were either NOS and/or Large cell, compared to only 17% of those with core biopsies.
Conclusion: Up to 19% of cases of NSCLC diagnosed at a major cancer centre may not have a specific pathologic subtype defined based on available diagnostic material. IHC was performed more commonly in those without a defined subtype, likely in an attempt to determine the subtype. CT-guided FNA and core biopsies of the primary were associated with the highest diagnostic yield.
Keywords: Non-small cell lung cancer, pathology, immunohistochemistry

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P4.211 CORRELATION OF PREDOMINANT HISTOLOGIC SUBTYPE, MUTATION STATUS AND OVERALL SURVIVAL IN STAGE III LUNG ADENOCARCINOMA.

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Background: A robust, reproducible adenocarcinoma classification system, with molecular correlate, is essential to facilitate research, define prognosis and inform treatment choice. The recently published IASLC/ATS/ERS adenocarcinoma classification correlates predominant histologic subtype with survival in stage I adenocarcinoma and demonstrated it to be prognostic. We investigated stage III(N2) lung adenocarcinomas to determine the relationships between histologic subclassification, mutational profile and overall survival (OS).
Methods: Histologic slides from 58 resected stage III adenocarcinomas were classified according to the IASLC/ATS/ERS classification. Predominant subtype was circled on the slide, a core punched from the paraffin block, DNA isolated and mutational profiling performed using Sequenom's MassArray platform. Predominant subtype, mutation status and OS were correlated using univariate and multivariate models.
Results: Median age was 64 (Range 29-86) years with 30 (52%) females. Predominant subtypes were: solid (n=21,36.2%), acinar (n=20,34.5%), micropapillary (n=12,21%), papillary (n=3,5.2%), and colloid (n=2,3.4%). EGFR and KRAS mutations occurred in 16 (28%) and 12 (21%) tumors respectively. EGFR mutations occurred most commonly in predominant acinar subtype (n=8,47%) compared to 5 (29%) micropapillary and two (12%) solid (p=0.048). In contrast, KRAS mutations occurred primarily in solid predominant tumours (n=7,58%). On univariate analysis acinar predominant tumours were associated with improved survival (p=0.02) and KRAS mutant tumours with inferior survival (p=0.003) (Figures 1 and 2). In multivariate analysis inclusive of age, sex and mutation status, acinar predominant histology remained an independent predictor of improved OS (HR 0.35;95%CI 0.15-0.80;p=0.014) and KRAS mutant tumors independently predicted poorer outcome (HR 3.35;95%CI 1.43-7.85;p=0.005).

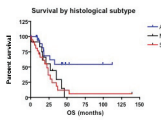

Figure 1: Survival by predominant histologic subtype in 58 stage III adenocarcinomas.

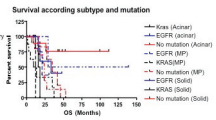

Figure 2: Survival according to predominant subtype and mutation status in 58 stage III adenocarcinomas.

Conclusion: In stage III adenocarcinoma, acinar and solid predominant tumours were the most frequent subtypes. Acinar predominant tumours were more likely to harbour EGFR mutations. KRAS mutation status provides important prognostic information that is independent of histologic subclassification. OS was superior in acinar predominant tumours regardless of mutation status. Histologic subclassification provides important prognostic information, independent of mutation status.
Keywords: Adenocarcinoma, Stage III, Predominant histologic subtype, EGFR

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P4.212 DIFFERENTIATING SUBTYPES OF NON SMALL CELL CARCINOMAS OF THE LUNG BY THE COMPLEXITY OF THEIR CELLULAR ARCHITECTURE

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Background: Lung cancer is most common cause of cancer mortality worldwide. Traditionally, carcinomas of the lung required only classification into small cell lung carcinoma and non-small cell lung carcinomas (NSCLC) for management decisions. However, NSCLCs, comprising 85% of lung cancers, consist of clinically and pathologically heterogenous entities. Differences in management between squamous and non-squamous NSCLCs are emerging highlighting the growing importance of accurate histopathologic classification. Furthermore, increasingly the diagnoses must be made with less tissue as minimally invasive procedures become more common and more tissue is kept for molecular studies. Inter-observer variability increases with smaller biopsy specimens, resulting in a need for an objective measure to distinguish histologic subtypes. We hypothesize that the complexity of the epithelial architecture, mathematically quantified by the correlation dimension, can be used to classify NSCLC subtypes. We have previously demonstrated that this is a promising approach in breast cancer. The objective of this study is to evaluate the potential of computing the architectural complexity of NSCLCs to differentiate adenocarcinoma (ADC) from squamous cell carcinoma (SCC), and compare such an approach in resected early stage cases against biopsies taken from patients with metastatic disease.
Methods: Patients with resected NSCLC tumors and patients with biopsies of stage IV NSCLC were identified from the Glans-Look lung cancer database at the Tom Baker Cancer Centre for the years 2003-2006. Tissue micro arrays (TMAs) were generated from formalin-fixed paraffin embedded resected tumor specimens and diagnostic biopsies of stage IV patients. These were stained with pan-cytokeratin to highlight the epithelial structure of the carcinoma, and digitally imaged using the HistoRx PM-2000 automated image acquisition platform. Architectural complexity of the carcinoma, as represented by the correlation dimension of the epithelial structure, was analyzed by computer. Mean correlation dimension of lung sections of ADC and SCC, as assigned by a pulmonary pathologist, were compared using the independent t-test.
Results: 137 cases of resected NSCLCs and 139 cases of stage IV NSCLC biopsies were identified. The resection series contained 89 cases of ADC and 48 cases of SCC. The stage IV biopsy series contained 90 cases of ADC and 49 cases of SCC. Pan-cytokeratin staining and automated image analysis was successful on all specimens. We found a statistically significant difference ($p = 0.01$) between the mean correlation dimension of ADC ($M = 1.74$, $SD = 0.06$) and SCC ($M = 1.77$, $SD = 0.07$) in the stage IV biopsies. The resected specimens yielded better discrimination than the stage IV biopsies because of greater architectural integrity.
Conclusion: Architectural complexity, as represented by the correlation dimension of the epithelial structure of NSCLC, has potential as a reproducible and automated measure to subtype NSCLCs into ADC and SCC from biopsy and resection specimens. This potentially objective method may provide an adjunct test in differentiating different NSCLCs and help reduce intra-observer variability. This is of growing importance as the distinction between subtypes of NSCLC, particularly between squamous and non-squamous NSCLC, is clinically important in patient management decisions.
Keywords: Non small cell carcinoma of the lung, architectural complexity, fractal dimension

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P4.213 IMMUNOISTOCHEMICAL EXPRESSION OF NEUROENDOCRINE DIFFERENTIATION IN NON-SMALL CELL CARCINOMA OF THE LUNG.

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Background: At the end of the 20th century, the lung cancer represent the most often malignancy and cause of death of neoplasm worldwide. Neuroendocrine neoplasms, represent the 16-17% of the primary lung carcinomas. Furthermore exist a non negligible percent (10-30%) of the non small cell lung carcinomas which present elements of neuroendocrine differentiation. Multiple research programs have been affected. Aim : To present our observations and studies about the immunoistochemical neuroendocrine expression of non-small cell lung carcinomas, on the purpose to classify the neoplasms of low grade differentiation in neuroendocrine tumors and/or neoplasms with neuroendocrine features
Methods: We examined ten (10) cases of non-small cell lung carcinomas with neuroendocrine differentiation and ten (10) cases of neuroendocrine small and large cell lung carcinomas. The immunoistochemistry methods used were of three steps (avidine-biotin-peroxidase) in paraffine embeded tissues.
Results: Differential diagnosis between neuroendocrine neoplasms of the lung and non small cell neoplasms with neuroendocrine differentiation requires the study of histological and immunoistochemical neuroendocrine characteristics. Furthermore the cytoplasmatic neuroendocrine positive expression of CD56 vs its membranic positivity can offer an additional parameter to the differential diagnosis and accurate definition of the neoplasm.
Keyword: Neuroendocrine differentiation, lung cancer, immunoistochemical neuroendocrine markers

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P4.214 CARCINOMA NOS (NOT OTHERWISE SPECIFIED) IS A COMMON HISTOLOGIC DIAGNOSIS IN NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS AND IS MOST FREQUENTLY DIAGNOSED CYTOLOGICALLY: RETROSPECTIVE ANALYSIS IN A COMMUNITY-BASED HOSPITAL.

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Background: Recent clinical trials have demonstrated differential survival benefits from chemotherapy regimens according to NSCLC histology, increasing the importance of accurate subtyping in small biopsy samples. While histological distinction between small cell and non-small cell lung carcinoma can be made on small biopsy samples with high accuracy and consistency, discrimination between NSCLC subtypes (squamous cell carcinoma, adenocarcinoma and large cell carcinoma) is more difficult. In some cases a lack of diagnostic features renders subtyping impossible and a diagnosis of NSCLC, not otherwise specified (NOS), has to be made. Cytological procedures are frequently used, but their ability to discriminate between NSCLC subtypes is not always possible.
Methods: We conducted a retrospective analysis in 415 NSCLC patients (p) diagnosed between January 2007 and December 2010. We analysed the distribution of NSCLC subtypes and correlated them with the histological diagnostic technique employed.
Results: Malignant diagnosis included squamous cell carcinoma in 199 p (48%), adenocarcinoma in 116 p (28%), large cell carcinoma in 12 p (2.9%) and and other carcinomas including NOS in 88 p (21.2%). The proportion of NSCLC patients diagnosed by biopsy as compared to the proportion of NSCLC patients diagnosed by cytology was 87.6% vs 12.4% respectively. Carcinoma NOS was most frequently diagnosed cytologically, 32% vs 11% (p=0.0001).
Conclusion: Carcinoma NOS is a common histologic diagnosis and is significantly higher in those p diagnosed citologically. An increased effort is needed to obtain sufficient tumour tissue in order to identify adequately NSCLC subtypes.

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P4.215 ANTITUMOR TREATMENT ON PULMONARY EPITHELOID HEMANGIOENDOTHELIOMA

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Background: Pulmonary epitheloid hemangioendothelioma (PEHE) is a rare tumour of endothelial origin, which is of borderline malignancy. It is often problematic to diagnose PEHE. This disease does not have any standard treatment. For this reason we made an in vitro experiment testing chemotherapeutic agents in cell cultures.
Methods: The histological examination of biopsy proved that the patient has PEHE. Cell cultures (monolayer, explant, 3D) were made from one part of bronchoscopy sample. The tissues were dissociated enzimatically and mechanically. These cell cultures were used to examine the efficiency of the chemotherapeutic agents by examining the activity of proliferation (^{3}H-thymidine incorporation, protein production) and the markers of toxicity. According to our in vitro examination, chemotherapy treatment was introduced by giving carboplatin-etoposide and docetaxel.
Results: The patient received 6 cycles (CBP-Vp) which resulted in partial regression. The chemotherapy treatment was completed by January 2010. After the chemotherapy treatment was started, osteolytic lesions were detected on the left lower arm resulting in pain. It was regarded to be bone metastases, so biphosphonate treatment was initiated. The patient was observed regularly, and progression was detected in May 2010. It was about 20 %, so second line docetaxel was begun. The patient received 4 cycles which resulted in partial regression (30 %).
Conclusion: Combining in vitro and in vivo methods proved to be a very effective anticancer treatment in case of our female patient. If there is not standard therapeutic protocol in any kind of tumour type, it is useful testing efficiency of different chemotherapeutic agents in the related cell cultures for finding the most effective anticancer treatment modality. This work was supported by: TAMOP 4.2.1./B-09-1/KNOV-210-0005
Keyword: hemangioedothelioma, therapeutic protocol, the activity of proliferation, cell culture

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P4.216 ASSOCIATION BETWEEN TUMOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION AND PULMONARY TUBERCULOSIS IN PATIENTS WITH ADENOARCINMA OF THE LUNGS

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Background: The possible association between pulmonary tuberculosis (TB) and lung cancer development has been studied for several decades, and many studies revealed that history of pulmonary TB infection is associated with increased risk of lung cancer. In addition, lung cancer tumor EGFR-mutations occurred most frequently in patients with adenocarcinoma. However, the relationship between EGFR mutation in lung cancer and pulmonary tuberculosis is unknown.
Methods: We retrospectively reviewed and updated the data of our adenocarcinoma patients about whether or not they had pulmonary TB infection history or their chest CT image showed pre-existing TB lesions at or before initial diagnosis of lung cancer, in those patients who had tumor tissue samples sent for tumor EGFR sequence analysis. The associations of EGFR mutation and history of TB infection or TB lesions on image were analyzed.
Results: 345 lung cancer patients who received tumor EGFR sequence analysis between 2008 and 2010 were enrolled into present study. Among them, 238 patients had tumor EGFR mutations and 107 patients had wild-type tumor EGFR. In these 345 patients, 17 patients had pulmonary TB infection history, and 67 patients had chest CT lesions in favor of previous TB infection, in addition to lung cancer lesions. There are statistically significant association between EGFR mutations and TB lesions on chest CT scan ($p=0.003$); EGFR mutations and scar cancer ($p=0.028$); exon 19 deletions and pre-existing TB lesions on chest CT scan ($p<0.001$); exon 19 deletions and scar cancer ($p<0.000$); and exon 21 mutations and pre-existing TB lesions on chest CT scan ($p=0.011$).
Conclusion: There are significant association of previous pulmonary tuberculosis infection and occurrence of tumor EGFR mutations in NSCLC patients.
Keywords: EGFR, tuberculosis

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P4.217 LARGE CELL CARCINOMAS (LCC) OF THE LUNG: A MONOCENTRIC, CLINICOLPATHOLOGIC STUDY OF FIFTY-TWO PATIENTS.

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Background: The rarety of large cell carcinoma of the lung (LCC) lead to the lack of clinical evidence based data for clinical decision making. Moreover LCC were previously diagnosed on morphologic features while at present electron microscopy and immunohistochemistry confirmed that different lineages can occur in LCC including squamous (in basaloid and some clear cell variants), glandular (LCC with rhabdoid features) or neuroendocrine differentiation (large cell neuroendocrine carcinoma -LCNEC- or LCC with neuroendocrine features).
Methods: The histologic characteristics of the patients with an initial diagnosis of LCC, of which 113 underwent to radical surgery in our Institution from November 1995 to December 2009, were retrospectively reviewed according to 2004 World Health Organization criteria. Immunohistochemistry with a panel of markers for glandular, squamous and neuroendocrine differentiation was performed in order to confirm different phenotypes. Outcomes and other clinical characteristics of LCC patients were retrospectively analyzed and compared with those of patients with not confirmed LCC.
Results: Among 130 tumors evaluated, 52 didn't change the diagnosis of LCC after the histologic review, while the further 88 patients shifted to poorly differentiated non-small-cell lung carcinomas (NSCLC). LLC were LCNEC (33), basaloid (8), clear cell (5), lymphoepithelioma like (1) and LCC with rhabdoid phenotype (2). With a median follow-up was of 3 years, no difference in overall survival was observed neither between LCC and poorly differentiated NSCLC patients, nor between LCNEC and the other LCC subtypes.
Conclusion: Prognosis of patients with revised LCC is not different from that of poorly differentiated NSCLC. This data can be of help to the adjuvant –chemotherapy decision-making process with patients with this rare tumor entity.
Keywords: LCC, LCNEC

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.218 ANALYSIS OF LUNG CANCER HISTOLOGY BY FAMILY ONCOLOGIC HISTORY IN A UNIVERSITY HOSPITAL IN LATVIA

Jelena Grusina Ujumaza[1], Genadijs Ambalovs[2], Andrejs Vanags[2], Ilze Strumfa[3], Jazeps Basko[4], Jānis Gardovskis[2], Uldis Kopeika[4], Ainis Pirtnieks[4]
[1]Division Of Doctoral Studies, Riga Stradins University/Latvia, [2]Department Of Surgery, Riga Stradins University/Latvia, [3]Department Of Pathology, Riga Stradins University/Latvia, [4]Department Of Thoracic Surgery, Pauls Stradiņš Clinical University Hospital/Latvia

Background: There are contradictory data in the literature on eventual connection between family anamnesis and histological type of lung cancer. Some studies mention close connection between squamose cell cancer and positive family cancer history, however, the data obtained from Swedish Cancer Register could indicate the higher incidence of adenocarcinoma in family lung cancer (Li and Hemminki, 2003). Recently summarized epidemiological data reveal that the number of adenocarcinoma-type cancer increase in people who have never smoked, mostly in women (Brambilla et al., 2010). In total the connection to the family history is more expressed in non-smokers than smokers, and it is more connected to non small cell cancer (Gao et al., 2009). Objective of the work: make analysis of tumour histogenesis in connection with the patient's family anamnesis.
Methods: Lung cancer patients who underwent treatment in the Centre of Thoracic Surgery of university hospital in Latvia due to histologically confirmed lung cancer diagnosis were included in the study. We assessed the lung cancer patient's family oncological history, presence and stage of tumour which was determined using modern examination methods (computer tomography of thoracic and

abdominal organs, fiber-optic bronchoscopy, mediastinoscopy), histological type and immune phenotype of the tumour. All patients gave consent to their participation in the study. The permission of Ethics Committee was obtained for the study.
Results: 55 patients were included in the preliminary patients' group, from them 11 patients had at least 1 blood relative with lung cancer in the family history, 17 patients had relatives with malignant tumours of different localisation, but 27 patients had no oncological diseases in their family history. The patients with lung cancer in their family history were diagnosed withy squamose cell cancer (46%), adenocarcinoma (18%), large cell cancer (9%), small cell cancer (18%), carcinoid (9%). The patients with extrapulmonary malignant tumours in their family history, were diagnosed with squamose cell cancer (35%), adenocarcinoma (24%), large cell cancer (17.5%), small cell cancer (17.5%), large cell neuroendocrine cancer (6%). The patients with negative family oncological history were diagnosed with squamose cell cancer (40.8%), adenocarcinoma (18.5%), large cell cancer (18.5%), small cell cancer (18.5%), and large cell neuroendocrine cancer (3.7%).
Conclusion: Tumours of various histogenesis were found in all groups of patients irrespective of their family anamnesis, moreover, a considerable part of the cases consists of non-small cell cancer which can be surgically treated in early stages. In order to find the eventual correlation between histological type of tumour and family history, the study has to be carried out in a larger group of patients. Hypothetically histological heterogeneity of tumours can indicate various hereditary mutations.
Keywords: histological type, Lung cancer, family anamnesis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.219 A HISTOLOGICAL GRADING SYSTEM HAS PROGNOSTIC SIGNIFICANCE FOR PATIENTS WITH RESECTED LUNG ADENOCARCINOMA THAT RECEIVED ADJUVANT CHEMOTHERAPY.

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Background: A pathologic grading system based on histological patterns of pulmonary adenocarcinoma was recently described which has prognostic significance for patients with stage I disease [Sica, Am J Surg Pathol 34(8), 2010]. In this study we evaluated the prognostic significance of this histological grading system in patients with stage I-III lung adenocarcinoma that received adjuvant chemotherapy.
Methods: Clinical information was collected on patients with resected stage I-III lung adenocarcinoma at Memorial Sloan Kettering Cancer Center who has surgery between Jan 2002-Oct 2009. All patients in data base received chemotherapy as per standard practice. Mutation status for EGFR and KRAS was available for all patients. Histological sections of 122 excised pulmonary adenocarcinomas were reviewed and scored according to the histological grading system previously described(Grade I- lepidic, grade II- acinar and papillary, grade III- solid and micropapillary patterns). Tumors were scored based on the sum of the two most predominant grades. Overall survival (OS) was calculated starting 8 weeks post-resection, by which time all patients had started adjuvant treatment.
Results: There were 34 patients with pathological stage I (10 Ia and 24 Ib), 43 with stage II (25 IIa and 18 IIb), and 45 stage III (37 IIIa and 8 IIIb). The histological score distribution was: 9 patients with histological score 3, 43 patients in score 4, 62 patients in score 5, and 8 patients in score 6. Because of the low number of patients in grade 3 and 6, the analysis was performed by combining patients with scores of 3 and 4 (low-risk) and those with scores of 5 and 6 (high risk). Patients in the low-risk group had significantly better overall survival (3yr OS = 75%) compared to patients in the high-risk group (3yr OS = 55%, p=0.033). This result was confirmed when patients were grouped by pathological stage, with low-risk group showing consistently better OS compared to the high-risk group. We did not detect any significant associations between EGFR/KRAS mutation status and histological score in this population.

Conclusion: Histological grading is a good prognostic indicator in a population of patients with resected pulmonary adenocarcinoma that received adjuvant chemotherapy. Similar to what has been established for stage I patients treated by surgery only, the histological score is also capable of stratifying patients with pathologic stage II and III treated with resection and adjuvant chemotherapy with respect to their risk of recurrence. In this small group of patients, we did not observe any association of histological grade and the incidence of EGFR or KRAS mutation. These results do not indicate that the histological grading system may predict benefits from adjuvant chemotherapy given prognostic trends are similar in populations who did not receive chemotherapy. An analysis of tumors from patients randomly assigned to adjuvant chemotherapy in a prospective trial would be necessary to explore this further.

Keywords: Adenocarcinoma, adjuvant therapy, prognostic marker, histological grade

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P4.220 EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION ANALYSIS IN NON-SMALL CELL LUNG CANCER (NSCLC) IN AN IRISH POPULATION

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Background: The presence of activating mutations in the EGFR in NSCLC provides prognostic and predictive information. Therefore, tumoural assessment of EGFR gene status has become standard. Series report EGFR mutations and deletions in approximately 10%-20% of NSCLC tumour samples (the majority of cases being adenocarcinoma) across varying populations. We reviewed all cases where EGFR genetic analysis was performed on NSCLC tissue in our institution.

Methods: A prospectively maintained database was retrospectively reviewed for all cases sent for EGFR analysis between December 2009 and December 2010. Clinicopathologic variables, e.g. tumour stage, smoking status, and ECOG performance status (PS) were recorded. Treatments were also documented. EGFR mutation analysis was carried out using real-time PCR to detect 6 key EGFR mutations in exons 18, 19, 20 and 21 in DNA extracted from formalin-fixed paraffin-embedded tumour.

Results: Sixty-six tumour samples were sent for analysis. Of these patients, 100% were Caucasian. Two patients were Dutch and 1 was Croatian, the remainder were Irish (95%). Forty-four patients (67%) were female and 10 (15%) were non-smokers. Median age at diagnosis was 66 years (range: 29-82). 73% of patients had ECOG performance status 0 or 1 at the time of diagnosis and 60% had disease stage IV. Thirty-nine patients (59%) remain alive at the time of analysis. Of all samples, 57 (86%) were adenocarcinoma. Tumour samples of 3 patients (4.5%) demonstrated an EGFR mutation. All of these were adenocarcinoma, two with L858R mutation in exon 21 and one with deletion in exon 19. All of these patients had stage IV disease at diagnosis, and were non-smoking, Irish females. Two patients with mutations in exon 21 received therapy with EGFR tyrosine kinase inhibitors (TKI) and are alive at the time of analysis, 10.5 and 18.8 months following diagnosis. Ten tumour samples were deemed unsuitable for analysis due to insufficient sample (15%). Sampling was deemed inadequate in 5 (13%) histopathology samples and 5 (19%) of cytology samples. Differences in sampling adequacy by modality used were compared using fisher's exact test and were not significant (p=0.729). One patient received an EGFR TKI following insufficient sampling. This was a 31 year old female, non-smoker with stage IV adenocarcinoma and ECOG PS of 1. Overall survival was 12.8 months with progression free survival of 5 months on TKI therapy.

Conclusion: The number of EGFR mutations detected among the population with NSCLC was markedly lower than documented in other European countries. A number of samples were deemed unsuitable for analysis, however, this did not appear to be due to sampling modality. Standardised and validated methods of EGFR mutation analysis

were used in all cases. The prevalence of EGFR mutations in NSCLC within the Irish population has not been previously studied. If representative of the region, review of this patient cohort suggests a low incidence of EGFR mutations in the Irish NSCLC population. In a similar fashion to enzyme polymorphisms, EGFR genetic change may reflect ethnicity or geography which could have implications for outcomes and the design of clinical trials in the future.

Keyword: epidermal growth factor receptor mutation

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P4.221 THE FREQUENCY OF EGFR AND KRAS MUTATIONS IN NON-SMALL CELL LUNG CARCINOMAS IN THE DUTCH POPULATION

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Background: Recently tyrosine kinase inhibitors have been introduced in the treatment of non-small cell lung cancer (NSCLC). Only patients who have tumors bearing certain EGFR mutations are eligible for this treatment, whereas patients whose tumors harbor KRAS mutations do not benefit from it. Thus far, EGFR mutation frequencies have been determined mostly in East Asian and North American populations, showing large differences between these populations. For the North European population, the prevalence of the mutations is not clear. The aim of the present study was to determine the frequency of EGFR and KRAS mutations in NSCLC in the Dutch population.

Methods: Results of EGFR and KRAS mutation tests performed at five large Dutch hospitals (four large regional hospitals and one academic hospital) in the period 2008-2011 were collected. Most of these results had been obtained by PCR followed by sequencing of the EGFR (exons 19, 20 and 21) and KRAS (exons 1 and 2) genes. For part of the more recent cases, the tests consisted of high resolution melting analysis, followed by sequencing only if the obtained melting curve was abnormal. The tests were performed on formalin-fixed paraffin-embedded tissue or cytological material of both primary lung tumors and metastases.

Results: EGFR mutation status was determined in 605 samples (78.0% adenocarcinomas (AC), 5.6% squamous cell carcinomas (SC), and 16.4% others (mainly undifferentiated large cell carcinomas)). EGFR mutations were detected in 51 out of these 605 (8.4%) samples. The frequency of EGFR mutations in AC was 48/472 (10.2%). These mutations comprised mainly deletions in exon 19 (53.8%) and point mutations in exon 21 (36.5%). EGFR mutations were significantly more common in female than in male patients (12.7% vs. 4.8%, $p<0.001$). KRAS mutations were found in 224 out of 651 (34.4%) tested samples, and in 192 out of 507 (37.9%) AC.

Conclusion: In the investigated cohort, the frequency of EGFR mutations in lung adenocarcinomas is 10.2%. KRAS mutations are observed in 37.9% of lung adenocarcinomas. Compared to East Asian populations, the frequency of EGFR mutations is considerably lower and that of KRAS mutations is considerably higher. The frequencies observed in the present study are more comparable to those observed in North American and South European populations.

Keywords: lung carcinoma, EGFR mutation, KRAS mutation, NSCLC

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P4.222 TTF-1: STILL A RELIABLE TOOL FOR ASSESSING PRIMARY ORIGIN. STUDY OF 650 CASES OF NON PULMONARY NEITHER THYROID PRIMARY CARCINOMAS

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Background: TTF-1 is used in daily practice as a highly specific marker for lung and thyroid primary

tumors. Patients with previous breast cancer have an increased risk to develop a second neoplasm, frequently pulmonary cancer. In such clinical setting, it is very important to confirm its origin in order to avoid misdiagnosis and treatment. Similar situation is observed in other primary tumors and their metastasis to the lung. Our aim was to study the expression of TTF-1 (Novocastra SPT24) in a wide serie of non pulmonary neither thyroid tumors.
Methods: 650 primary tumors, including gastric (51), ovarian (102), prostate (99), pancreatic (42), breast (74), colon (137), endometrial (45) and urothelial bladder (100) primary carcinomas were collected from our files . Tissue micro arrays (TMA) were performed, taking three samples for each case. Negative controls (lymph node tissue) were also included in each TMA. TTF-1 staining was evaluated by two independent pathologists (percentage and intensity of staining). Whenever a major discrepancy was observed, the cases were discussed under a multiheaded microscope. In order to see the pattern of expression, immunohistochemistry was repeated in whole paraffin sections of every positive case and in 25 negative tumors.
Results: TTF-1 expression was observed in 29 cases (4,4 %), mainly in urothelial (1,4 %) and colonic carcinomas (0,8 %). Weak and focal expression was observed in 7,1 % of pancreatic , 4,4 % of endometrial, 4 % of prostatic, 3,6 % of gastric and 2,7 % of breast cancer .However, strong and diffuse expression (>50% of positive cells), was only found in 8 cases (1,2 %: 3 urothelial, 3 ovarian, 1 colonic and 1 endometrial carcinomas).
Conclusion: In our opinion strong and diffuse TTF-1 positivity is highly specific for pulmonary and thyroid primary tumors. Similar results were only found in a low percentage of cases (1,2%), mainly in ovarian and urothelial carcinomas. These results support the role of TTF-1 as an important tool to differentiate primary pulmonary from metastasis. However, weak and focal expression seen in some tumors has not to be interpreted as indicative of pulmonary or thyroid origen and can lead to misdiagnosis in small biopsy or cell blocks from fine needle aspiration. In these setting others specific markers have to be performed
Keywords: specific markers, Lung cancer, TTF-1

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P4.223 ALK GENE REARRANGEMENT : PREVALENCE AND CLINICAL OUTCOMES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) IN EUROPE – A EUROPEAN THORACIC ONCOLOGY GROUP (ETOP) LUNGSCAPE STUDY

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Background: ALK gene rearrangement (ALK+) has been identified as a viable therapeutic target for NSCLC but its prevalence appears to be low, varies depending on the population screened, and on the method used for detection. There is little data on ALK+ in European populations or the natural history of ALK+ NSCLC. Also, there is no consensus on the gold standard test for ALK+. ETOP has established the LUNGSCAPE translational research program to address the challenges of studying rare molecular subtypes of NSCLC by creating a decentralised NSCLC tissue bank linked to clinical, pathological and molecular data held in a central web-based database. The first LUNGSCAPE study will investigate the prevalence and clinical outcomes of ALK + in NSCLC patients in Europe.
Methods: ETOP members will retrospectively identify NSCLC cases (resected stage I-III) with tumour tissue available for research. Clinical (demographic and outcome) and pathological

data will first be submitted to the central database then tissue samples of cases meeting predefined acceptance criteria, to control quality of clinical data, will be analysed. Tissue samples will be analysed at local sites using the same methods, and after the site has passed a pathology quality assurance exercise. The objectives are to 1) evaluate the expression and clinical significance of ALK+ in a cohort of 1500 NSCLC patients with resected stage I-III tumors. 2) Conduct a nested case-control study of ALK+ versus ALK- patients (matched 1:2) with a target sample size of 50 ALK+ patients to give a HR for survival of 1.72 with 80% power, p=0.05 (80% events). 3) Compare a panel of antibodies for ALK+ using immunohistochemistry (IHC) on full tissue sections and on a tissue microarray (TMA) 4) Compare IHC to fluorescent in situ hybridization (FISH) in TMA (all) samples 5) Compare IHC ALK+ cases with FISH in full sections 6) Correlate TMA results with results for full sections.

Results: 19 ETOP member sites have registered to participate. More than 5000 surgically resected, clinically annotated samples with at least 3 and not more than 8 years of follow up are potentially available. The database is constructed with data entry scheduled to commence in April 2011 and analysis of tissue samples through Q2 - Q3.
The organizational structure, standard operating procedures for clinical data collection and molecular testing, results from the pathology QA exercise, and the progress of the study will be reported.

Conclusion: A consortium approach is essential to rapidly acquire knowledge of the prevalence and context of rare molecular subtypes. The ETOP LUNGSCAPE 001- ALK study provides a mechanism to address the questions of who to test and how to test in a large cohort of patients. The coordinated effort with built in QA processes and sharing of knowledge will harmonise practices and raise standards of tissue biobanking, clinical data collection and molecular testing across Europe, ultimately for the benefit of patients and better access to new treatments.

Keywords: Non-small cell lung cancer, ALK gene rearrangement

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P4.223 INVESTIGATION OF POLY (ADP-RIBOSE) POLYMERASE 1 (PARP1) AS A NOVEL THERAPEUTIC TARGET IN SMALL CELL LUNG CANCER (SCLC)

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Background: Small cell lung cancer (SCLC) is an aggressive disease characterized by initial sensitivity to chemotherapy and radiation followed by the invariable development of treatment resistance. New therapies are needed to improve clinical outcomes for these patients. Using high-throughput protein array profiling, we previously demonstrated overexpression of poly (ADP-ribose) polymerase 1 (PARP1) in a panel of 35 SCLC cell lines. Here we investigated PARP1 expression in patient tumors and as a potential new therapeutic target.

Methods: PARP1 mRNA levels were assessed in publically available databases. At the protein level, total PARP1 was measured by immunohistochemistry (IHC) in a tissue microarray of archival tumor specimens. IHC scores were calculated based on the percentage of tumor cells staining positive times the staining intensity (0-3+) (possible scores 0-300). For the in vitro studies, cells were treated with a commercially available PARP inhibitor for 14 days +/- 7 days of chemotherapy and relative cell viability assessed by cell count.

Results: PARP1 mRNA was overexpressed in SCLC tumors relative to non-small cell lung cancer (NSCLC) (p=0.005) and normal lung tissue (p=9.7 x 10^{-8}) when compared by t-test. In neuroendocrine lung tumors, total PARP1 protein levels correlated with the degree of differentiation. Highest levels were seen in SCLC (n=12, mean IHC score

262/300) and large cell neuroendocrine (n=20, mean 237/300), while intermediate levels were seen in atypical carcinoid (n=9, mean 230/300) and typical carcinoid (n=55, mean 197/300). In contrast, PARP1 expression was significantly lower in NSCLC with squamous (n=15, mean 120/300) and adenocarcinoma (n=24, mean 104/300) histologies. Preliminary in vitro testing showed sensitivity of SCLC and LCNEC cell lines to PARP inhibition, but resistance in NSCLC lines. When combined with cisplatin and etoposide in a SCLC line, cell viability was further decreased beyond that of chemotherapy or PARP inhibitor alone.

Conclusion: PARP1 is highly expressed in high-grade neurodendocrine lung tumors at the mRNA and protein level. PARP1 inhibition alone and in combination with chemotherapy showed activity in SCLC and LCNEC lines. These findings support further investigation of PARP1 as a potential novel therapeutic target in high-grade neuroendocrine lung cancers.

Keywords: SCLC, PARP1, Large cell neuroendocrine

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P4.224 HILAR OR MEDIASTINAL LYMPHADENOPATHY IN PATIENTS WITH CONCURRENT OR PREVIOUSLY DIAGNOSED EXTRATHORACIC MALIGNANCY : RELEVANCE OF TRANSBRONCHIAL NEEDLE ASPIRATION (TBNA)

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Background: Transbronchial needle aspiration (TBNA), conventional or ultrasound-guided (EBUS-TBNA), is a minimally invasive method in the initial staging (N) of patients with NSCLC. Other applications can be discussed. We investigated the effectiveness of TBNA in the diagnosis of hilar or mediastinal lymphadenopathy in patients with a concurrent or previous known extrathoracic malignancy.

Methods: Between 2007 and 2010, 451 consecutive TBNA (conventional and EBUS-guided) procedures were performed in the our Chest Department. We analyzed data of patients with a concurrent or previously diagnosed extrathoracic malignancy referred for TBNA with a suspicion of mediastinal or hilar metastasis based on ≥10mm lymphadenopathy or <10mm lymph node with 2-fluoro-2-deoxy-D-glucose (FDG) uptake on positron emission tomography (PET). Previous hemopathy were excluded. Procedures were realized in outpout patients. Rapid on site examination was systematically performed. Tumor differentiation markers (TTF1, P63, CK7/CK20, Hormonal Receptors...) were performed whenever it was needed, depending on the diagnostic orientation and morphology.

Results: 68 patients with concurrent (n=15) or previously diagnosed (n=53) extrathoracic malignancies were evaluated. They were 21 breast, 11 head and neck, 8 kidney, 7 prostatic, 6 colorectal carcinomas, 5 melanomas and 18 others various sites; 8 patients having two extrathoracic malignancies. A total of 70 procedures were performed among which 16 conventional TBNA and 54 EBUS-TBNA (2 patients had the both procedures). A total of 129 lymph nodes was analyzed. Mean number of needle passes performed by procedure was 5 (1 to 10). The median size of lymph nodes was 12mm (6 to 40). All procedures were contributive except 2 (final diagnosis were SCLC). In 40 procedures (59%), TBNA detected lymph node metastatic spread: 20 metastasis of the known extrathoracic tumour (29%), 18 from a second malignancy (26%) (12 NSCLC and 6 SCLC) and 2 from undifferentiated carcinoma. In 28 procedures (41%), lymph node material was obtained, without malignancy (negative TBNA) but in 4 cases, epitheliod cells granulomas were observed suggesting sarcoidosis or sarcoid-like reaction. In cases with negative TBNA, 9 subsequent surgical stagings were performed: malignancy was diagnosed in only 1 patient. Contributive material was obtained in 97% of the procedures and a final pathological diagnosis available in 49 (72%). In the contributive procedures with pathological diagnosis available, sensitivity and negative predictive values of lymph node metastatic spread were 97% and 85%

with 100% specificity. No complication had occured.
Conclusion: TBNA is a safe and effective modality to evaluate mediastinal or hilar lymphadenopathy in patients with extrathoracic malignancy. The application of this diagnostic tool is likely to have significant clinical implications : to confirm the lymph node spread by extrathoracic malignancies or to perform alternative diagnosis as a second cancer, especially lung cancer or granulomatosis.
Keywords: EBUS, TBNA, Staging, lymphnode

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P4.226 EVALUATION OF DIAGNOSTIC ACCURACY AND COST-EFFECTIVENESS ON INTRAOPERATIVE FINE NEEDLE ASPIRATION CYTOLOGY FOR LUNG TUMORS

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Background: The number of small-sized lung tumors is increasing in association with development of imaging methods such as multi detector-row CT (MDCT) and PET. In some cases we find difficulty to diagnose preoperatively even though transbronchial lung biopsy (TBLB) or percutaneous CT-guided biopsy is done. We perform intraoperative fine needle aspiration cytology (IFNAC) in such cases. We evaluate whether IFNAC is reliable, safe, and cost-effective approach or not.
Methods: We performed 234 IFNAC during five years from 2005 to 2009. After intrathoracic observation, a central part of tumor was aspirated through 22G needle and the diagnosis was reported within 30minutes. We examined the specificity, sensitivity, false positive, false negative, and a correlate of pathological diagnosis. Amount of cost was also calculated.
Results: Among 234 cases, 219 were diagnosed as malignant tumors (including 200 primary lung cancers, 19 metastatic tumors), and 15 belonged to Class I and II (5 lung cancers, 7 granulomas, 2 benign tumors, 1 fungus ball). Sensitivity was 97.7%, and there was no false positive, which means specificity was 100%. On the other hand, 5 false negative had occurred. Among 219 malignant cases, it was quite easy to predict pathological subtypes in adenocarcinoma (86%) and squamous cell carcinoma (92%), but had difficulty in large cell carcinoma (17%), pleomorphic carcinoma (0%), and metastatic tumors (21%). There was no recurrent case which is suspected involvement in dissemination due to puncture. IFNAC was extremely costless in comparison to VATS lung biopsy.
Conclusion: This study showed IFNAC is a reliable (high sensitivity and specificity), safe, and cost-effective approach for diagnosis on lung tumors.
Keywords: intraoperative diagnosis, fine needle aspiration cytology, Lung cancer

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P4.227 IMPORTANCE OF IMMUNOHISTOCHEMISTRY (IHC) ON THE DIAGNOSIS OF LUNG CANCER

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Background: Increasingly in Lung Cancer central review of initial histopathology reports is being undertaken. This allows for site specialized Lung pathologists to review the histology specimens and also for IHC to be undertaken in central pathology laboratories. This is especially important in the sub-classification of Lung Cancer, not only into Small cell Lung Cancer (SCLC) or Non Small cell Lung Cancer (NSCLC), but also for the subclassification of NSCLC into squamous and non-squamous, which now has major therapeutic implications.
Methods: Between 2006 and 2010, histopathology specimens from patients referred to the BOCOC in Nicosia, coming from private histopathologists in Cyprus (without IHC being undertaken) were referred for central review to a specialized Lung pathologist (CC) in the Nicosia General Hospital. This was undertaken in 86 cases. Comparison was made between the initial histology diagnosis and the

final diagnosis following central review and IHC.
Results: There were 18 major changes in diagnosis (21%): 4 NSCLC changed into SCLC, 2 SCLC into lymphoma, 2 SCLC changed into NSCLC, 2 adenocarcinoma into mesothelioma, 1 squamous into SCLC, 1 lymphoma into adenocarcinoma, 1 carcinoid into metastasis from bladder cancer and finally 5 patients with poorly differentiated tumours or wide differential diagnosis were classified into 1 lymphoma, 1 SCLC, 2 adenocarcinomas and 1 squamous cell cancers. There were also 22 minor changes (26%) where the subclassification of NSCLC changed, only 19 (22%) with treatment implications, ie from squamous to non-squamous and vice versa. Hence in total for 37 patients (43%) there were potential treatment implications as a result of this review.
Conclusion: This study shows the importance of undertaking central review including IHC for all patients referred with an initial diagnosis of lung cancer
Keywords: histology review, immunohistochemistry, Lung cancer

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P4.228 PREVALENCE OF MUTATIONS IN EGFR, KRAS AND BRAF IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) AS ASSESSED BY A PANEL OF PCR-BASED ASSAYS

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Background: The identification of specific somatic mutations is increasingly important in the clinical management of NSCLC as they identify molecular subsets of lung cancer and may predict responsiveness to specific therapies. For example, EGFR mutations identify patients with advanced NSCLC who have a high likelihood of responding to anti-EGFR tyrosine kinase inhibitors. We performed a systematic assessment of the prevalence of mutations in EGFR, KRAS and BRAF in a large panel of formalin-fixed paraffin-embedded tissue (FFPET) samples of NSCLC, using 3 investigational PCR-based assays.
Methods: EGFR mutation status was assessed using the cobas EGFR Mutation Test which is designed to detect 43 mutations within exon 18 to exon 21 of the EGFR gene, including G719A/S/C in exon 18, deletions in exon 19, S768I/T790M and insertions in exon 20, and L858R/L861Q in exon 21. KRAS mutation status was assessed using the cobas KRAS Mutation Test, which detects ≥ 21 mutations within codons 12, 13, and 61 of the KRAS gene. BRAF mutation status was assessed using the cobas 4800 BRAF V600 Mutation Test, which was designed to detect the V600E (1799T>A) mutation in exon 15 of the BRAF gene. Test results for each assay, which requires 100-150 ng DNA, can be generated within 8 hours.
Results: A total of 941 FFPET NSCLC vendor-purchased samples were analyzed. Among 941 samples, 904 (96.1%) were NSCLC, 17 (1.8%) were small cell lung cancer (SCLC), 11 (1.2%) had indeterminate histology; and 9 (1.0%) had no tumor cell present. The 904 NSCLC and 17 SCLC samples were analyzed for EGFR mutations. 893 of 921 (97%) (876 NSCLC and 17 SCLC) samples gave a valid test result. Among the 17 SCLC, no EGFR mutations were detected. In the 876 NSCLC samples, EGFR mutations were detected in 90 (10.3%) samples, including 85 (11.5%) in non-squamous cell carcinoma and 5 (3.0%) in squamous cell carcinoma. . The EGFR mutations detected included: 46 exon 19 deletions, 22 L858R, 4 G719X, 5 L861Q, and 6 exon 20 insertions as single mutations. Interestingly, there were 6 samples with more than one EGFR mutation (5 samples with 2 mutations, 1 sample with 3). Three of these cases involved L861Q mutations and 4 involved exon 20 insertions. 544 NSCLC samples which had no detectable EGFR mutations were further analyzed for KRAS and BRAF mutations. 127 of 541 (23.3%) samples contained KRAS mutations. 122/127 (96%) KRAS mutations were located at codon 12/13 and 5/127 (4%) were located at codon 61. Only 4 of 544 (0.7%) samples contained a BRAF V600E mutation.
Conclusion: These data indicate that: a) EGFR mutations occur in approximately 11% of unselected non-squamous NSCLC and 3% of squamous NSCLC; b) multiple EGFR mutations within a sample are not unusual, especially involving L861Q and S768I; c) EGFR mutations are rare in SCLC; d)

in NSCLC, KRAS and BRAF V600E mutations are mutually exclusive; e) all 3 assays can be performed on as little as 375 ng of total FFPET-derived DNA.
Keywords: EGFR mutations, Kras mutations, BRAF mutations, molecular diagnostics

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P4.229 SPECIAL PATHOLOGIC EXAMINATION IMPROVES LYMPH NODE (LN) RETRIEVAL IN RESECTED LUNG CANCER.

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Background: Pathologic nodal staging is the main determinant of prognosis in patients following resection for lung cancer. Both surgeons and pathologists share the responsibility for examination of mediastinal LNs, however, the examination of intrapulmonary LNs is exclusively performed in the pathology laboratory. A prior analysis from the Memphis Metropolitan Area Quality of Surgical Resection Cohort showed that the median number of N1 LNs was 3. This was similar to the findings of the multi-institutional ACOSOG Z0030 study in which the median number was 5. We sought to determine the frequency with which intrapulmonary LNs are left unexamined and test the impact of a special pathology examination protocol on nodal staging.
Methods: Prospective case-control study of remnant lung cancer resection specimens using a special pathology examination protocol of thin-section lung dissection and light microscopy on all retrieved material, after completion of routine pathologic examination. We compared findings of this examination to the routine pathologic examination, and an external control cohort matched for pathologist and extent of resection.
Results: Additional LNs were discovered in 93% of specimens (table, N=41). Four hundred and sixty one LN-like samples were submitted, 305 (66%) were actual LNs, of which 32 (10%) had metastasis. Six patients (15%) were pathologically upstaged by the special pathology examination: two with satellite nodules, four with LN metastasis. Of the 12 patients with LN metastasis detected by the routine pathologic examination, 6 (50%) were found to have additional positive LNs. The median size of metastatic LNs was 1.3cm (range 0.1-2.4cm) versus non-metastatic LNs 0.6cm (range 0.1-2.7), p<0.0001. The median time for the special examination was 30 minutes (range 12-80 minutes) for the entire trial and decreased significantly from the first group of ten cases (median 44 minutes) to the last group of ten cases (median 25 minutes), p=0.0029.

	Median number of N1 LNs examined (range)	Median number of all LN examined (range)
Control, era before special protocol	2 (0-13)	3 (0-19)
After routine pathology examination	4 (0-15)	7 (1-27)
After special pathology examination	6 (0-46)	6 (6-46)
Routine pathologic examination + special pathologic examination	10 (0-61)	15 (1-62)
	Median patient increase in total LNs examined	P-value
Control compared to routine pathology examination	3	0.0045
Routine pathology examination compared to routine pathology examination + special pathology examination	6	<0.0001
Control compared to routine pathology examination + special pathology examination	8	<0.0001

Conclusion: A special pathologic examination protocol retrieved a significant number of undetected N1 LNs, some of which harbored metastatic disease. A clinically meaningful number of patients were pathologically upstaged with the special examination, indicating a potential impact on prognosis and treatment recommendations. Despite a statistical difference in the size of LNs containing metastasis, broad overlap precludes using size as a discriminating characteristic. The time for the special examination declined significantly throughout the trial, demonstrating the value of experience and supporting the clinical feasibility of the special protocol. Additional studies are indicated to determine if the use of this technique influences outcomes.
Keywords: Lymph node, Lung cancer, Staging

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oster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.230 SIZE CHARACTERISTICS OF LYMPH NODE MATERIAL RETRIEVED FROM REMNANT TISSUE AFTER ROUTINE PATHOLOGY EXAMINATION OF LUNG CANCER RESECTION SPECIMENS.

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Background: Lymph node (LN) stage is the most important prognostic determinant after resection of lung cancer. Eighteen percent of all lung cancer resections in the US and 12% of our Memphis Metropolitan Area Quality of Surgical Resection (MMA-QSR) cohort have no LN examined (pNx). We previously showed that patients with pNx have inferior survival to T-category matched pN0 patients with at least 1 examined LN. Only a median of 3 N1 LNs are examined after resection of lung cancer in the US, this is identical to the MMA-QSR cohort. We hypothesized that a significant number of intrapulmonary LN are left unexamined in lung resection specimens and sought to determine the proportion of such nodes that harbor undiagnosed metastases. We report the size characteristics of the additional material retrieved by our re-dissection protocol.
Methods: Prospective study of lung resection specimens re-dissected after signout of the final pathology report. Remnant lung material was dissected with thin cuts and all anthracotic material was retrieved for microscopic examination, irrespective of size or location. The size of non-LN tissue, LN without metastasis and LN with metastases were compared using the Wilcoxon-Mann-Whitney test.
Results: 41 remnant lung resection specimens were examined, from which 461 LN-like materials were retrieved. Of these, 156 (34%) proved to be non-LN tissue. Thirty two of the 305 (10%) LN retrieved had metastasis. These LN were found in 16 of 41 (39%) patients, 4 of whom (25%) had been reported to be pN0 after routine examination. The non-LN tissue was significantly smaller than LN material ($p<0.0001$); LN with metastases were significantly larger than those without metastases ($p <0.0001$). However, there was significant overlap in size between non-LN and LN tissue and between LN with and without metastasis (Table 1).

Number of LNs	Mean size, cm	Standard deviation	Minimum size, cm	25th percentile size, cm	Median size, cm	75th percentile size, cm	Maximum size, cm
Non-lymph node samples							
156	0.57	0.44	0.1	0.25	0.5	0.7	2.1
Lymph node samples, all							
305	0.73	0.49	0.1	0.4	0.7	0.8	2.7
Lymph nodes without metastasis							
273	0.66	0.42	0.1	0.4	0.6	0.8	2.7
Lymph nodes with metastasis							
32	1.33	0.59	0.1	0.75	1.3	1.7	2.4

Conclusion: A third of material retrieved as LN was non-LN tissue. This probably also occurs during routine pathologic examination and likely contributes to the low LN counts from N1 stations. However, we also found a mean of 7 discarded LN per patient. The statistically significant difference in size between non-LN and LN, and between LNs harboring and not harboring metastasis, is clinically meaningless because of the broad overlap in size between the 3 different types of tissue material. Therefore, LN size is not an adequate arbiter of likelihood of LN metastasis. The protocol for routine pathologic examination of lung resection specimens needs to be modified to facilitate more thorough examination for intrapulmonary LN.
Keywords: Staging, pathology, Lymph node, quality of care

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P4.231 EXAMINATION OF THE INFLUENCE THAT VASCULAR INVASION AND LYMPHATIC INVOLVEMENT GIVES PROGNOSIS OF STAGE I NON SMALL-CELL LUNG CANCER IN NEW TNM CLASSIFICATION

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Background: Some reports that vascular invasion and lymphatic involvement is a prognostic factor have appeared in Stage I non small-cell lung cancer in previous TNM classification. The new classification (UICC-TNM 7th) has been already used, but in this classification, the vascular invasion and lymphatic

involvement is not yet considered in the stage.
Methods: We investigated the influence that vascular invasion and lymphatic involvement (assumed v/ly factor as follows) gives recurrence rate of Stage I non small-cell lung cancer in new TNM classification. We analyzed 250 Stage IA-IB cases that prognosis is clear among 563 cases of non small-cell lung cancer to whom radical operation was performed in Tokyo medical and Dental University Hospital in Nov.1993 - Jan.2006. We used Kaplan Meyer analysis for survival rate, the chi-square test for comparison of recurrence rate and Logistic regression analysis for multivariate analysis.
Results: In 250 cases, p-T1a, p-T1b and p-T2a cases were 80, 55 and 115. And five year survival rate was 95%, 87% and 73% in each stage. Analysis of all cases showed that recurrence rate is significantly high in v/ly factor positive cases ($p<0.001$), and subclass analysis in p-T1a groups showed the same results (p-T1a:$p=0.003$). In multivariate analysis of the p-T2a group, p factor was the only significant recurrence factor ($p=0.04$), but v/ly factor was the only significant recurrence factor ($p=0.005$) when the p2 cases were excluded from this group.
Conclusion: It is supposed that vascular invasion and lymphatic involvement may be an important recurrence factor of Stage I non small-cell lung cancer (except p2 cases) in a new classification same as a previous classification.
Keywords: Stage I non small-cell lung cancer, vascular invasion and lymphatic involvement, recurrence factor, Prognosis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.232 SMOKING EFFECTS ON TOLERANCE TO PHYSICAL EXERCISE IN SEDENTARY YOUNG WOMEN

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Background: Introduction: Smoking is now worldwide considered a public health problem, which is responsible for the increased prevalence of lung cancer, chronic obstructive pulmonary diseases and coronary artery disease. Smoking is even more harmful when associated with a sedentary lifestyle, which is seen as a primary factor for cardiovascular disease. The six-minute walk test is being used as an alternative to evaluate the physical capacity of patients with heart or lung disease. The test measures the distance a patient can walk on their own in a corridor for six minutes. Along with the test, the Borg scale was used, therefore the subjective perception of intensity of effort by the patient could be measured in numerical values (degree of fatigue), contributing greatly to the interpretation of results. OBJECTIVE: Investigate the effects on tolerance to physical exercise in sedentary young women.
Methods: The evaluation of 40 sedentary women was divided into two groups: Control group (20 non-smokers) and Smoking group (20 smokers). Firstly, data was collected on respiratory rate, heart rate and blood pressure. In sequence, they took the six-minute walk test. Immediately after the test, the level of effort on the Borg scale was verified and the women were assessed again, according to the parameters mentioned above. The distance covered in the walking test was also measured. The data were analyzed using the "Student's t test"
Results: In the control group of nonsmokers, there was no statistically significant difference between the results of the pre-test and the test. Taking into consideration the distance traveled by these patients (628m), the difference was statistically greater than the distance traveled by the smoking group (536m). The smokers showed statistically significant difference for heart rate and respiratory rate in relation to its preliminary assessment. As for the Borg scale, this group had an average value of five, higher than the control group, whose average value was three.
Conclusion: After the six-minute walk, there was a marked increase in respiratory rate, heart rate and feeling of tiredness in the smoking group. Also, the distance traveled by the smoking group was statistically lower than the distance traveled by the control group.
Keywords: physical exercise, Smoking effects

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P4.233 ROS RECEPTOR TYROSINE KINASE EXPRESSION IN NON-SMALL CELL LUNG CANCERS AND CLINICAL IMPLICATION

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Background: Several microarray analyses showed significantly elevated ROS expression in 20 to 30% of non-small cell lung cancers (NSCLC). As a mechanism, oncogenic translocation of ROS in NSCLC has been identified. However, there is great difference in the frequencies of expression by microarray data and gene translocation. Recent report of an epigenetic mechanism of gene activation in brain tumors suggests presence of alternative mechanism of ROS activation in NSCLC other than translocation. We aimed to evaluate the frequency of ROS expression in NSCLC at protein level and its prognostic significance for future use of recently developed ROS kinase inhibitors.
Methods: Four hundred and twenty five cases of resected stage I NSCLC between 2000 and 2005 were recruited to tissue microarray. Among them, 252 adenocarcinomas, 159 squamous cell carcinomas and 14 NSCLC, NOS were included. Immunohistochemistry using monoclonal antibody against ROS protein and statistical analyses with clinicopathologic data were performed. As a positive and negative control, we used HCC78 and NCI-H460 cell blocks, respectively after confirmation of their ROS expression status by real time PCR. The expression levels were arbitrarily scored and more than moderate intensity is considered as positive. To elucidate mechanism of expression, a subset of samples was subjected to copy number measurement by array CGH and FISH, and methylation analysis of the gene.
Results: Cell block of HCC78 showed strong membranous and cytoplasmic ROS expression, in contrast to complete negativity of NCI-H460 cells. Similarly to pervious microarray data, overall expression rate of ROS in NSCLC was 34.4% (33.3% for squamous cell carcinoma, 34.5% for adenocarcinoma, 42.9% for NSCLC, NOS). Patients were followed up to 8.8 years (median follow-up period; 4.0 years). ROS expressing group showed lower recurrence-free survival (RFS) rate than non-expressing group (p=0.121). In subgroup analysis, ROS expressing adenocarcinomas showed significantly lower RFS than non-expressing adenocarcinoma group (p=0.032). However, RFS of ROS expressing squamous cell carcinomas and overall survival of ROS expressing adenocarcinomas were not significantly different in each subgroup (p=0.592 and p=0.253, respectively). Array CGH analysis showed copy number gain in 15.8% (3/19) of adenocarcinomas, which was confirmed by FISH analysis. Methylation study showed no meaningful result.
Conclusion: A subset of NSCLC showed over-expression of ROS receptor tyrosine kinase possibly in relation to gene copy number gain. In adenocarcinoma patients, its over-expression is related to poorer prognosis. The results suggest that ROS can be a potential therapeutic target of a subgroup of NSCLC. Further studies are needed to validate our results and to elucidate the mechanism of ROS activation in NSCLC.
Keywords: receptor tyrosine kinase, Non-small cell lung cancer, ROS

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P4.234 DIAGNOSTIC ACCURACY OF TUMOR MARKERS IN SEROUS EFFUSION

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Background: Elucidation of the etiology of serous effusions is a challenge for the clinical diagnosis. Several studies have demonstrated the clinical utility of tumor markers (TM) for diagnosing neoplastic effusions, but the results are highly disparate. The reported sensitivity varies from 20% to 80%, depending on the combination of markers, and the specificity from 70% to 100%. The main

conditions resulting in false-positive TM results, tuberculous, complicated parapneumonic effusions and empyema, can be identified by analysis of several biological magnitudes, such as adenosine deaminase (ADA), C-reactive protein (CRP) and % of polymorphonuclear (%PN). The aim of tihs study is to evaluate the diagnosis performance of TM in serous effusions and to assess whether ADA, CRP and %PN allow identify false positives.
Methods: We determinated in 537 serous effusions CEA, CA19-9, CA15-3, ADA, CRP and leukocyte differential count. We classified in two groups: those effusions with ADA <45U/L, CRP <50mg/L or differential leukocyte count <90% PN group A and those with ADA >45U/L, CRP >50mg/L or >90%PN group B (identify most frequent diseases with no malignant elevations of TM). In group A (n=438) the effusions were considered to have a malignant etiology when TM values were over the serum cut-off for CEA, CA15-3, and CA19-9; and when fluid/serum ratio was >1.2 for CEA, CA15-3 and CA19-9.
Results: Based on these criteria, sensitivity for the combination of all TMs was 77.65% at 100% specificity. In Group B (n=109) cut-off established for CEA, CA15-3 and CA 19-9 was 50 ng/mL, 70 U/mL and 7700 U/mL respectively. We obtained a sensitivity of 68.4% at 100% specificity. With a sensitivity for while effusion of 84% at a maximum specificity
Conclusion: The identification of pathological conditions and other factors that result in false-positive TM findings when analyzing serous effusions yields high sensitivity and maximum specificity for these determinations.
Keywords: Serous effusions, Tumour markers, Diagnostic accuracy, Neoplasia

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P4.235 TESTING FOR EGFR AND KRAS MUTATIONS IN THE NORTHERN NETHERLANDS: BIOPSIES WITH SUFFICIENT TUMOUR TISSUE

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Background: The availability of EGFR and KRAS testing in patients with advanced non small cell lung cancer has recently been introduced in the Northern Netherlands. We explored the number of tumour biopsies used for EGFR and KRAS mutation.
Methods: Between November 2008 and August 2010 chest physicians from 8 hospitals in the Northern Netherlands send in lung biopsies to the laboratory of Molecular Pathology at the department of Pathology within the University Medical Center of Groningen for EGFR/KRAS mutation analysis and EGFR FISH status using Colorade criteria. For the detection of mutations in exons 18-21 of EGFR and exon 1 of KRAS bidirectional sequence analysis was performed on DNA extracted from an enriched region in the PFFE slide marked by the pathologist containing >50% tumor cells. Patient files were studied for sex, smoking status, age, stage at diagnosis, first three lines of treatment (including TKI), progression free survival (PFS) and overall survival. A total of 257 tumour biopsies were tested and for 187 patients complete clinical data were available. Median age at diagnosis of patients was 61 (38- 88) with 43% of patients being women. Smokers 40%, non smokers 16%, former smokers 42%. Two patients had a second primary tumor which were both analysed.
Results: We were able to extract adequate DNA from 144 of 189 samples send to our lab (76%). A relative large number of biopsies (42/189; 24%) was not used for DNA testing because no sufficient tumor cells were present. In 3 cases the quality of DNA was not suitable for mutation testing. 11/144 (8%) patients had an EGFR mutation, 2 patients had non-functional mutations. No TKI-resistant mutations were found. 49/120 (40%) patients had a positive FISH according to the Colorado criteria (43 EGFR polysomy and 6 amplification). 46/144 (32%) patients had a KRAS mutation, 1 patient had both a EGFR and KRAS mutation. Of the 189 tested patients, 55 were treated with an EGFR TKI. Of these 55 patients, 28 had wildtype EGFR and 9 had an EGFR mutation, 1 patient had an intron mutation and EGFR mutational status was unknown in 16 patients because of insufficient material for mutation testing. Presently, follow-up data of these patients are collected to evaluate the TKI-response in relation to EGFR-mutations
Conclusion: Increasing EGFR mutation testing is implemented in advanced NSCLC. Sufficient tumour tissue for adequate mutation analysis remains an issue in testing advanced NSCLC both by better instruction of chest physicians regarding biopsy material and selection of appropiate samples, and the introduction of EGFR-mutation tests with

higher analytical sensitivity such as High-Melting-Resolution-Analysis.
Keywords: EGFR, EGFR TKI, Kras, EGFR FISH

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P4.236 THREE-DIMENSIONAL RECONSTRUCTION OF PAPILLARY ADENOCARCINOMA OF THE LUNG: SHEEP LOOKING LIKE A WOLF?

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Background: Recently new multidisciplinary classification of lung adenocarcinoma has been described. The Papillary predominant adenocarcinoma (PA) shows a major component of a growth of glandular cells along central fibrovascular cores. Myofibroblastic stroma is not needed to diagnose this pattern. During resection of the lung, compression / atelectasis of the lung is a normal phenomenon. The hypothesis is that if the air component is minimal a seemingly papillary pattern may arise. The clinical relevance is that in contrast to AIS, PA is by definition invasive. The purpose of this study was to make 3- dimensional reconstruction of a strongly "papillary" tumor.
Methods: From a patient with transthoracic biopsy (TTB) and lobectomy of a tumor serial hematoxilin-eosin (H&E) stained sections were available for review. From the resection specimen 30 serial H&E slides were digitised (20x objective). The panoramic viewer software in combination with the 3D module (3DHISTECH, Budapest, Hungary) was used to make a 3 dimensional reconstruction.
Results: For a papillary tumor it was expected to find cross sections of papillae. However, this was rarely the case. In contrast the 'so called' papillae appeared to be continuous in space and were thin walls. Moreover, this architecture was similar to that of the adjacent lung and tumor cells at the edge were merging seamless with the pre-existing alveolar walls. Thus the papillary pattern was created by strongly compressed cut alveolar walls covered with monotonous tumor cells, making the diagnosis AIS in stead of PA. In addition the TTB consistently showed not-compressed lung with AIS.
Conclusion: In microscopic sections of strongly compressed resection specimen with AIS a pseudopapillary pattern may be present mimicking true PA. Taken the clinical consequences into account, care should be taken not to overdiagnose AIS as PA. This overdiagnosis of PA may be avoided, by 1) realization that the chance to cut a papilla exactly longitudinal is as small as an exactly longitudinal hair in the skin 2) by using an elastic stain as elastin is a component of pre-existing alveolar wall and NOT produced by a papillary tumor (absent in papillary tumors in other organs and absent in metastases of papillary carcinomas of the lung).
Keywords: papillary carcinoma, overdiagnosis, elastin, adenocarcinoma in situ

Poster Session 4 – Pathology Thursday, 7 July 2011 10:00-12:30

P4.237 CLINICAL VALUE OF INTRAOPERATIVE PLEURAL LAVAGE CYTOLOGICAL POSITIVITY IN LUNG CANCER PATIENTS

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Background: The clinical significance of intraoperative pleural lavage cytology (PLC) for lung cancer has been insufficiently elucidated. Whether the intraoperative PLC has effect on the independent factor as a prognostic marker or the impact of a positive result on stage-adjusted survival.
Methods: Between 2000 and 2008, PLC was performed both after thoracotomy of the thoracic cavity in patients with lung cancer without malignant pleurisy .
Results: We examined 30cases. this was shown to be correlated with lyhph-angio-invasion.
Conclusion: PLC status after thoracotomy provides useful information in the detection of high-risk subgroup for pleural recurrence. Although PLC status is closely associated with survival, its prognostic value is not independent.
Keywords: Pleural lavage cytology, Prognosis

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.238 CORRELATION OF CO MORBIDITY, PATIENT CHARACTERISTICS AND THE OCCURRENCE OF TOXICITY DUE TO CONCURRENT, SEQUENTIAL CHEMO RADIOTHERAPY OR HIGH DOSE RADIOTHERAPY ALONE, IN PATIENTS WITH LOCALLY ADVANCED NON SMALL CELL LUNG CANCER

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Background: The prognosis of locally advanced non-small cell lung cancer (NSCLC) is poor with a median overall survival of 15 months. The treatment of choice is concurrent chemo radiotherapy with a 12% increase in the overall survival compared to radical radiotherapy alone. Sequential chemo radiotherapy or radiotherapy alone is indicated in case of a large involved field and the estimation of poor tolerance. Objective parameters for patient selection are missing
Methods: . Prospective study in patients with locally advanced NSCLC in the Netherlands Cancer Institute- Antoni van Leeuwenhoek hospital, , treated in 2008 and 2009 with radical radiotherapy with or without chemotherapy, except SBRT. Patients were referred from field hospitals or presented as new patients directly to the Antoni van Leeuwenhoek hospital. Tailored treatment was identified during multi disciplinary consultation. Because of the incompleteness of data in patients receiving sequential chemo radiotherapy and radiotherapy alone, analysis on toxicity was done in the concurrent group. .For the assessment of co-morbidity the Charlson Index and for acute toxicity scores the Common Toxicity Criteria of Adverse Events (Vs. 3.0) were used. Statistical methods included for age Wilcoxon Mann-Whitney Rank Sum Test, for treatment Fisher's Exact Test for Count Data, for the Charlson index and performing status Linear-by-Linear Association Test
Results: 155 patients underwent concurrent chemo radiotherapy, 33 patients sequential chemo radiotherapy and 62 patients radiotherapy alone. No significant correlations were found between co morbidity, age ≥75, weigh loss ≥ 10%, 6 months before treatment and induced acute toxicity CTC ≥2. PS ≥ 2 led to discontinuation of chemotherapy (0.009) and hospital admission (0.05) in concurrent chemo radiotherapy.
Conclusion: Co-morbidity and upfront weight loss, do not have a significantly clinical impact on acute toxicity induced by concurrent chemo radiotherapy. Although baseline poor performing status and age ≥ 75 contributes to discontinuation and hospitalisation during treatment, no relation was seen with toxicity.
Keyword: non small cell lung cancer, chemo radiotherapy, co-morbidity, toxicity

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Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.239 A SAFETY ANALYSIS OF CONCOMITANT CHEMORADIOTHERAPY AND CETUXIMAB IN STAGE III NON-SMALL CELL LUNG CANCER (NSCLC): SECOND COHORT OF THE SCRATCH STUDY

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Background: Cetuximab is under investigation in a number of trials in stage III NSCLC. The SCRATCH cohort I study showed early and late toxicity of synchronous cetuximab and radical RT to be acceptable in patients with stage III NSCLC following induction chemotherapy. The SCRATCH study cohort II assessed the safety of concomitant chemoradiotherapy and cetuximab. The early toxicity data (during treatment and until 6 weeks

following completion of treatment) of this phase I study are presented below.
Methods: 18 patients with inoperable stage III NSCLC were recruited into the study between Feb 2009 and Oct 2010. Participants received cisplatin 75mg/m^2 on days 1 and 29 with vinorelbine 20mg/m^2 on days 1, 8, 29 and 36 in addition to weekly intravenous cetuximab (initial dose 400mg/m^2; maintenance dose 250mg/m^2) weeks 0-7 and concomitant radiotherapy (64Gy/32 fractions/45 days). The primary end-point, toxicity, was assessed using NCI and RTOG Common Toxicity Criteria (CTC) version 3.0 during RT and at regular follow-up intervals.
Results: The median age was 63 years (range 31-72). All patients commenced treatment according to the study protocol and completed RT as scheduled. 1 patient withdrew from the study for personal reasons and received no further chemotherapy or cetuximab after the loading dose of cetuximab. 4 patients (22%) had chemotherapy and/or cetuximab interrupted or discontinued due to toxicity (1 upper GI bleed, 1 rash, 1 pneumonia, 1 diarrhoea with renal impairment). Rates of grade 3 or 4 haematological toxicity follows with rates from other chemoradiotherapy trials in parentheses. Anaemia 6% (10% Furuse et al., 1999); neutropenia 22% (58% Gandara et al., 2003); thrombocytopenia 11% (12-52%). 22% reported grade 3 infection (3-20%). Rates of grade 3 or 4 RT-related toxicity were: pneumonitis 6% (1-16% O'Rourke et al., 2010); oesophagitis 17% (18% Auperin et al., 2010). 1 patient died 2 weeks following completion of treatment as a result of massive haemoptysis. Table of all grade 3 and 4 toxicities

Grade	Anaemia	Thrombo-cytopenia	Neutro-penia	Infection (neutropenic)	Infection (non-neutropenic)	Alopecia	Skin	Fatigue	Oesophagitis	Pneumo-nitis	Pneumo-thorax	Dehydration
3	0	2	1	1	3	1	1	4	3	1	1	1
4	1	0	3	0	0	0	0	0	0	0	0	0

Conclusion: Chemoradiotherapy and cetuximab was well tolerated in the majority of patients and could be completed as scheduled in 13 patients (72%). 2 patients (11%) experienced massive bleeding. The patient who experienced upper GI bleeding was known to have a history of duodenal ulcers and in the case of fatal haemoptysis imaging had shown a poor response to treatment with disease adjacent to major pulmonary vessels. Toxicity results from this series compares favourably to other chemoradiotherapy studies suggesting the addition of cetuximab does not add significantly to toxicity.
Keywords: cetuximab, chemoradiotherapy, Stage III, Lung cancer

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.240 LONG TERM RESULTS OF MULTIDISCIPLINARY TREATMENT OF CARCINOMA OF THE SUPERIOR PULMONARY SULCUS

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Background: Superior sulcus tumors are a complex subset of tumors, because of their specific anatomical location, these tumors pose significant technical challenges to thoracic surgeons .They are relatively rare tumors accounting for less than 5% of lung cancer.
Methods: Between 2001 - 2009, 27 patients with superior pulmonary sulcus tumor were included. Contrast enhanced CT scan of the chest was considered the primary diagnostic and staging investigation for all patients. Pre operative tissue diagnosis was achieved in all patients by trans thoracic CT guided biopsy. Pre operative cervical mediastinoscopy was done in 18 patients . Radiation therapy was given pre operative to 24 patients in a dose of 45 Grays. Neo adjuvant chemotherapy was given to17 patients.
Results: There were 25 males and 2 female. The mean age was 55 years. Lobectomy was performed in 24 patients and wedge resection was done for 3 patients. Three to five ribs were resected in all patients . Extended resections were performed in 9 patients. Positive mediastinal lymph nodes were found 6 patients. Squamous cell carcinoma was found in 18 patients , 4 with undifferentiated carcinoma and the remaining 5 patients had adenocarcinoma. The final staging was: Stage IIB (T3N0M0) 14, Stage IIIA (T3N2M0) 4, Stage IIIB (T4N0M0) 7 and Stage IV (T4N2M0) 2. Negative microscopic resection margin was achieved in 17 patients. Morbidity developed in 10 (37%) patients, we had one operative related mortality. Tumor recurrence developed in 18 (66.6%) patients and was loco-regional in 7 patients, distant in 7 patients, and

both loco-regional and distant in 4 patient. We had only 2 patients with local recurrence are surviving with disease, all the remaining patients with tumor recurrence died due to disease progression. Another 2 patients died during follow up period and were free of recurrence. The mean survival time was 2.9 years and the overall 5 years survival was 33.3%.
Conclusion: Radical surgery as part of multi modality treatment gives satisfactory results with low morbidity and mortality rates and acceptable survival in patients with superior pulmonary sulcus tumors. Surgery is considered the cornerstone therapy for this type of lung tumors. Great effort should be made to achieve microscopic negative resection margin.
Keyword: superior , sulcus , carcinoma , multidisciplinary, treatment

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.241 DOCETAXEL (D) AND CISPLATIN (C) INDUCTION CHEMOTHERAPY FOLLOWED BY BIWEEKLY D AND C WITH CONCURRENT THORACIC RADIOTHERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC). A GALICIAN LUNG CANCER GROUP STUDY.

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Background: Concurrent chemoradiation (CChRT) is recommended as the evidence-based approach for the management of patients (p) with locally advanced stage III NSCLC and a good performance status, although a clearly superior regimen has not been identified. D has been shown to possess good single agent activity against NSCLC as well as radiosensiziting properties, both alone and sinergisitically with C. The aim of our study was to evaluate the feasibility of induction chemotherapy with D-C followed by CChRT with biweekly D-C.
Methods: 85 p with inoperable locally advanced NSCLC, stage IIIAN2/IIIB (no pleural T4), were included in a phase II study with induction chemotherapy consisting of three cycles of D 75 mg/m2 on day 1 and C 40 mg/m2 days 1-2 every 3 weeks and, if no surgery and no progresion, then underwent CChRT with D 30 mg/m2 and C 30 mg/m2 every 2 weeks for four courses, during conformal thoracic radiotherapy (60-66 Gys, 180 cGy/day). The primary objective was overall survival (OS); secondary objectives were progression free survival (PFS), response rate (RR) and toxicity. Median follow-up: 16 months.
Results: The p characteristics were: mean age 61 years (44-75); male/female 77/8; ECOG PS 0/1 in 25/60 p; squamous/adeno/large cell carcinoma: 51.8%/28.2%/20%; stage IIIAN2 20 p (23.5%) and stage IIIB 49 p (76.5%). 78 p were evaluable for response and 82 p for toxicity. Induction D-C response: 2 CR, 46 PR (RR 61.5%; 95% CI:51-72), 21 SD (26.9%) and 9 PD (11.6%). 9 p were treated with surgery: 1 pCR, 5 pPR, 1 pEE and 2 p unresectable. 56 p completed CChRT and 55 p were evaluable (one toxic death) with 8 CR, 37 PR (RR 80%; 95% CI:70-90), 3 SD and 7 PD. The median PFS was 11 months (95% CI:8-14) and median OS was 19 months (95% CI:15-23). The PFS and OS at 1/2 years were 46%/21% and 64%/33% respectively. A total of 235 cycles of D-C were given (2.8 per p); main toxicities (NCI-CTC 3.0) per p Grade (g) 1-2/3-4 (%) were as follows: neutropenia 10.9/25.6; anemia 30.4/3.5; nausea/vomiting 30.4/7.3; fatigue 28/0; diarrhea 17/9.7; there were ten episodes of febrile neutropenia and there was one treatment-related death. Main toxicities per p in CChRT (D-C doses: 211, 3.6 per p; mean doses RT: 55,4 Gys) were: g1-2 neutropenia/anemia 12/34.4%; g1-2/3 esophagitis in 51.7/1.7% and g1-2 pneumonitis in 24.5%; there was one treatment-related death.
Conclusion: Induction chemotherapy with Docetaxel and Cisplatin followed by concurrent thoracic radiotherapy with biweekly Docetaxel and Cisplatin is a feasible treatment option for locally advanced stage III Non Small Cell Lung Cancer,

showing good clinical activity and tolerability with acceptable long-term survival.
Keyword: Concurrent radiotherapy and chemotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.242 A PHASE II STUDY EVALUATING CONCURRENT PEMETREXED/ CISPLATIN/RADIATION (RT) FOR UNRESECTABLE STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Although concurrent chemoradiotherapy is standard treatment for patients with unresectable stage IIIA/B NSCLC, the best chemotherapy regimen/schedule has not been established. In a previous phase I study (Brade et. al, Int J Radiat Oncol Biol Phys, 2010 ePub), pemetrexed was the first third-generation chemotherapeutic deliverable at full dose concurrently with full-dose RT and cisplatin. This combination was evaluated further in this completed phase II study.
Methods: SFrom April 16, 2007 to August 24, 2009, patients with unresectable stage IIIA/B NSCLC entered this single-arm, phase II trial at five Canadian centers. Patients had to have ≥5% weight loss, Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1, no malignant effusions, forced expiratory volume in one second ≥1.3 L, and adequate organ function. Staging positron emission tomography scans were not routinely performed. Patients received pemetrexed 500 mg/m^2 on day 1 and cisplatin 20 mg/m^2 on days 1-5, q21 days, for two cycles concurrent with RT (61-66 Gy in 32-35 fractions over 6-6.5 weeks) followed by pemetrexed/cisplatin alone for two cycles q21 days (pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 on day 1). Patients were fully supplemented with folic acid and vitamin B_{12}.
Results: As of data lock, January 11, 2011, 39 patients were accrued (median follow up, 14.2 months). Demographics included: median age of 63 years (range: 37-79); male/female (18/21); stage IIIA/B (15/24); ECOG PS 0/1 (23/16); and histology of adenocarcinoma (21), squamous (10), large cell (2), and NSCLC-NOS (6). Median RT dose was 64.0 Gy (range: 14.4-66.0); 5 patients received significant RT dose reductions (total doses of 52.0, 50.8, 45.0, 40.0, and 14.4 Gy). All four cycles of chemotherapy were delivered in 30/39 patients; three, two, and one cycle(s) only were delivered in 3, 5, and 1 patient(s), respectively, due to adverse events (5), disease progression (1), patient refusal (1), and other (2). Preliminary toxicity analysis demonstrated that at least one high-grade (≥grade 3) toxicity (excluding leuko/lymphopenia) deemed possibly/ probably/definitely related to study treatment was experienced by 29/39 patients. High-grade toxicity occurred mainly during concurrent therapy, with a maximum grade of 3/4/5 in 19/6/1 patient(s), respectively. Common toxicities during therapy included grade 3/4 neutropenia in 8/4 patients, and 1 death due to neutropenic sepsis; grade 3 esophagitis in 2 patients, and grade 3/4 syncope (in the absence of high-grade esophagitis) in 3/1 patient(s); and grade 3/4 electrolyte abnormalities in 11/2 patients. After completion of therapy, grade 3/4 pneumonitis occurred in 1/1 patients and grade 3 esophageal stenosis in 1 patient. Median overall survival was 28.7 months (95% confidence interval [CI]: 19.6-30.5) and median progression-free survival was 20.2 months (95% CI: 13.9-30.5). One-year overall survival was 79.0% (95% CI: 66.1%-92.0%) and 1-year progression-free survival was 75.4% (61.4%-89.4%).
Conclusion: Full-dose concurrent and adjuvant pemetrexed/cisplatin with full-dose RT is relatively well tolerated compared with other concurrent chemo-radiation regimens for stage IIIA/B NSCLC and shows encouraging efficacy. These data provide

support for an ongoing phase III registration trial (PROCLAIM) evaluating a similar regimen.
Keywords: Non-small cell lung cancer, Pemetrexed, Cisplatin, Radiotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.243 INDUCTION CHEMOTHERAPY FOR NSCLC: INSTITUTIONAL EXPERIENCE WITH 343 PATIENTS

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Background: As a means of reducing the risk of recurrence after surgery, there has been a growing interest in combining chemotherapy (CT) with surgical resection. However, the role of induction chemotherapy in resectable non-small cell lung cancer (NSCLC) remains undefined. Thus it is necessary to select patients who are suitable to receive CT. The purpose of the present study is to assess the activity of induction CT in stage I-IV NSCLC patients (pts) and to identify prognostic factors for CT efficacy.
Methods: We reviewed the prospective database (2000-2007) of all NSCLC patients operated at our centre after CT. The database included patients' complete medical history. Staging was performed according to 1997 Mountain's revision. Stage IV pts were included in cases of previous complete resection of their metastasis. The prognostic factors of overall survival (OS) and response to CT were respectively investigated using Cox model and multiple linear regression.
Results: 343 pts entered the study. Indications for induction CT were: clinical trial (n = 35), N2 involvment (n = 104) or lung sparing in case of respiratory insufficiency (n = 13), metastasis (n = 9), initially unresectable tumour (n = 68), other n.p. (113). Main clinico-pathological features included: male gender (81%), age < 60 yrs (53%, median 60 yrs, ranging from 36 to 81), squamous cell carcinoma subtype (41%), preoperative stage IIIA (67%), smokers (95%), PS 0 /1 (100%). Induction CT consisted in platinum-based association in 93%. Median number of cycles was 2 (ranging from to 1 to 8), [3] 3 side effects were found in 12%. Clinical response rate to CT was 73%, ranging from 61% to 79%, according to the stage. Complete response rate was 3 % and major response (>50%) rate 45%. Surgery included pneumonectomy, lobectomy, wedge / segmentectomy or exploratory thoracotomy in respectively 26%, 58%, 5% and 10%. There were 10 postoperative deaths. Pathologic complete resection was performed in 79%. A pathologic mediastinal downstaging was found in 53% and a pathologic complete response in 9% of pts The OS was 36% at 5 years (median: 30 months). For patients who had complete resection, the median survival and 5-year survival were respectively 42 months and 42%. Multivariated analyses identified stage, radicality, and type of resection as strongly prognostic for increased OS. Age, number of CT cycles and radicality were associated with response to CT.
Conclusion: These results demonstrate that induction CT produces high rates of response and complete resection.
Keywords: Non small cell lung cancer, preoperative chemotherapy, Surgery

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P4.244 PHASE II STUDY OF CONCURRENT RADIOCHEMOTHERAPY WITH WEEKLY CISPLATIN PLUS ORAL VINORELBINE IN FIT ELDERLY PATIENTS WITH NONRESECTABLE LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER (RACCOSA, GFPC 08-06 STUDY).

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Background: Non small cell lung cancer (NSCLC) in elderly patients is an important problem because

of the increase of the incidence of NSCLC and the aging of the population. Elderly patients constitute a heterogeneous population with a group of fit patients which should benefit from the reference treatment. Currently the reference treatment of a locally advanced NSCLC (nonresectable IIIA and IIIB) is concomitant radio-chemotherapy. Few studies appraise this treatment in elderly patients.
Methods: This phase II multicentric nonrandomized opened frensch study aims to evaluate tolerance of concomitant radio-chemotherapy in elderly patients (more than 70 years old) juged fit after a geriatric evaluation with locally advanced NSCLC. The other main inclusion criteria are: PS ≤ 1, weight loss < 10% during last 3 month, creatinine clearance ³ 50 ml/mn calculed with shortened Levey-MDRD formula, appropriate respiratory function with VEMS ³ 40%, PaO2 ³ 60 mm Hg, KCO ³ 60%. The treatment is oral vinorelbine (30 mg/m²/week) and cisplatine IV (30 mg/m²/week) during 6 weeks in concomitance with radiotherapy (66 Gy, 33 fractions, 6 and a half weeks). The first end-point is to evaluate tolerance of the treatment. The secondary end-points are evaluation of efficiency 4 weeks after treatment end, quality of life, tolerance of the treatment 6 month after the end of the treatment, survival without progression and overall survival at 1, 2 and 3 years. We used a Simon's optimal plan in 2 steps. The total number of patients to be included is 59 with an intermediate analysis at 19 inclusive patients. An independent committee of experts oversees toxicities.
Results: The study started in july 2010. 35 teams of the GFPC team participate to the study. Currently 6 of planned 59 patients have been enrolled. The end of the study is expected in july 2012.
Conclusion: Our study aims at demonstrating that fit elderly patients can benefit from concomitant radio-chemotherapy. It will permit to improve the care of fit elderly patients with locally advanced NSCLC by allowing them to benefit from the reference treatment.
Keywords: Concomitant radiochemotherapy, elderly patients, Non small cell lung cancer

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P4.245 CONSOLIDATION S-1 AFTER CONCURRENT CHEMORADIOTHERPAY WITH CISPLATIN AND VINORELBINE FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: JAPAN NATIONAL HOSPITAL STUDY GROUP FOR LUNG CANCER 0501

Tomoya Kawaguchi[1], Minoru Takada[2], Masahiko Ando[3], Shinji Atagi[4], Kyoichi Okishio[1], Yuka Fujita[5], Yoshio Tomizawa[6], Kenji Hayashihara[7], Yoshio Okano[8], Shiro Takahashi[9], Ryusei Saito[6], Akihide Matsumura[4], Atsuhisa Tamura[10]
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Background: To evaluate the efficacy and feasibility of S1 consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer
Methods: The eligibile patients had unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Chemoradiotherapy consisted of cisplatin 80 mg/m2 on days 1 and 29, vinorelbine 20 mg/m2 on days 1, 8, 29 and 36, and concurrent thoracic radiotherapy at total dose of 60Gy. Sequential consolidation S1 at dose of 120 mg/m2 per day started on day 57 with 2 cycle of 4 week administration and 2 week withdrawal.
Results: Of 67 patients enrolled between 2006 and 2009, 66 (56 males and 10 females with a median age of 63:45-73) could be evaluated. Chemoradiotherapy was well tolerated and was completed in 58 (87.9%). Grade 3 or 4 neutropenia, anemia, esophagitis, and pneumonitis developed in 35, 5, 2, and 1 patients, respectively. S-1 consolidation was administered in 45 (68.2%) patients, but two cycles were completed in 31 (47.0%) patients. During consolidation therapy,

grade 3 or 4 neutropenia, anemia, esophagitis, and pneumonitis developed in 1,4, 0, and 0 patients, respectively. One patient died of pneumonitis. The response rate was 61.5% (95% confidence interval [CI], 48.6– 73.3%), with 1 complete and 39 partial responses. The median progression-free survival was 9.3 (CI, 10.2–15.4) months, and median survival was 19.4 (CI, 24.5–36.3) months. The 1-and 3-year survival rates were 72.7% (62.0-83.5) and 33.5% (20.9-46.2), respectively.
Conclusion: This regimen produced tolerable toxicity and promising overall survival in patients with stage III NSCLC.
Keywords: consolidation, S1, chemoradiotherapy, stage III NSCLC

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P4.246 A RANDOMISED PHASE II STUDY OF CETUXIMAB (ERBITUX®) IN COMBINATION WITH TWO CISPLATIN-BASED CHEMORADIATION REGIMENS IN PATIENTS WITH STAGE IIIA/B NON SMALL CELL LUNG CANCER (NSCLC). PRELIMINARY RESULTS OF THE GFPC 08-03 TRIAL

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Background: Concurrent chemoradiotherapy (CRT) with cisplatin doublets represents the standard of care in patients with unresectable stage III NSCLC. The anti-Epidermal Growth Factor Receptor monoclonal antibody cetuximab has recently demonstrated efficacy in first-line combination with chemotherapy, and feasibility in combination with radiotherapy in patients with stage III NSCLC. The purpose of this non comparative phase II randomised trial was to demonstrate the feasibility of the concurrent association of cetuximab with two worldwide standard cisplatin-based CRT regimens (cisplatin-vinorelbine-radiotherapy and cisplatin-etoposide-radiotherapy) in selected stage III A/B NSCLC patients, with a planned sample size of 62 randomised patients (PTS) (31 per arm).
Methods: Eligibility criteria included age ≤ 70 years, performance status (PS) ≤1, weight loss ≤10% over the past 3 months, FEV1 ≥40% th, and adequate hematologic, renal and hepatic functions. After inclusion, PTS received on day 1 (D1) one cycle of cisplatin (75mg/m2)-docetaxel (75mg/m2) induction chemotherapy. On D21, PTS with suitable dosimetric parameters (V20 ≤ 35% and Mean Lung dose (MLD) ≤ 20 grays) were randomized and received an initial dose of 400 mg/m^2 cetuximab. Concurrent treatment started on D28. Between D28 and D71, PTS received a concurrent combination of weekly cetuximab (250mg/m2, 7 doses), radiotherapy (66 Gy/6.5 weeks) and two cycles of cisplatin (80 mg/m2 D1)-vinorelbine (15mg/m2 D1, 8) in arm A, or two cycles of cisplatin (50 mg/m2 D1,8)-etoposide (50 mg/m2 D1-5) in arm B. Toxicity and compliance were monitored every week between D1 and D71. The primary endpoint was feasibility, evaluated by the percentage of PTS developping ≥ grade 3 non hematologic toxicities (NHT) (NCI-CTC V3) at D71 in each arm. Secondary endpoints were compliance, toxicity and response evaluated at D113. Toxicities and responses were centrally reviewed.
Results: On January 2011, 76 PTS had been enrolled in the study. PTS characteristics were: 75 % male, median age: 58 years, 63 % PS=0, 38% stage IIIA, 64% non squamous histology. 52 PTS have been randomised (28 in arm A, 24 in arm B, randomisation rate=66%). The major reason for non-randomisation was dosimetric failure at D21 (V20>35% or MLD >20Gy). 29 grade ≥ 3 NHT were reported at D71: 4 before randomisation, 18 in arm B (11/24 PTS, 45%) and 7 in arm A (5/28 PTS, 17%). Two patients died: 1 before randomisation from acute respiratory failure, and one on D71 from massive hemoptysis. No toxic death was noted. The most common toxicities were grade 3 oesophagitis (6 PTS, 11%) and febrile neutropenia (5 PTS, 9%). Only one grade 3 acne was recorded. Responses were reviewed in 23 PTS, with 1 CR, 17 PR (73%), 1 SD and 4 PD (17%).
Conclusion: In this preliminary evaluation, the concurrent association of cetuximab with cisplatin-based CRT seems to be safe in both arms, with promising responses rates. Uptated results will be presented at the meeting.

Keywords: cetuximab, concurrent chemoradiotherapy, stage III NSCLC, feasibility

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P4.247 THE IMPACT OF EGFR MUTATION STATUS ON CLINICAL OUTCOMES IN PATIENTS WITH LOCALLY ADVANCED LUNG ADENOCARCINOMA.

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Background: Concurrent chemoradiotherapy (CCR) is the standard care for locally advanced non-small cell lung cancer (LA-NSCLC). Epidermal growth factor receptor (EGFR) mutation is well known predictive marker in metastatic NSCLC. In vitro, NSCLC cell lines with EGFR mutation demonstrated radio-sensitivity, but it has not been fully evaluated about the role of EGFR mutation in LA-NSCLC patients treated with CCR.
Methods: Between September 2002 and December 2009, 83 adenocarcinomas of 166 LA-NSCLC patients who received CCR were retrospectively reviewed. Forty-four tissues of these 83 adenocarcinoma were available. The 44 patients were included in this study, and EGFR mutation status was investigated.
Results: EGFR mutation was observed in 12 (27.3%) of 44 adenocarcinoma patients. The median progression free survival was 10.8 months in EGFR wild type group (n=32) and 9.1 months in EGFR mutant group (n=12), demonstrating no significant difference (p=0.60). Median survival time was 29.7 months in EGFR wild type group and 57.1 months in EGFR mutant group, demonstrating no significant difference (p=0.18). Different pattern of relapse was revealed between EGFR mutation status (locoregional relapse; 8.3% among EGFR mutant group versus 31.3% among EGFR wild type group), and most frequent site of relapse was brain among EGFR mutant group (5 of 9 patients).
Conclusion: Frequency of EGFR mutation in locally advanced adenocarcinoma of the lung was about 30%. EGFR mutation was not a predictive marker treated with conventional CCR. But, EGFR mutant patients demonstrated better locoregional control compared with EGFR wild type patients.
Keyword: locally advanced,NSCLC,EGFR,chemor adiotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.248 CONCOMITANT CHEMO-RADIOTHERAPY IN LOCALLY ADVANCED NON SMALL CELL CARCINOMA OF LUNG: A SINGLE CENTRE EXPERIENCE

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Background: Concomitant chemo-radiotherapy (cCRT) has been superior to sequential (sCRT) therapy in terms of progression-free and overall survival in stage III non-small-cell-lung-cancer (NSCLC) in multiple randomized controlled trials (RCT) and meta-analyses, albeit at the expense of greater loco-regional toxicity.
Methods: At the Lincoln County Hospital we treated 12 patients with inoperable NSCLC with cCRT from December'2009 till December'2010. All patients had a baseline PET, after staging CT of chest and abdomen. Patients with equivocal/negative mediastinal nodes on PET underwent mediastinoscopy and biopsy to complete staging. All had good performance status (WHO 0-1) and lung function (FEV1≥1 litre, FVC≥1.5 litre). Patients older than 65 years received primary prophylaxis against neutropenia with GCSF. There were six stage IIIA, five IIIB and one IIA. Nine were male and three were female. There were six squamous-cell-carcinomas, two adeno-carcinomas, three unspecified NSCLC and one patient had carcinoma-in-situ but declined further biopsy. Median age was 60 years (47–73 years). Chemotherapy comprised of cisplatin 75 mg/m^2 on day-1 and vinorelbine on days 1 and 8 for four 21 day cycles. Radiotherapy commenced on day-1 of second cycle. Vinorelbine dose was 25 mg/m^2 iv on day-1 and 60 mg/m^2 orally on day-8 in cycle-1, reduced to 15 mg/m^2 iv on day-1 and 40 mg/m^2

orally on day-8 in cycles 2-4 in the concomitant phase. Radiotherapy was by 3D conformal planning to a dose of 64 Gy in 32 fractions over 6.5 weeks. Following dose constraints were maintained for critical organs – lung V20≤35%; spinal cord–44 Gy; oesophagus–33%<60 Gy, 100%<55 Gy ; heart–33%<60 Gy, 66%<45 Gy and 100%<40 Gy. Toxicity was monitored weekly as per the RTOG acute radiation toxicity score, during the course and repeated a month after completion. There were no grade 3/4 toxicities. Commonest toxicity was acute oesophagitis that was treated with antacid/ oxetacaine preparations and NSAID. No patient developed any grade 3/4 chemotherapy related toxicity.

Results: Response was assessed with three-weekly chest x-rays whilst on treatment and with a CT scan 3 months after completion. Patients with an excellent response on CT, had a PET to assess for surgery of residual disease. Two patients underwent lobectomy and mediastinal lymph node sampling for residual PET abnormality confirming complete pathological response (CR). A third patient showed CR on post-treatment PET. Remaining 9 patients showed partial response (PR). There was 100% response with 25% CR and 75% PR. All three CRs had squamous-cell-cancer with two IIIA and one IIIB disease.

Conclusion: cCRT is an effective and safe option in an appropriately selected group of patients. Toxicity can be minimized by modern RT techniques and adherence to critical organ dose constraints. The follow up period in our centre was not long enough at the time of submission to comment on survival although several other studies have demonstrated improvement in survival with cCRT. There was considerable variation in the degree of response among partial responders. This suggests the need for a RCT of cCRT with tailored chemotherapy to improve the response rate and survival.

Keywords: concomitant chemo-radiotherapy, locally advanced non small cell lung cancer

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.249 BENEFITS AND ADVERSE EVENTS AMONG ELDERLY PATIENTS RECEIVING CONCURRENT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: ANALYSIS OF THE OKAYAMA LUNG CANCER STUDY GROUP TRIAL 0007

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Background: Standard treatment for elderly patients with locally advanced non-small cell lung cancer (LA-NSCLC) is thoracic radiotherapy (RT) without chemotherapy. The OLCSG 0007 phase III trial with patients up to 75 years old showed that with concurrent RT, docetaxel and cisplatin (DP) chemotherapy was preferable to mitomycin, vindesine, and cisplatin (MVP) chemotherapy. We analyzed the benefits and adverse events according to patient age.

Methods: Of the 99 patients the DP arm of the OLCSG 0007 trial, 73 were <70 years old and 26 were ≥70 years old. Of the 101 patients in the MVP arm, 75 were <70 years old and 26 were ≥70 years old. Overall survival (OS) and progression-free survival (PFS) were calculated according to age and treatment arm using the Kaplan-Meier method and were compared using an early period weighted log-rank test. Toxicities and treatment intensities were compared by chi-square and t-tests, respectively.

Results: OS and PFS tended to be longer in the DP arm vs. MVP arm: median OS (months), 27.5 vs. 22.9 (P = 0.109) and 25.6 vs. 23.4 (P = 0.064) in the ≥70-y and <70-y groups, respectively; median PFS (months), 19.0 vs. 11.5 (P = 0.175) and 12.0 vs. 9.3 (P = 0.132) in the ≥70-y and <70-y groups, respectively. Severe toxicity (neutropenia, esophagitis, pneumonitis) rates did not differ between age groups. Radiation intensity was similar between the groups, but chemotherapy intensity was lower in the ≥70-y group.

Conclusion: Chemotherapy with concurrent RT may be effective and tolerable in elderly patients with LA-NSCLC.

Keywords: Non-small cell lung cancer, Elderly, RADIATION, Chemotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.250 TOLERANCE AND FEASIBILITY OF NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY WITH PLATINUM AND VINORELBINE IN THE UNIVERSIY HOSPITAL ARNAU DE VILANOVA OF LLEIDA (SPAIN).

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Background: Chemoradiotherapy (CTRT) is the standard treatment for N3 non-small cell lung cancer (NSCLC), and a promising approach for neoadjuvant therapy in non-N3 locally advanced NSCLC.
Methods: We retrospectively analyzed 27 male patients diagnosed of stage II (T>5cm)-IIIB NSCLC and consecutively treated with 4 cycles of neoadjuvant Cisplatin 75 mg/m2 (N= 21) or Carboplatin AUC 5 (N= 3) day 1 plus Vinorelbine 30 mg/m2 day 1 and 8 every 21 days with concurrent radiotherapy to 50 Gy in the third and fourth cycle since May, 2008 to May, 2010. Three patients received CBDCA plus concurrent radiotherapy only, due to elderly or comorbidity. After a second evaluation, operable cases underwent surgery and the non-operable ones continued radiotherapy to radical dose of 60 Gy.
Results: Mean age of the patients was 68.3 ± 10.16 years old, and all of them referred antecedent of smoking. Initial ECOG was 0-1 (92.6%) or 2 (7.4%). Initial stage was IIA 3.7%, IIIA 44.4% and IIIB 51.9%. Initial clinical T-size was T2 22.2%, T3 40.7% and T4 37.1 initial N was N0 7.4%, N1 11.1%, N2 51.9%, and N3 29.6%. Histological subtypes were squamous carcinoma 77.8%, adenocarcinoma 11.1% and non-defined NSCLC 11.1%. The 81% of patients received the whole programmed program of CTRT (mean cycles 3.8+/-0.56). A 48.1% of them underwent surgery and a 51.9% received radical radiation. Operability was 81.22% for non-N3 NSCLC after neoadjuvant CTRT (2 atypical resections, 9 lobectomies, and 2 pneumectomies) with mediastinal lymph node dissection. Tolerance of concurrent CTRT was excellent. Maximum toxicity was grade 3 non-febrile neutropenia in a 15.4% of cases. No grade 4-5 toxicity, pneumonitis or esophagitis were reported. Two patients died after lobectomy due to surgery complications (aspergillosis and massive hemoptysis), and a case of bronchopleural fistula was reported also after pneumectomy.
Conclusion: This protocol of neoadjuvant CTRT based on cisplatin or carboplatin plus vinorelbine is feasible and tolerable, simple to applied and with a high rate of operability.
Keywords: treatment, Neoadjuvant chemoradiotherapy, Non small cell lung cancer

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.251 RISK OF MORBIDITY AND MORTALITY AFTER INDUCTION CHEMORADIOTHERAPY AND SURGERY FOR LOCALLY LUNG CANCER: AN ANALYSIS OF 108 RESECTED PATIENTS

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Background: The role of multimodal treatment including surgery for locoregionally advanced lung cancer is still matter of debate. Aim of the study was to evaluate the risk of treatment-related morbidity and mortality of a trimodality approach as well as to identify predictors of complications.
Methods: The charts of 108 consecutive patients undergoing trimodality therapy for loco-regionally advanced (stage IIB-IIIB) lung cancer were reviewed. Induction therapy consisted of two to three cycles of platin-based doublet (platin/etoposide [PE] in 45%, platin/gemcitabine [PG] in 44%, platin/other substance in 11% of cases), followed by concurrent radiochemotherapy (45 Gy hyperfractionated accelerated radiotherapy combined with cisplatin weekly). All patients underwent thoracotomy. Toxicity of induction therapy, mortality and surgical morbidity were statistically analyzed.

Results: Of 108 consecutive patients, 87 (81%) had a NSCLC, and 21 (19%) a SCLC. Overall compliance to induction therapy was 95%. Grade 3-4 toxicity was observed in 16% of patients. Resections included 69 (64%) lobectomies, 25 (23%) sleeve-lobectomies, and 12 (11%) pneumonectomies; 2 (2%) patients had an exploratory only. Surgical mortality rate was 5.6%. Twenty-three (21%) patients suffered one or more major complications: bronchial stump/anastomosis fistula (14%), pneumonia/ARDS (12%), bleeding requiring reoperation (2%), myocardial infarction (1%), and pulmonary embolism (1%). Significant risk factors for morbidity were chemotherapy protocol other than PE/PG (P=.007), pneumonectomy (P=.034), and perioperative blood transfusions (P<.001); mortality was influenced by perioperative blood transfusions (P=.006). Among patients with major complications, the associated risk of death for pneumonia was 33%, for bronchial fistula 33%, and for bleeding 50%, respectively.
Conclusion: In patients with locoregionally advanced lung cancer, trimodality therapy including surgery can be feasible with acceptable mortality and morbidity. As major complications are linked to high risk of death, accurate preoperative patient selection and intraoperative management including protection of bronchial stump/anastomosis are mandatory. Sleeve lobectomy – when technically feasible – should be preferred to pneumonectomy.
Keywords: Surgery, Lung cancer, multimodality therapy, chemoradiotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.252 VORINOSTAT, A HISTONE DEACETYLASE INHIBITOR, IN COMBINATION WITH THORACIC RADIOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER: A DOSE ESCALATION STUDY

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Background: Histone deacetylase (HDAC) inhibitors have shown activity against non-small cell lung cancer (NSCLC) and act as radiosensitizers in preclinical models. Vorinostat is an HDAC inhibitor that is FDA-approved for the treatment of cutaneous T-cell lymphoma in specific circumstances, and under investigation in NSCLC in combination with systemic chemotherapy. This study was designed to assess the tolerability of vorinostat given concurrently with thoracic radiotherapy in patients with advanced or metastatic NSCLC.
Methods: Eligible patients had metastatic NSCLC, or locally advanced NSCLC not suitable for curative therapy, and were referred for palliative thoracic radiotherapy. Patients were treated with a standard palliative regimen of 30 Gy in 10 fractions, and were enrolled in cohorts of escalating vorinostat dose using a standard 3 x 3 design. Vorinostat was administered orally one hour prior to radiation, on each day of radiation, in cohorts of 200mg, 300mg, and 400mg per day. Following the completion of thoracic radiation, vorinostat could be continued as a single agent (400 mg daily) or in combination with carboplatin and paclitaxel (400 mg daily for 14 days, every 21 days). Toxicity was graded by the NIH common toxicity criteria for adverse events, version 4.0. The primary endpoint was to determine the maximum tolerated dose of vorinostat when given concurrently with thoracic radiotherapy.
Results: Between July 2009 and December 2010, 17 patients were enrolled and 12 patients completed study therapy. Five patients were withdrawn from the study: two were ineligible, two withdrew consent, and one died of unrelated cause. Patients were enrolled in cohorts of escalating vorinostat dose: 3 completed therapy at 200mg per day, 3 at 300mg per day, and 6 at 400mg per day. Most adverse events were grade 1 or 2, and included fatigue, nausea, anorexia, and hematologic changes. Grade 3 adverse events included anemia, thrombocytopenia, nausea, and fatigue. Treatment-related dose-limiting toxicity occurred in one of six patients in the 400mg cohort (nausea). The maximum tolerated dose of vorinostat given concurrently with thoracic radiotherapy was therefore found to be 400 mg per day.
Conclusion: Vorinostat can be safely combined with thoracic radiotherapy in patients with advanced or metastatic NSCLC. This study suggests that the combination of an HDAC inhibitor with radiotherapy may be worthy of investigation as a component of chemoradiotherapy, in the treatment of patients with locally advanced disease.
Keyword: Histone deacetylase inhibitor

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.253 NEOADJUVANT TREATMENT AND SURGERY FOR CLINICAL T4 NON-SMALL CELL LUNG CANCER WITHOUT N2 DISEASE

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Background: In this study, the results of neoadjuvant treatment followed by surgery for clinical T4 non-small cell lung cancer without N2 disease is investigated.
Methods: The medical records and follow-up data of 115 patients (112 males, 3 females) with clinical T4N0/1M0 non-small cell lung cancer operated after neoadjuvant treatment between January 1998 and January 2010 is analyzed. The patients having histopathologically proven preoperative N2 disease are not included in the study. Adjuvant theraphy is applied for patients having pT4 or pN1-2 diseases.
Results: The histological type of the tumor was squamous cell carcinoma in 78 and adenocarcinoma in 23 pateints. 14 patients had tumor necrosis which did not allow the subclassification of the histopathological type. The type of the resection performed was pneumonectomy in 55 (47.8%) lobectomy in 60 (52.2%) patients. Two patients (1.7%) died in the early postoperative period. Median follow-up time was 35.0±2.3 months. Five year overall survival was 55.5%. The five year survival rates of patients having a downstaged tumor according to T factor was 58% versus 0% in pT4 patients and the difference was statistically significant (p=0,005). Survival was better in pN0-1 diseases than pN2 disease (p=0,035).
Conclusion: Neoadjuvant treatment for clinical T4 non-small cell lung cancer improves the chance of resectability. pT4 or pN2 disease are the poor prognostic factors.
Keywords: Neoadjuvant Therapy, Non-small cell lung cancer, Surgery, T4 diseases

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.254 SURVIVAL IN PATIENTS WITH STAGE III NON-SMALL CELL LUNG CANCER (NSCLC) RECEIVING CONCURRENT CHEMOTHERAPY WITH HYPOFRACTIONATED RADIOTHERAPY: EXPERIENCE AT THE NORTHERN CENTRE FOR CANCER CARE (NCCC), UK

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Background: Standard treatment for stage III NSCLC involves bimodality therapy, but varies between either sequential or concurrent regimens. A meta-analysis[1] has confirmed an absolute and progression-free survival benefit using concurrent chemoradiotherapy compared to sequential modalities. However, Auperin and colleagues excluded the SOCCAR trial[2] (sequential or concurrent chemotherapy and radiotherapy) as the data from that (Phase II) trial was not yet mature at time of the meta-analysis. We wished to assess if we could deliver safe and effective concurrent chemoradiation using this UK hypofractionated radiotherapy technique to a North of England population of patients. Reference: 1. Auperin, A., et al., Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. Journal of Clinical Oncology, 2010. 28(13): p. 2181-90. 2. A Randomized Phase III Trial of Sequential Chemotherapy Followed By Radical Radiotherapy Versus Concurrent Chemo-Radiotherapy Followed by Chemotherapy in Patients With Inoperable Stage III Non-Small Cell Lung Cancer and Good Performance Status NCT00309972
Methods: We performed a retrospective audit of the notes for patients who were diagnosed with stage III NSCLC and received concurrent chemoradiotherapy at the Northern centre for Cancer Care during a five year period from January 2005 to December 2009. The main end point was overall survival, which was evaluated from the date of diagnosis until death due to any cause. Living patients were censored at the date of their last clinic appointment. We also assessed the completeness of chemotherapy regimen attained.

Results: 35 patients received concurrent chemoradiotherapy with vinorelbine and cisplatin plus radical Radiotherapy as management of their stage III NSCLC. The radiation regimen was 55Gy in 20 fractions delivered once daily, five days per week. 83% patients completed chemotherapy. One fatal PE occurred.

Characteristic	**No.**	**%**
Male Female	23 12	65.7 34.3
Median age, years	55.5	
Performance Status 0 1 2 Not recorded	17 10 1 7	48.6 28.6 2.9 20
Chemotherapy Regimen Single therapy Double therapy	1 34	2.9 97.1

	Overall survival (%)		Progression-free survival (%)	
	NCCC (n= 31)	Meta-analysis	NCCC (n=35)	Meta-analysis
1 year survival	73.3	NA	48.6	40.5
3 year survival	26.7	23.8	25.7	16

Conclusion: This study confirms that the NCCC can provide safe and effective concurrent chemoradiotherapy for patients diagnosed with stage III NSCLC - using a UK hypofractionated RT regimen.

Keywords: concurrent chemoradiotherapy, Non-small cell lung cancer

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.255 CONCURRENT CHEMORADIOTHERAPY (CRT) FOR LOCALISED UNRESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC): 10-YEAR EXPERIENCE FROM AN AUSTRALIAN GENERAL TEACHING HOSPITAL.

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Background: Lung cancer is the leading cause of cancer related mortality worldwide. CRT is the standard treatment for unresectable or medically inoperable localised NSCLC. We retrospectively analysed treatment outcome and toxicity data of patients with localised NSCLC, treated with CRT at our institution, over a 10-year period.

Methods: Medical records of eligible NSCLC patients who received CRT at Flinders Medical Centre and Flinders Private Hospital in Adelaide, South Australia, were reviewed. Details of demographics, management, toxicity and survival were recorded and analysed.

Results: 68 patients were identified to have received concurrent CRT for NSCLC between May 2000 and June 2010. Median age was 66.4 yrs (range 44 - 85 yrs). 63% were male, 63 % were ex-smokers and 10% never smokers. Diagnosis was confirmed in the majority of patients by bronchial biopsy (41%), bronchial washings (18%) and image guided biopsy (18%). PET scan staging was performed in 65% of patients. Histology included adenocarcinoma (40%), large cell (26%) and squamous cell carcinoma (23.5%). Stage IIIB (41%) and IIIA (22%) constituted the bulk of our patients and a minority of stage IV (2.9%) were also given concurrent CRT. Median time to initiation of radiotherapy and chemotherapy from the date of cancer diagnosis was 34 days and 39 days respectively. Radiotherapy was given with 60 Gy in 30 fractions in the majority of cases applying a three field single phase or a two-phase technique. The majority of patients (81%) received platinum based doublet chemotherapy; Cisplatin/Etoposide (59%) and Cisplatin/Vinblastine (11.7%) being the most common regimens. Eight patients (11.7%) were treated as part of clinical trial. 34% of patients had CRT interrupted due to toxicity. Most frequent grade 3/4 early side effects included neutropenia (28%) and oesophagitis (10%). There were 2 episodes of febrile neutropenia. Radiation induced pneumonitis (28%) was the predominant delayed toxicity. 34% of patients had local relapse and 32% had distant metastasis. Sixty three patients were evaluable for survival. Median progression free survival was 13.6 months and median overall survival was 20.9 months. Survival at 2yrs, 3 years and 5 years was 49 %, 35% and 20% respectively.

Conclusion: Our data confirms that CRT for localised inoperable NSCLC is associated with significant toxicity but long-term survival is achievable, with 1 in 5 patients alive at 5 years. Further studies aimed at optimising outcome while minimising toxicity in this group of patients are needed.

Keywords: concurrent chemoradiotherapy, localised NSCLC, median overall survival

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.256 CONCURRENT CHEMORADIOTHERAPY WITH TOMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): PHASE I, DOSE-ESCALATION STUDY

Alessandra Bearz[1], Emilio Minatel[2], Imad Abu Rumeileh[3], Carlo Gobitti[3], Tanja Baresic[4], Annalisa Drigo[5], Renato Talamini[6], Emanuela Vaccher[1], Sandra Santarossa[1], Gianni Franchin[3]
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Background: Concurrent chemoradiotherapy is the standard treatment for patients affected by stage III, unresectable NSCLC and good PS. Recommended systemic treatment in stage III NSCLC consists of 2-4 cycles of platin-combination. To improve overall survival (OS) different schemes for induction or consolidation therapy have been used, without any clear superiority between them. It is believed that higher radiation doses may result in improved local tumour control; however, current radiation delivery techniques, in particular concurrently with chemotherapy, may lead to unacceptable lung toxicity. Therefore, the search for better radiotherapy approaches is important. Helical Tomotherapy (HT) is a novel approach to deliver highly conformal dose distributions using intensity-modulated radiation fan beams, bringing adequate radiation dose to the tumor, while limiting the dose to surrounding tissues. Integral dose (ID) delivered to the normal tissues during intensity modulated radiotherapy (IMRT) treatment is clinically relevant. Aim of the study was to evaluate any change in lung toxicity due to ID received by healthy lungs, in combination with chemotherapy. In Phase II studies radiotherapy with concurrent docetaxel and after cisplatin-docetaxel induction has been shown to be feasible, with encouraging OS in NSCLC; recommended dose of docetaxel concurrently with radiotherapy is up to 30 mg/m2/week from previous Phase I studies.

Methods: This was a mono-institutional, phase I, dose-escalation study to assess the dose-limiting of docetaxel concurrently with HT in stage III, NSCLC patients. Eligibility criteria: NSCLC with multiple N2 or N3 mediastinal lymph nodes (excluding sovraclavear lymph nodes and pleural effusion), PS 0-1. At baseline and during follow-up, whole-body PET/CT scan, consisting of helical CT scanning followed by a 2D PET acquisition, and pulmonary function test were mandatory. In the induction all patients received 3 cycles of cisplatin 80 mg/m^2 and docetaxel 75 mg/m^2. Patients with stable disease (SD) or partial response (PR) were included in the phase I chemo-radiotherapy, consisting of once-weekly docetaxel concurrently with HT, 2.4 Gy/day, 5 days/week for 5 consecutive weeks (total dose: 60 Gy). Docetaxel was escalated in cohorts of 3 patients according to a modified Fibonacci design, starting from 10 mg/m^2/week.
Results: From 2008 overall 28 patients were treated; 3/28 patients did not proceed into concurrent chemo-radiotherapy, 1 for PD and 2 for consent withdrawal; F:M=6:22, median age: 61 years (40-77), 13 patients with squamous cell- (46%) and 15 with adeno-carcinoma (64%), PS 1 in 13 patients (44%) and 0 in 15 (64%), 50% in stage IIIA and 50% IIIB. All 28 patients were evaluable for response after induction chemotherapy: PR was achieved in 22/28 (78%), 1 (3.5%) showed PD, 5/28 (18%) SD. 25 patients were subsequently enrolled in dose-escalation study. In the concurrent treatment 2 patients had leucopenia G2, esophagitis was G2 in 25% of patients; no late esophageal toxicity was observed. No pneumonitis was ever reported.
Conclusion: Data reported here are at the completion of dose-level of 30 mg/m^2 of docetaxel; till now radiotherapy HT concurrently with docetaxel is not more toxic than standard radiotherapy. For the time of the meeting we will show the completed study.
Keywords: combined modality, Tomotherapy, NSCLC, local advanced disease

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.257 INDUCTION CHEMOTHERAPY FOLLOWED BY 3-DIMENSIONAL HYPOFRACTIONATED ACCELERATED RADIOTHERAPY (3D-HAR) IN LOCALLY ADVANCED (LA) NON-SMALL CELL LUNG CANCER (NSCLC): OUR EXPERIENCE.

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Background: Standard treatment of LA-NSCLC is represented by chemotherapy infused concomitantly to standard fractionated radiotherapy. Actually there is no worldwide agreement neither to chemotherapic nor radiotherapic schedule. Hence 3D-HAR may improve local disease control and reduce the duration and incidence of side effects due to therapy.
Methods: Patients with LA-NSCLC treated with induction chemotherapy containing platin combined to third generation drug followed by 3D-HAR were eligible for the analysis.
Results: From May 2007 to December 2010, 30 patients were analyzed of whom 6 (20%) females and 24 (80%) males with a median age of 65 years (range: 50 – 74) and with a biopsy proven of NSCLC (17 adenocarcinoma, 1 great cell carcinoma, 10 squamous cell carcinoma, 2 NSCLC not other specified). Side disease was left in 13 (43%) patients, right in 14 (47%) patients and unknown in 3 (10%) patients. Stage disease was IIIA in 15 (50%) patients and IIIB in 15 (50%) patients; biopsy proven mediastinal lymph node involvement was available in 13 (43%) patients. All patients received 3 – 4 courses of induction chemotherapy containing platin and in particular: 6 (20%) patients with Carboplatin associated to Gemcitabine (4 patients), Paclitaxel (1 patient) or Vinorelbine (1 patient) whereas 24 (80%) patients with Cisplatin associated to Docetaxel (9 patients) or Gemcitabine (15 patients). Afterword all patients received 3D-HAR (25-30 Gy in 5 fractions at the reference isodose delivered by helical tomotherapy) on the primary tumor and mediastinal lymph nodes involved; responders patients performed a rechallenge of 3D-HAR (15-18 Gy in 3 fractions). No grade 3/4 toxicity was recorded during, at 30 and 60 days from the end of radiotherapy. We recorded 14 (47%) partial response, 13 (43%) stable disease 2 (6%) progression disease and 1 (4%) not evaluable disease, with an overall thoracic control of disease of 90%. Preliminary efficacy results show a 24 months overall survival of 62% (95% Confidence Interval: 42 – 83).
Conclusion: In our series, induction chemotherapy followed by 3D-HAR produces efficacy results similar to those reported by concomitant chemo-radiotherapy administrated with standard fractionation. The advantage of 3D-HAR is represented by reducing the incidence of severe pulmonary and esophageal toxicity. Supported by GIPO.
Keyword: 3-dimensional hypofractionated accelerated radiotherapy (3D-HAR)

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.258 CONCURRENT CHEMORADIOTHERAPY (CONCRT) USING CISPLATIN-VINORELBINE IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (LA NSCLC) FROM THE BANK OF CYPRUS ONCOLOGY CENTRE (BOCOC).

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Background: ConCRT is considered the standard of care in LA NSCLC. We used cisplatin-vinorelbine concurrently with RT for appropriately selected patients with LA NSCLC since 2005. This updated analysis includes consecutively treated patients over the last 6 years.
Methods: From Feb 2005 to Feb 2011 we treated 44 consecutive patients with LA NSCLC, most of who were deemed unresectable. This included LA

NSCLC staged (using the 6th Edition of TNM) as T4/ N3/ "bulky" N2 disease or locally recurrent disease after initial surgery. Patients had ECOG performance status (PS) 0-2 and were treated with Cisplatin (Cis, 75mg/m2 d1) and Vinorelbine (Vin, 30mg/m2 d1-8) 3-weekly. Chemotherapy was administered at full doses for 1-2 cycles and thereafter radical RT was delivered concurrently with subsequent chemotherapy cycles. During the phase of concurrent CRT Vinorelbine was reduced to 12.5mg/m2 d1-8. After ensuring the toxicity of the first 11 patients treated was acceptable, subsequent patients received Vinorelbine at 15mg/m2 d1-8 during ConCRT. The number of treatment cycles was also escalated to a maximum of 6. Patients received definitive CRT (59.4 Gy) unless, surgery was planned. This decision was taken following restaging evaluation, for potentially resectable patients, performed at 45Gy. Since 2008 we have used PET-CT increasingly to stage patients at baseline.
Results: Patient and disease demographics: Of 44 patients there were 39 men and 5 women. Median age was 64 (43-81); PS 0-1 n=37, PS 2 n=6, unknown n=1; 42/44 were smokers with a median 66 (0-140) pack-year history and 10/44 (23%) had documented weight loss ≥5% of baseline weight; radiological stage IIIB n=30 (68%), IIIA n=9 (20%) , IIB n=5 (11%); histology, squamous n=26, adenocarcinoma n=9, unspecified NSCLC n=9. Treatment delivered: total cycles of chemotherapy 190, median 4 (range 1-7). 40 patients (91%) received concurrent therapy most commonly during cycles 2-4. Radiological response rates: Objective responses n=26 (4 complete(CR), 22 partial(PR)), yielding a response rate of 59%; stable disease(SD) n=5; progressive disease(PD) n=6; of the remaining 7 non-evaluable patients 2 had a PR and 1 SD on chest radiograph. 6/40 (15%) patients who received ConCRT underwent surgery (5 lobectomies, 1 pneumonectomy). 5 of these 6 patients had a complete pathologic response (pCR) and 1 a near pCR. After median follow-up of 23.7 months (for patients who are alive) the survival figures are: median progression-free survival (PFS) 15.4 months (95% C.I. 9.1-21.7) and median overall survival (OS) 20.2 months (95% C.I. 12.2-28.3). Toxicity was manageable. The incidence of grade 3-4 oesophagitis or pneumonitis was < 10%. There was 1 toxic death from neutropenic sepsis in a patient who did not seek medical attention promptly. Detailed toxicity data will be presented in due course.
Conclusion: These results are very encouraging considering most patients in this cohort had IIIB disease. The 20.2 month median OS achieved is higher than that reported previously from some randomized phase III studies of ConCRT. The Kaplan-Meier OS plot suggests that 35% patients treated may achieve long-term survival. This Cis-Vin ConCRT regimen appears effective and we therefore believe it merits further investigation.
Keywords: concurrent chemoradiotherapy, cisplatin-vinorelbine, Locally advanced non-small cell lung cancer

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.259 A RANDOMIZED PHASE II TRIAL OF ADJUVANT CHEMOTHERAPY WITH DOCETAXEL (DOC) PLUS CISPLATIN (CIS) VERSUS PACLITAXEL (PAC) PLUS CARBOPLATIN (CAR) IN PATIENTS WITH COMPLETELY RESECTED NON-SMALL CELL LUNG CANCER (NSCLC): TORG 0503

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Background: Adjuvant chemotherapy is standard of care for patients with completely resected stage IB, II and IIIA NSCLC. However, the optimum chemotherapy regimen has not been determined. TORG 0503 was conducted to evaluate platinum-based third generation regimens in this clinical setting.
Methods: Patients with completely resected stage IB, IIA, IIB or stage IIIA NSCLC were stratified by stage (IB/IIA vs. IIB/IIIA) and institution and randomized to receive 3 cycles of DOC (60mg/

m2, day 1) plus CIS (80mg/m2, day 1) or 3 cycles of PAC (200mg/m2, day 1) plus CAR (AUC 6, day 1). Both regimens were repeated every 3-4 weeks. Other eligibility criteria included ECOG PS 0-1, age >=20, and =<70 years old, adequate organ function, no prior chemotherapy or radiotherapy. Patients who underwent pneumonectomy were excluded. The primary endpoint was 2-year relapse free survival (RFS), and secondary endpoints were overall survival (OS), quality of life (QOL), feasibility and toxicity.
Results: 111 patients were randomized between April 2006 and July 2008, 58 patients to DOC+CIS (DC) and 53 to PAC+CAR (PA). Patients' demographics (DC/PA): median age 63/59 years, 60%/66% male, 17%/22% PS 1, 79%/73% adenocarcinoma, 40%/40% of patients were stage IB/IIA, 60%/60% IIB/IIIA. The two-year RFS rate was 74.1% (95%CI: 68.4-79.8) in the DC arm and 72.5% (66.3-78.7) in the PA arm. The two-year survival rate was 89.6% (85.6-93.6) in the DC arm and 86.3% (81.5-91.1) in the PA arm. Feasibility: 93% (54/58) of patients allocated to DC and 92% (49/53) patients in the PA arm completed 3 planned cycles of chemotherapy. Toxicities: DC vs. PA: Grade (G) 3/4 neutropenia (86%/75%), G3/4 anemia (2%/0%). G 3 febrile neutropenia (10%/4%), G2 ALT (0%/10%), G2 creatinine (17%/0%), G2-4 allergy (0%/4%), G2/3 anorexia (43%/22%), G2/3 nausea (47%/22%), G2/3 vomiting (31%/12%), G2 diarrhea (12%/8%), G2/3 sensory neuropathy (3%/33%), G2/3 arthralgia (0%/31%), G2 myalgia (2%/8%). No treatment related deaths were observed in either arm.
Conclusion: Docetaxel plus cisplatin demonstrated promising activity with favorable 2-year RFS, safety and feasibility as adjuvant chemotherapy in patients with completely resected NSCLC. Updated survival data will be presented at the meeting.
Keywords: phase II trial, Adjuvant chemotherapy, Non-small cell lung cancer, TORG

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.260 MEASUREMENT OF HYPOXIA WITH 18F-FAZA PET IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER TREATED WITH DEFINITIVE CHEMORADIOTHERAPY

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Background: Intratumoural hypoxia is a recognised adverse prognostic factor in several cancers, and may contribute to resistance to radiation and chemotherapy but its importance in lung cancer is unproven. This trial evaluated tumoural hypoxia using [^{18}F]-fluoroarabinofuronosyl-2-nitroimidazole (^{18}F-FAZA) positron emission tomography (PET) scans among patients with locally advanced non-small cell lung cancer (NSCLC) treated with definitive chemoradiation.
Methods: Patients with stage IIIA-IIIB NSCLC underwent ^{18}F-FAZA PET scans and [^{18}F]-2-deoxyglucose (FDG)-PET scans within 4 weeks prior to commencing and 8 weeks following completion of concurrent platinum-based chemoradiation (60 Gy). Intra-tumoural hypoxic volumes were determined for the primary and nodal masses, and compared with FDG-PET tumoural volumes to determine the intratumoural hypoxic fraction. The presence of baseline intratumoural hypoxia was correlated with metabolic volume and disease free survival.
Results: 17 patients underwent baseline ^{18}F-FAZA PET and FDG-PET scans. Intra-tumoural and/or nodal hypoxia was qualitatively identified on 11 scans (65%). Tumoural hypoxic volumes were consistently smaller than volumes of FDG metabolic activity at baseline evaluation (median FDG-PET volume 42.22 cm^3 [6.42-137.47]; median ^{18}F-FAZA PET volume 15.18 cm^3 [0.51-82.88], p=0.012). FDG-PET volumes were not, however, statistically different according to hypoxia status (p=0.38). Eight patients with baseline hypoxia had post treatment 18F-FAZA scans - 6 of 8 (75%) patients had resolution of imageable hypoxia following chemoradiation. Two of 6 patients without imageable baseline hypoxia were alive at last follow up 7.8 years after treatment. Only 1 of 11 patients with baseline hypoxia did not experience disease progression, and died of heart failure at 6 years. The disease free survival was not significantly different

between the baseline hypoxic and non-hypoxic groups (median 0.8 years and 1.3 years respectively, p=0.42).
Conclusion: Intratumoural hypoxia, as detected by 18F-FAZA PET, was present in 65% of patients with locally advanced NSCLC and became undetectable in the majority of patients who had repeat scans following chemoradiation. Larger studies are required to evaluate the prognostic significance of the presence and resolution of imageable tumour hypoxia in NSCLC.
Keywords: Hypoxia, FAZA PET scan, Non-small cell lung cancer, chemoradiation

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P4.261 TREATMENT RESULTS IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS: A SINGLE CENTER EXPERIENCE

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Background: Although combined-modality treatment with chemotherapy and radiotherapy has improved survival in some patients with stage III NSCLC, most still succumb to the underlying disease. Tumor progression remains problematic, both locally within the chest and in extrathoracic sites.
Methods: Sixty-two patients with a diagnosis of locally advanced non-small cell patients followed at Medical Oncology Department in Baskent University School of Medicine were enrolled into the study. Patients and clinico-pathologic charactheristics including age, gender, lymph node status, smoking history, histopathology that may affect disease free and overall survival were analyzed.
Results: Of all patients, 4 (6,5%) were female and 58 (93,5%)were male. Median age was 60(range, 43-). Median follow-up period was 24 months. For histopathologic subgroups, 34 (54,8%) were squuamouscell carcinoma, 17 (27,4%) adenocarsinomo, 2 (3,2%) large cell carcinoma and 9 (14,5%) other NSCLC subtypes. Twenty seven (43,5%), patients were in stage IIIA, 35 patients in stage IIIB (56,5%) . In 7 (11,3%) patients, there were positive lymph nodes. In 7 (11,3%) patients, 36 (58,1%) patients and 2 (3,2%) patients, there were N1, N2 and N3 disease, respectively. Recurrence was observed in 24 (54,8%) patients. Twenty-six (41,9%) patients had an operations. 20 (32,3%) patiens received chemotherapy (mostly vinorelbine+cisplatinum) and 16 (25,8%) received chemoradiotherapy. Of all patients who had operation, 15 (57,6%) also receieved neoadjuvant chemotherapy. There was signigicant association found between surgery and overall survival in locally advanced NSCLC patients. However, this significant association was not observed between, age of the patient at diagnosis, gender, nodal statatus, hisyologic subgroups, stage at the diagnosis, results of PET-CT scan and disease and overall survival of the patients.
Conclusion: Our preliminary results indicate that, multimodality approach for treatment of locally advanced NSCLC is obligatory and neoadjuvant chemotherapy with cisplatin+vinorelbine is well tolerated and effective teratment option.
Keywords: locally advanced, Non-small cell lung cancer, Vinorelbine, neoadjuvant

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P4.262 HIGH DOSE PREOPERATIVE CHEMORADIATION PRODUCES HIGH RATE OF COMPLETE RESPONSE IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Trimodality therapy has been shown to be an effective treatment for stage III Non-small cell lung cancer (NSCLC). In the Intergroup trial (Albain et al) 45 Gy of radiation was delivered with a nodal downstaging rate of 46%. We hypothesized that with advanced radiotherapy techniques high dose radiotherapy (>66 Gy) could be given without increasing toxicity.
Methods: Patients who underwent preoperative chemoradiation at Rabin Medical Center followed

by surgery were retrospectively reviewed. Chemotherapy was either Carboplatin (AUC 6) and Paclitaxcel (200 mg/m2) q3 wk or Cisplatin d1&8 (50mg/m2)/Etoposide d1-5 (50mg/m2)concurrent with RT. No induction chemotherapy was given. RT was limited to the involved tumor and nodes based on FDG-PET, no elective nodes were treated. RT was delivered with IMRT using ECLIPSE treatment planning system with dynamic multileaf collimator delivery. One month following completion of CRT a restaging FDG-PET was performed. Patients without progressive disease were taken to surgery.
Results: From November 2007- August 2010 thirty patients underwent preoperative chemoradation followed by surgery. A majority of patients were male (53%) and the median age was 62 years (range 47-76). Performance status was ECOG 0-1 in all but one patient. 54% presented with stage IIIA and 46% were staged IIIB. 75% received cisplatin/etoposide concurrent with RT and the remainder received carboplatin/paclitaxcel. Median PTV dose of RT was 72 Gy (range 66-72). Median gross tumor volume was 110 cm3 (range 27.3-353 cm3) 13/30 (43%) underwent pneumonectomy and the remainder lobectomy. There were no post-operative deaths. 97% of patients underwent nodal downstaging . 74% of patients had pathologic compete response. The median V20 was 24% and median mean lung dose was 14 Gy. With median follow-up of 14.5 months four patients have died. One patient developed a fatal pulmonary artery rupture 3 months after surgery and two patients developed grade 3 radiation pneumonitis. 6 patients have experienced distant failure, 5 with brain metastases and one with pleural effusion. No patients have developed local recurrence. 67% of patients remain alive without evidence of disease. The median survival has not yet been reached.
Conclusion: High dose preoperative CRT produces provocative response rates and is tolerable. This approach is ongoing and worthy of further investigation.
Keywords: combined modality, NSCLC, Surgery, Radiotherapy

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P4.263 PULMONARY RESECTION AFTER HIGH DOSE RADIATION THERAPY (>59 GY) AND CONCURRENT CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER.

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Background: Preoperative concurrent chemoradiotherapy (ChT/RT) for locally advanced NSCLC improves local control and has curative potential. Standard preoperative RT dose is 45-50 Gy. Higher dose RT results in higher response rates and has resulted in longer survival but is also plagued with higher complication rates, particularly after pneumonectomy. RT dose of 60-66 Gy is routinely used to treat LA-NSCLC at the Medical College of Wisconsin (MCW) with curative intent and also in the preoperative setting for resectable and marginally resectable locally advanced disease. High dose radiation is used to improve response rates and resectability and also to avoid treatment interruptions if surgical resection is not performed.
Methods: The medical records of patients undergoing surgery at the MCW who received RT >59 Gy between 2000 and 2010 were reviewed. Data abstracted included demographics, complications, pathologic response rates, failure patterns, and survival.
Results: Forty patients were identified with a median age of 61 (40-82 years). 23% were over 70 years. Median radiation dose was 63 Gy (59.4-68.4 Gy). The most common dose was 66 Gy. All but one patient received concurrent ChT. Reasons for concurrent ChT/RT included pathologic confirmation of N2 disease (9), marginally resectable or unresectable primary tumor (18), clinical N2 disease (12), and recent cardiac surgery (1). Median time from completion of RT to surgery was 75 days (20-602). Surgeries performed following ChT/RT were: 27 lobectomies, 9 left pneumonectomies, and 4 right pneumonectomies. Muscle flaps were used in 3 cases. 20% of patients

experienced major 30-day complications with no 30-day postoperative deaths. Acute perioperative complications requiring reoperation included: 3 hemorrhages, 2 bronchopleural fistulas, and 1 chylothorax. Muscle flaps were not used in these cases. Late complications included: 2 contralateral pneumothoraces, 1 hemorrhage, 1 chest-wall abscess, and 1 esophageal fistula. 50% (2/4) patients with right pneumonectomy and 11% (1/9) with left pneumonectomy experienced major 30-day complications including hemmorrage, pulmonary embolus, and SVC obstruction. Complete pathological response (pCR) rate was 60% for all patients. For patients with preoperative biopsy proven N2 involvement pCR was 56% and complete nodal clearance was 78%. Median follow-up from end of RT was 26 months (5 months -10 years). Overall survival (OS) and disease free survival (DFS) at 1 year was 95% and 77% and at 3 years 55% and 44%. Three-year OS for pN0 and pN+ disease was 64% and 17%, (p=0.0051). 40% of patients had surgery for radiographic residual or progressive disease > 90 days after completing RT. 50% are alive without disease with median follow-up of 32 months and no major complications.
Conclusion: Pulmonary resection, including pneumonectomy after high dose RT/ChT can safely be performed with high pCR, OS, and DFS rates. Long term survival is possible in patients with residual N2 disease after high dose ChT/RT. Surgical salvage > 90 days after high dose ChT/RT is well tolerated.
Keywords: Non-small cell lung cancer, high dose radiation therapy, Surgery, chemoradiotherapy

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P4.264 RANDOMIZED, MULTI-CENTER PHASE II STUDY INVESTIGATING ADDITIONAL WEEKLY CETUXIMAB TO CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CARCINOMA: FINAL REPORTING ON SAFETY

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Background: The encouraging, but modest benefits from concurrent chemoradiotherapy (CRT) in patients with locally advanced NSCLC warrant more effective treatment regimen. Cetuximab, a monoclonal antibody against the epidermal growth factor receptor has shown activity in NSCLC and in combination with RT in head and neck cancer. We report on the final safety assessment of the combination of daily dose Cisplatin and CRT with or without weekly Cetuximab. Feasibility data have been published previously.
Methods: Patients with non-operable locally advanced NSCLC received high dose accelerated RT (66 Gy in 24 fractions) and concurrent daily Cisplatin (6 mg/m2) with (arm A) or without (Arm B) additional weekly Cetuximab (400 mg/m2 loading dose one week prior to the RT start followed by weekly 250 mg/m2).
Results: Between February 2009 and February 2011, 87 patients entered this multicenter phase II study. The median age was 63 years (range: 29-78) and 70% were male. Baseline NSCLC staging was: II (10%), IIIa (41%), and IIIb (49%). 52 patients were evaluable for toxicity. The CRT was generally well tolerated. Radiation esophagitis was the most common side effect (grade 3 according to CTCAE v 3.0) (see table). Using a prophylactic regimen against acneiform dermatitis the percentage of grade III skin toxicity was 11%. All other side effects were comparable between both groups. In the arm A 16 patients had SEAs reported and 7 in arm B.

	CCRT	CCRT + Cetuximab	P-value
Fatigue	20%	30%	0.53
Acneiform dermatitis	0%	11%	0.24
Anorexia	12%	22%	0.47
Constipation	4%	4%	0.99
Dyspnea	0%	4%	0.99
Dysphagia	20%	22%	0.99
Nausea	12%	7%	0.66
Neutropenia	8%	4%	0.60
Pain	4%	11%	0.62

Conclusion: Concurrent chemoradiotherapy consisting of high dose accelerated radiotherapy and daily dose Cisplatin with additional weekly Cetuximab in patients with NSCLC was well tolerated. These results justify further evaluation of the efficacy of this multimodal regimen.

Keywords: chemoradiotherapy, Non-small Cell Lung Carcinoma, cetuximab, safety

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.265 THE IMPACT OF HISTOLOGY ON OVERALL SURVIVAL AND PROGRESSION FREE SURVIVAL FOLLOWING INDUCTION CHEMOTHERAPY WITH PACLITAXEL AND CARBOPLATIN AND RADIOTHERAPY OR SIMULTANEOUS RADIOCHEMOTHERAPY WITH WEEKLY PACLITAXEL

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Background: The choice of systemic therapy in stage IV NSCLC is increasingly individualized; the precise histology and, increasingly, tumour molecular biology, are taken into account. However, this approach has not yet been broadly applied to patients treated with chemoradiotherapy for inoperable stage IIIa and IIIb disease. There is some preliminary evidence that response to chemoradiotherapy varies with histology. Xu and Colleges (XuY,etal. Concomitant chemoradiotherapy using pemetrexed and carboplatin for unresectable stage III non-small cell lung cancer (NSCLC): Preliminary results of a phase II study. Lung Cancer (2010),doi:10.1016/j.lungcan.2010.09.012) treated 21 patients with pemetrexed (500mg/m2) plus carboplatin (AUC 5) and simultaneous radiotherapy, and found that the patients with adenocarcinoma (n=16) experienced longer progression free survival (p= 0.068) than those with squamous cell carcinoma (n=5).

The CTRT 99/97 Study from the Bronchial Carcinoma Therapy (BROCAT) Group. (Huber et al., JCO 2006) showed that, following induction chemotherapy with paclitaxel and carboplatin, simultaneous chemoradiotherapy with weekly paclitaxel is superior to radiotherapy alone. The role of histology in the response to chemoradiotherapy with paclitaxel and carboplatin has not yet been described.

Methods: We conducted a retrospective analysis of histology-based subgroups in the CTRT99/97 BROCAT study, looking at overall survival as well as progression free survival.

Results: Three hundred and three patients were enrolled in the BROCAT trial including 59 adenocarcinoma, 171 squamous cell, 28 large cell, 10 mixed and 35 NSCLC not otherwise specified (NOS). After induction chemotherapy 214 patients were randomized to either radiotherapy alone (22 adenocarcinoma, 67 squamous cell, 12 large cell, 4 mixed, 7 NOS) or radiotherapy plus simultaneous paclitaxel (19 adenocarcinoma, 62 squamous cell, 4 large cell, 3 mixed, 8 NOS).

Independent of histology, patients randomized to receive chemoradiotherapy experienced longer progression free survival than those who received radiotherapy alone (11.5 vs. 6.3 months, HR 1.747, p<0.001), and there was a strong trend towards improved overall survival (18.7 vs. 14.1 months, p=0.091).

Analyses of histology subgroups showed a trend towards improvement in overall survival in all subgroups which did not reach statistical significance. Patients with squamous cell carcinoma showed a statistically significant improvement in progression free survival after randomization to chemoradiotherapy compared to radiotherapy alone (HR 1.75, p=0.007). In the adenocarcinoma, mixed histology and NSCLC NOS subgroups there

was a trend to improved progression free survival following chemoradiotherapy. Unexpectedly, patients with large cell tumours showed a trend towards shorter progression free survival after treatment with chemoradiotherapy (HR 0.589).
Conclusion: This analysis did not identify a statistically significant effect of histology on the efficacy of induction therapy with paclitaxel plus carboplatin and simultaneous chemoradiotherapy with paclitaxel in locally advanced NSCLC. However the benefit of simultaneous chemoradiotherapy was most clear in patients with squamous cell carcinoma. There was a surprising trend towards worsened progression free survival in patients with large cell tumours.
Further analyses are required to bring clarity to the role of histology in the treatment of locally advanced tumours. In particular in studies investigating new combinations of systemic therapy (including EGFR-TKIs and other targeted therapies) and radiation, the relevance of histology, and of tumour molecular biology, is likely to increase.
Keywords: paclitaxel, Carboplatin, Radiochemotherapy, histology

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P4.266 SOCCAR: SEQUENTIAL OR CONCURRENT CHEMOTHERAPY AND HYPOFRACTIONATED ACCELERATED RADIOTHERAPY IN INOPERABLE STAGE III NSCLC

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Background: Local tumour control and recurrence is a major problem in the management of inoperable stage III NSCLC. A strategy to avoid the detrimental effects of accelerated repopulation - administration of a radical radiotherapy dose within a period of 28 days - might improve local control rates and hence survival for this group of patients. To test this hypothesis, we have conducted a randomised phase II trial in which patients received a radiation dose of 55Gy in 20 fractions in four weeks, given either sequentially after four cycles of cisplatinum and vinorelbine or concurrently with the same chemotherapy
Methods: 130 patients were randomised to receive 55Gy at the ICRU reference point in 20 fractions over 4 weeks, with four cycles of cisplatinum and vinorelbine given either prior to RT or starting concurrently with the first fraction of radiation. Trial entry required: pathologically confirmed stage III NSCLC judged inoperable by a thoracic surgeon, and treatable within a radical RT volume with v20 ≤30% and ≤12 cm of oesophagus within PTV; PS 0 or 1, FEV1≥ 1L and TLCO≥ 50%. Patients with weight loss and N3 disease were included, with no upper age limit. Treatment was with either 3D conformal RT or 4D. Required GTV-PTV margin was 1.5 cm for conformal and 1cm for 4D planning. Median age was 62(range 39-77); 61% were male; histology 64% squamous, 27% adenoca; 52% were PS 0; 44% had IIIA and 56% had IIIB disease. Patient characteristics were well balanced between the two arms.
Results: 67 patients received concurrent (con) treatment and 60 sequential (seq). This report is at a median follow up of 31 months.
The median number of chemotherapy cycles was 3 con vs 4 seq; 53% vs 60% of patients had chemotherapy dose delays. Incidence of SAEs was 46% con vs 47% seq. there were 43 grade 3 or 4 toxicities (29% vs 38%) - 15 were grade 4 (7 con, 8 seq). Six con patients and one seq suffered grade 3 oesophagitis. Grade 4 oesophagitis did not occur. There were two treatment related deaths in the con arm and one in the seq arm. Deaths within six months of randomisation were three con vs two seq. 52.2% of patients in the con arm and 68.3% in the seq arm have died. Median survival in months is 27.4 con vs 18.6% seq. Two year survival is 54% in the concurrent arm and 42% for patients receiving sequential treatment. Survival at three years is 38% con vs 27% seq.
The incidence of local tumour recurrence within the radiation treatment volume was 10% in the concurrent arm and 22% in the sequential arm.
Conclusion: This is the first randomised trial in stage III NSCLC to achieve a two year survival rate in excess of 50%, with a local relapse rate of 10% for patients receiving concurrent treatment. A strategy

to minimise the effects of accelerated repopulation using accelerated hypofractionated radiotherapy with chemotherapy is feasible, safe and effective for patients with stage III NSCLC.

Keywords: accelerated, hypofractionated, Radiotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.267 PATIENT QUALITY OF LIFE IN A RANDOMISED TRIAL OF SEQUENTIAL VERSUS CONCURRENT CHEMORADIATION USING ACCELERATED HYPOFRACTIONATED RADIOTHERAPY (SOCCAR)

Joe Maguire[1], Rhona Mcmenemin[2], Noelle O'rourke[3], Clive Peedell[4], Michael P. Snee[5], Stuart Mcnee[3], Veronica Kelly[1], Iftekhar Khan[6], Rachel Slade[6]

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Background: SOCCAR is the first trial comparing concurrent and sequential chemotherapy and radiotherapy in stage III NSCLC to prospectively measure quality of life (QoL) in both treatment arms. In this phase II trial patients received four cycles of cisplatinum and vinorelbine, with 55Gy in 20 fractions over four weeks either sequentially after four cycles of chemotherapy (seq) or concurrently with the same radiotherapy schedule starting on day one of radiotherapy (con). We have reported a two year survival rate of 54% in the concurrent arm and 42% for patients in the sequential arm.

Methods: 67 patients received con and 60 seq. Patients were asked to complete the QLC-C30, LC-14 and EQ-5D questionnaires prior to randomisation and at specific intervals during treatment and follow up. This report relates to patient reported QoL using the QLC-C30 instrument at three and six months from randomisation, and twelve months after starting treatment, in patients who remained free from recurrence at 18 months from randomisation. Scores were compared with the patient's pre-randomisation assessments. This group of patients was chosen to facilitate assessment of the effects of the two treatment arms on QoL, while avoiding the detrimental effects of tumour progression on QoL scores.

Results: Patient compliance was high, with pre-randomisation assessments completed by 63/67 patients receiving con treatment and 50/60 patients in the seq arm. This compliance rate was maintained at three months from randomisation; six months after randomisation the completion rate was 41/67 con and 35/60 seq and slightly more forms were completed by patients at twelve months after starting treatment.

Patient scores using the QLQ-C30 prior to randomisation were fairly well matched in both the "role functioning " and "physical functioning " domains across both the con and seq groups, with mean scores of 85.2 con vs 79.3 seq in role functioning and 88.6 con vs 84.5 seq for physical functions. At three months scores dropped in both treatment arms - mean scores for role functioning were 71.0 con and 60.7 seq, and for physical functions 80.0 con vs 74.6 seq. QoL scores appeared to recover more quickly in patients receiving sequential treatment; at six months mean role functioning scores were 69.1 con vs 72.4 seq, and mean scores in the physical function domains were 77.7 con vs 80.1 seq.

At twelve months after starting treatment mean role functioning scores were 73.8 in the con group and 70.4 for seq patients, and mean scores for physical function were 80.8 con vs 78.1 seq.

Conclusion: QoL measurement is feasible in a trial of chemoradiation in stage III NSCLC. Our findings indicate that patient reported QoL falls at three months for patients receiving both concurrent and sequential treatment; recovery towards pretreatment levels occurs more quickly in seq patients. Twelve months after commencing treatment the degree of recovery towards pre treatment levels of QoL is similar for patients in both concurrent and sequential treatment arms. The overall degree of recovery in reported QoL is slightly greater for physical function compared to role functioning as assessed using the QLC-C30 instrument.

Keywords: Quality of Life, chemoradiation

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P4.268 INDUCTION CHEMORADIATION THERAPY WITH EGFR RECEPTOR INHIBITOR (ERLOTINIB) FOR STAGE IIIA/B NON-SMALL CELL LUNG CANCER IS WELL TOLERATED AND DOES NOT COMPLICATE SUBSEQUENT RESECTION.

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Background: Survival from locally advanced (Stage IIIA/B) non-small cell lung cancer (NSCLC) is poor despite aggressive multimodality therapy. We report the feasibility and surgical outcomes of a novel phase 1 induction.
Methods: Thirty patients with resectable pathologic stage IIIA/B NSCLC were enrolled in a non-randomized trial of induction therapy. Patients received three cycles of paclitaxel (50mg^m2/week) and carboplatin (AUC 2/week) with hyper-fractionated radiotherapy (150cGy BID X 2 weeks). In addition, patients were treated with concomitant erlotinib (150mg/daily) during their induction period. After restaging, non-progressors as well as those deemed fit enough for surgery, underwent pulmonary resection. Consolidation therapy (identical to the induction course) was planned and there was an intent to maintain patients on erlotinib (150mg/daily) for 2 years. Charts were reviewed and down-staging, operability, surgical mortality/morbidity, and ability to complete the intended treatment were assessed.
Results: The median age of participants was 61 yrs (32-76) and 43% were male (13/30). The planned induction course was completed in 29 of 30 patients. Interval assessment demonstrated a 13% progression rate to stage IV disease (4/30), and of the remaining 26 patients, all underwent resection. The median interval from staging mediastinoscopy until operative intervention was 10.7 weeks (7-13.7 weeks) and the FEV_1 pre and post induction therapy was unchanged (89% vs. 88.5%. Dermatologic and gastrointestinal toxicities from the induction regimen were seen in almost 90 % of patients, though only one was significant enough to truncate/alter therapy. All 26 patients underwent anatomic pulmonary resection and mediastinal lymphadenectomy with 10 pneumonectomies (38%) and 16 lobectomies (62%) performed. Length of stay was 6 days (range 4-20 days) and median ICU care was 1 day (range 1-9). Only one patient required a perioperative blood transfusion. At least one major peri-operative complication occurred in 10 of 26 patients (38%) with atrial fibrillation (17%) and pulmonary insufficiency (10%) being the most common. There were no operative mortalities. Final pathologic assessment showed that 12 of the initial 30 patients (40%) were down-staged by this induction regimen. There were no late surgical complications and all patients recovered sufficiently to begin consolidation therapy as planned.
Conclusion: Surgical resection following an induction chemoradiation therapy with concomitant EGFR receptor inhibition (erlotinib) for stage IIIA/B NSCLC is technically feasible and safe. No surgical mortality was seen in this preliminary study, even after pneumonectomy, and a surprisingly high percent of patients completed their entire intended therapy. Longer follow-up will be important to establish efficacy prior to expanding this novel treatment regimen.
Keywords: Non-small cell lung cancer, erlotinib, chemoradiation, Surgery

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P4.269 THE RETROSPECTIVE ANALYSES OF 96 CASES WITH PRIMARY LUNG CARCINOMA

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Background: Lung cancer is the most common cause of cancer death and closely associates with cigarette smoking. In early stage of disease the patients are usually asymptomatic and when the symptoms consist, the cancer is in advanced stage.
Methods: According to clinical, radiological and bronchoscopical findings 96 cases which were diagnosed pathologically between January 2007 and December 2010 years were analyzed retrospectively.
Results: Male/Female: 87/9, median age: 59. Eighty- two (85.4 %) patients were smokers (mean

exposure = 45 ±22.5 packet/year). According clinical findings, cough (n: 86) 89.58 %, weight loss (n: 74) 77.08 %, phlegm (n: 68) 70.83 % were seen in the most patients. The most findings detected on chest X-ray were mass (n: 90) 93.75 %, mediastinal enlargement (n:54) 56.25 %, atelectasis (n: 52) 54.6 %. Histological subtypes of these 96 patients were 6 small cell lung cancers (SCLC) (6.25 %), 82 non-small cell lung cancers (NSCLC) (85.41 %); (32 unclassified 39, 2 %, 12 adenocarcinoma 14.6 %, 38 squamous cell cancer 46.3 %) and 8 malignant epithelial tumors (8.33 %). Radiological and bronchoscopical examination revealed that primary tumor was located more frequent on the left lung 56 (58.33 %) and the lower lobes (right: 20, (20.8 %), left: 40, (41.6 %) respectively). The tumorial lesions were evaluated as endobronchial n:54 (56.25 %) and 26 submucosial (27.8 %) during bronchoscopy. The most diagnostic methods were fiberoptic bronchoscopy and transthorasic needle biopsy, 83 % and 16 % respectively. SCLC patients were defined as 2 limited 33.3 % and 4 66.6 % extensive stage. NSCLC and malignant epithelial tumors were defined as 38 (39.58 %) operable and 52 (54.16 %) inoperable. Metastases were detected in 25 patients (26.4 %). The most frequent metastatic organ was bone.

Conclusion: Detailed history, physical examination, radiological investigations are precious for staging due to treatment of patient with suspected lung cancer. As a result, squamous cell carcinoma was the most common type of lung cancer and it was frequently related with smoking habbit ($p<0.05$). The common site of tumor localization, independent of histopathological classification, was the left lung and lower lobes.

Keyword: Lung cancer, cigarette, symptom, radiology, bronchoscopy, transthorasic needle biopsy, location.

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.270 THE EARLY DETECTION OF LUNG CANCER WHEN ENDOBRONCHIAL LESION IS VISUALIZED BY FLEXIBLE BRONCHOSCOPY (FB)

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Background: Malignant lesions of the respiratory system may present as endobronchial lesions. Flexible bronchoscopy (FB) is the most often used invasive technique in the examination of the tracheobronchial tree; it is also the most helpful technique in the diagnosis and staging of bronchial carcinoma. Objetive: To evaluate the role of FB in the detection of endoscopically visible pulmonary malignacies which indicate the presence of lung cancer, and to compare the role of endobronchial biopsies with cytological examinations, including bronchial brushings and washings.

Methods: From June 2008 to August 2009, 84 consecutive patients with endoscopically visible tumors were enrolled. All patients underwent FB and 6 patients underwent repeated FB, before a definitive histological or cytological diagnosis of pulmonary malignancy was made.

Results: Eighty four patients underwent FB, and an endoscopically visible tumour was identified in all 84 patients. Eighty three percent of the patients were males. Their average age was 67,3 years old. Of the 84 procedures using FB, 73 were followed by a definitive histological or cytological diagnosis of pulmonary malignancy, amounting to 81% of the endoscopically visible tumours. Repeat bronchoscopy for inconclusive results improved the diagnostic yield in four patients. Seventy patients (85 %) of the 82 who underwent endobronchial biopsy were found to have pulmonary malignancy; 40 patients of the 55 who underwent bronchial brushing (73%) had the malignancy confirmed; and 46 of the 81(57%) patients who underwent bronchial washing also had the malignancy confirmed. The histological type of lung cancer diagnosed by FB included 55 nonsmall-cell lung cancer (NSCLC) (75%), 16

small-cell lung cancer (SCLC) (22%), and two carcinoid tumors (3%). NSCLC subtypes included 26 squamous carcinoma, 21 adenocarcinoma, and 1 large-cell carcinoma. In eight cases we were unable to specify a NSCLC subtype.
Conclusion: Flexible bronchoscopy is highly sensitive in the detection of endobronchial disease. Bronchial biopsy and brush cytology are exceptionally valuable tools in the diagnosis of lung cancer. Bronchial wash cytology is also a valuable tool. Thus, all three tests combined should be performed routinely in cases of suspected malignancy. The distinction between SCLC and NSCLC, including histologic types of NSCLC by all three tests appears to be accurate. Repeat bronchoscopy for inconclusive results with adequate sampling improves the diagnostic yield of suspected endobronchial lesions.
Keywords: flexible bronchoscopy, endobronchial biopsy

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P4.271 IMPACT OF PROLONGED IRRADIATION TIME FOR UNRESECTABLE STAGE III NON-SMALL-CELL-LUNG-CANCER PATIENTS TREATED WITH CONCURRENT CHEMORADIATION: QUALITY ASSURANCE RESULTS OF THE GFPC-IFCT 02.01 STUDY

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Background: To study deviations from the radiotherapy trial guidelines and their potential consequences on patients' outcome in a multicentre randomized phase II trial of combined modality treatment (cisplatin-vinorelbine with 66 Gy 3D conformal radiotherapy) in locally advanced unresectable non small cell lung cancer (NSCLC).
Methods: Radiotherapy files of 101 patients who completed the treatment were reviewed by the GFPC panel of Radiation Oncologists and compared to the trial radiotherapy guidelines for major (MD) and minor (md) deviations. The impact of deviations on survival and toxicities were analysed.
Results: MD and md were observed respectively in 69 (68.3%) and 27 (26.7%) patients. There is a significant correlation between the 2-years overall survival (OS) and total radiation dose (TD) < 60 Gy (0% vs. 47.8 % respectively, p = 0.0001) and treatment interruption (TI) > 7 days (p = 0.003) wich was correlated with total dose. The 2-years OS was lower, but non-significantly for patients with one MD as compared to those without MD (40% vs. 53.1% respectively). Median V20 was 31.4% (9% to 64%), without correlation with OS and pulmonary toxicity.
Conclusion: This study demonstrates a high rate of deviations from the trial radiotherapy guidelines with a detrimental impact on 2-years OS of treatment interruption.
Keywords: unresectable NSCLC, combined modality treatment, prolonged treatment time

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P4.272 PATIENT-REPORTED HEALTH OUTCOMES AFTER LUNG CANCER TREATMENT: AN INTERNET BASED STUDY

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Background: Lung cancer patients may be at risk for myriad late effects after multimodality therapy, the impact of which may difficult to evaluate using conventional methods. In addition, lung cancer patients are at risk for numerous co-morbidities. This Internet based study evaluates patient perceptions of health outcomes after treatment for lung cancer.
Methods: Patient-reported data was gathered via a convenience sample frame from lung cancer survivors voluntarily utilizing a publically available, free, Internet-based tool for creation of survivorship care plans. Available at) website, the tool allows survivors to enter data regarding diagnosis,

demographics, and treatments, and provides customized guidelines for future care. During use of the tool, lung cancer survivors are queried regarding late effects associated with specific treatments, as well as potential co-morbidities, and asked to answer "yes," "no," or "I don't know." All data have been maintained with IRB approval.
Results: 106 lung cancer survivors answered queries regarding health outcomes; 58% were female and 92% Caucasian. Median diagnosis age was 57 (range 25 – 83) and median current age 60 (27 – 85). Most reported receiving follow-up care from an oncologist only (56%), 10% a primary care physician only, and 29% both. Most had undergone chemotherapy (82%), surgery (67%; of these, 83% lobectomy/ pneumonectomy, 37% lymph node dissection), and radiation (48%). Health outcomes and comorbidities reported by lung cancer survivors included hypertension (30%), hyperlipidemia (19%), restrictive lung disease (29%), and hypothyroidism (7%). Survivors using this tool also reported the following symptoms following treatment: hearing loss (31%), peripheral neuropathy (36%), cognitive changes (47%), chronic pain related to surgery (34%), difficulty swallowing/speaking/breathing (22%), and sexual changes (27%).
Conclusion: Survivors using this tool anonymously and voluntarily report significant comorbidities and late effects after lung cancer treatment. Many are followed only by an oncologist, and may require attention to major health concerns in survivorship. This tool offers a unique way for survivors to report their experiences; the data reported here may be of significant impact in future study of quality of life, as well as patient counseling and survivor care.
Keywords: survivorship care plan, late effects after lung cancer, Patient Reported Outcomes, internet

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P4.273 G-CSF ADMINISTRATION IN PATIENTS WITH LUNG CANCER: AN OBSERVATIONAL STUDY OF CURRENT ITALIAN PRACTICE.

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Background: The OBSERVE observational, prospective study was designed to describe the use of G-CSF in Italian practice, after a series of expert panels had suggested that many different administration schedules were employed.
Methods: Patients were eligible at their first administration of a G-CSF following chemotherapy (CT) for a non-hematologic malignancy. Primary outcome measures were G-CSF type, timing of administration and number of doses administered during each CT cycle.
Results: 512 eligible patients, of whom 93 (18.2%) had lung cancer, were enrolled at 23 Oncology Units in Italy. Of the 93 lung cancer patients, 68.8% had NSCLC and 31.2% had SCLC. 191 CT cycles with G-CSF support were observed overall: 133 (69.6%) with daily G-GSFs and 58 (30.4%) with pegfilgrastim. While 91.4% of pegfilgrastim was administered 24-72 hours post CT, only 56.4% of daily G-CSFs were initiated within the 24-72 hours post CT timeframe. When using daily G-CSFs, less than 4 daily doses were given in 51.9% of CT cycles with daily G-CSF support, 4 to 5 daily doses in 31.6% of cycles, and at least 6 daily doses in 16.5% of cycles. In 18.4% of cycles with daily G-CSF support, daily G-CSF doses were not administered on consecutive days.
Conclusion: Study outcomes suggest G-CSF administration practice frequently does not correspond to the recommendations of Italian (AIOM) guidelines, and current practice for daily G-CSFs with short duration of treatment is unsupported by an evidence-based rationale; obtaining a better adherence to guidelines through educational initiatives would be highly desirable.
Keywords: G-CSF, Myelotoxicity

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P4.274 ANALYSIS OF PERITUMORAL EDEMA AROUND THE LUNG CANCER BRAIN METASTASIS

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Background: The peritumoral edema surrounding brain metastases in lung cancer is very common, although the exact mechanisms of its development during bronchial carcinogenesis has barely been studied.
Methods: We analyzed the clinicopathological data of 163 lung cancer patients with brain metastasis diagnosed and treated at the Semmelweis University. The peritumoral edema surrounding brain metastases was determined and categorized according to CT and MRI results. The edema was considered significant if it was wider than 10 mm, moderate: between 1-10 mm.
Results: Solitary brain metastasis was found in 70 cases and 93 patients developed multiple brain metastases. 127 patients had the appearance of peritumoral edema (77.9%), of them 77 patients had significant, 50 patients moderate edema. No edema was detected in 36 patients. In case of no detectable edema, tumor diameter was significantly smaller (16,1 mm vs 23,6 mm p< 0,05). The presence of peritumoral edema predicted worse survival (4,4 months vs 6,6 months). When compared small cell lung cancer either to adenocarcinoma or to squamous cell carcinoma, the appearance of wider edema was significantly lower in both cases (20% vs 59,7% or 63,6% p<0,05). These differences were also significant in chemotherapy-naïve patients. In 48.8 % of small cell lung cancer patients no edema was detected. Among the adenocarcinoma and squamous cell carcinoma patients the proportion of early brain metastasis (within 3 months after the diagnosis of primary tumor) was significantly higher than in small cell lung cancer cases (p<0,05).
Conclusion: Our study indicates that in lung adenocarcinoma and squamous cell carcinoma the development of remarkable peritumoral oedema is more frequent when compared to small cell lung cancer cases and not influenced by the first-line chemotherapy. The presence of peritumoral edema may be considered a wrong prognostic factor.
Keywords: peritumoral edema, Brain Metastasis

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P4.275 COMBINED ENDOSCOPIC METHOD FOR MONITORING THE EFFECTIVENESS OF NEOADJUVANT CHEMOTHERAPY OF NSCLC WITH THE USE OF AUTOFLUORESCE AND SPECTROSCOPIC METHODS

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Background: Bronchoscopy is a subjective method of research, where success depends largely on the level of specialist training. In recent years, developed and implemented techniques that allow to objectify this method of diagnosis, in particular spectroscopy. The aim of our study was to estimate the informativity of autofluorescence bronchoscopy and spectroscopy for evaluating the effectiveness of neoadjuvant chemotherapy (NCT) for lung cancer.
Methods: The study included 46 patients with central NSCLC IIIa / IIIb stage who underwent 2-4 courses of platinum-based NCT. Endoscopy was done before treatment started and repeated each 21 day. Combined endoscopic investigation included: bronchoscopy in conventional mode (CB), spectroscopy in conventional mode (CS), bronchoscopy in autofluorescence mode (AFB) and spectroscopy in autofluorescence mode (AFS). Integrated system for autofluorescence and spectroscopy was used. The data obtained were compared with the results of histological study of biopsy samples from the respective sites.
Results: The sensitivity and specificity of the combination of AFB and AFS was 97.1% and 88.3%, respectively vs. CB and CS - 66,7% and 86,9%, respectively. Combined endoscopy revealed that the NCT was effective in 41,3% cases (n = 19 - partial endoscopic response), in 4 patients (10,3%) endoscopic tumor progression was found. Endobronchial spread of the tumor in 30.4% of cases (p = 0.03) was defined more accurately by AFB and AFS in comparison with CB and CS, it was important for choosing a volume of further resection. In 97,1% of cases, the data AFB and AFS is fully consistent with the results of histological studies (p = 0,02).
Conclusion: The combination of AFB and AFS is effective in determination of margins of central lung cancer spread and effectiveness of NCT.
Keywords: Endoscopy, Autofluorescence, spectroscopy, Lung cancer

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P4.276 THE COMBINATION OF SORAFENIB AND EVEROLIMUS IN PATIENTS WITH SOLID TUMORS – RESULTS OF A PHASE I STUDY

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Background: The combination of the multi-kinase inhibitor sorafenib (S) and the mTOR inhibitor everolimus (E) may increase anti-tumor efficacy by dual inhibition of key nodules of signaling pathways regulating angiogenesis and cellular proliferation. FDG-PET might be a suitable method for the assessment of pharmacodynamic activity of E.
Methods: Patients with advanced solid tumors after failure of standard therapy were treated with E in a dose escalating schedule of 1x 2.5-10mg daily in combination with a fixed dose of 2x 400mg S daily. The primary objective was to determine the maximum tolerated dose (MTD) of the combination. Dose limiting toxicity (DLT) was defined as any of the following toxicities occurring during the first 29 treatment days (DLT interval): hematological or non-hematological toxicity of CTC grade IV, any toxicity requiring hospitalization or any toxicity leading to delay of treatment for more than 2 weeks. In addition to pharmacokinetics, pharmacodynamic analyses using dynamic FDG-PET were performed on days 0, 5 and 14. Response after 8 weeks of treatment was assessed by CT.
Results: Seventeen patients have been enrolled. The DLT was not reached according to protocol definition. However, at a dose level of 1x 10mg E daily and 2x 400mg S daily the following toxicities occurred in the non DLT interval: pneumonia III°, treatment delay caused by leukopenia III° and thrombopenia III° and sudden cardiac death probably due to arrhythmia. Based on these observations, the dose level of 1x 7.5mg E daily and 2x 400mg S daily was defined as MTD. Currently 5 patients are treated on MTD without any DLT. Response after 8 weeks could be evaluated in 9 patients, showing progressive disease in one patient (pancreatic cancer) and stable disease in 8 patients (NSCLC, melanoma, CUP, ovarian, colorectal, vaginal and breast cancer). The median progression free survival and overall survival were 4 and 5.1 months, respectively.
Conclusion: Combination of S and E is feasible for the treatment of patients with advanced solid tumors. The full analysis including pharmacodynamics and pharmakokinetics will be presented. Extension phase in NSCLC patients is planned.
Keywords: everolimus, sorafenib, solid tumors, NSCLC

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P4.277 TREATMENT OUTCOMES OF STAGE III NON-SMALL CELL LUNG CARCINOMA (NSCLC) IN THE ELDERLY (AGE >70)

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Background: The standard of care for treatment of inoperable stage III non-small cell lung carcinoma (NSCLC) consists of radiation therapy with concurrent chemotherapy, however elderly patients are under-represented in clinical trials. In this study, the treatment patterns (radiation, chemotherapy)

for elderly patients with stage III NSCLC in our institution were reviewed and comparisons were made to a series of younger patients (age <70).
Methods: A retrospective review was conducted of patients treated with radiotherapy for stage III NSCLC between January 1998 and February 2010. Patient and treatment characteristics analyzed included age, performance status, weight loss, pre-treatment hemoglobin, radiation therapy intent (palliative vs. definitive), chemotherapy sequencing (concurrent vs. sequential), chemotherapy dosing (systemic vs. low-dose weekly), and platinum drug used (cisplatin vs. carboplatin). Fisher's exact test of significance and Kaplan-Meier survival analysis were utilized, as well as log-rank testing of variables to determine impact on survival.
Results: 189 stage III NSCLC patients were treated with ages ranging from 28 to 92 years. Patients age > 70 (n=86) were more likely to have performance status ≥2 (p=.035) and pre-treatment hemagloblin less than 12g/dL (trend, p=.067). Elderly patients were more likely to be treated with palliative intent (29% versus 13% respectively, p<.007) and to a lower total radiotherapy dose (median 60Gy versus 66Gy respectively, p<.01) than the younger cohort. Likewise, elderly patients were less likely to receive concurrent chemoradiotherapy (p<.0001), concurrent full-dose cisplatin (p=.04), or systemic doses of chemotherapy (52% vs. 70%, p<.03). Median survival was 10.3 months for elderly patients compared to 17.2 months for younger patients (p =.001). Additionally, elderly patients with good performance status had inferior outcomes when compared to the younger cohort (12.1 vs 19.8 months, p=.006). A similar effect was seen for patients treated with definitive concurrent chemo-radiotherapy: median survival for elderly patients was 12.2 months compared to 18.9 months for younger age (p=.01). Factors associated with improved outcome in elderly patients include definitive treatment (p=.04), the addition of chemotherapy to radiotherapy (p=.026), performance status of 0-1 (p<.0004), and pre-treatment hemoglobin >12 g/dL (p<.05).
Conclusion: Overall, elderly patients with stage III NSCLC experience inferior outcomes than younger patients with comparable disease, but are also more likely to receive suboptimal therapy. Further studies are needed to determine whether advanced age alone portends a worse prognosis, or if more aggressive treatment is appropriate.
Keywords: Elderly, chemoradiotherapy, locally advanced, Non-small Cell Lung Carcinoma

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P4.278 PREOPERATIVE TREATMENT WITH CHEMOTHERAPY (CHT) AND HIGH DOSE RADIOTHERAPY (RT) (>59GY) IN PATHOLOGICALLY PROVEN CLINICAL STAGE IIIA-N2 NON SMALL CELL LUNG CANCER (NSCLC). INITIAL RESULTS OF A CLINICAL PROTOCOL.

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Background: The role of preoperative ChT-RT in patients with stage IIIA-N2 NSCLC is not well established. The use of high dose RT is supposed to provide a better local control of the tumour. The objective of this preliminary study is to evaluate the results of multimodal treatment with high dose RT in patients with stage IIIA-N2 NSCLC.
Methods: Prospective study (April09-January11) of 13 patients (9 men, median age: 56 years; range: 44-72 years) with N2 NSCLC who underwent cisplatinum-based induction ChT-RT with high dose RT (average: 60.5 Gy; range: 46-70 Gy). One patient was given 46 Gy because of a grade III esophagitis (included in the intention to treat study). N2 disease was diagnosed by mediastinoscopy in 10 patients, and by endoscopic ultrasound-guided fine needle aspiration in 3 cases. Re-staging included: thoracic/abdominal computerized tomography (CT), positron emission tomography and brain CT. Patients in whom these studies didnt show tumour progression underwent surgical exploration of the mediastinum (SEM), and those with no evidence of mediastinal disease underwent thoracotomy for lung resection and systematic nodal dissection (SND). SND was considered the gold standard to validate the negative results of the SEM. The follow-up was completed in February11.
Results: Three patients out of 13 showed distance tumour progression after or during the induction

treatment. The rest underwent mediastinal restaging with a technique providing cyto-histologic evidence (10 SEM): 2 mediastinoscopies and 8 re-mediastinoscopies. A bleeding of the superior vena cava was treated by median sternotomy, but the patient died in the postoperative period. SEM was negative in 8 patients and all underwent thoracotomy. SND validated that all these SEM were true negative. There was pathologic complete response (PCR) in 5 cases. The postoperative morbidity rate was 25% (1 pneumonia and 1 empyema) with no post-thoracotomy deaths. 3 out of 8 patients with resected tumours presented with disease progression: 2 cases with single brain metastases that were resected (both with PCR post-thoracotomy), and another with hepatic and bone metastases.

N	Sex	Age	Cyto-histological confimation of N2	RT dose (Gy)	Re-staging (CT, PET)	Mediastinal re-staging	Thoracotomy	ypTNM
1	F	52	EUS (#7)	60	Hepatic and bone M1	-	-	-
2	M	55	EBUS (#4R)	66	No progression	Negative MS	RUL	ypT0N0M0
3	F	55	MS (#4R)	60	No progression	Negative reMS	RUL	ypT0N0M0
4	M	57	MS (#4R)	65	No progression	Negative reMS	RUL	ypT0N0M0
5	M	47	MS (#7)	60	No progression	Negative reMS	Left Pneum.	ypT0N0M0
6	M	56	MS (#4L)	60	Meningeal carcinomatosis *	-	-	-
7	M	57	EUS (#5)	60	No progression	Negative MS	LLL	ypT1aN0M0
8	M	72	MS (#4R)	60	No progression	Positive reMS (#4R)	-	-
9	M	45	MS (#5)	70	No progression	Negative reMS	Left Pneum.	ypT1aN0M0
10	M	44	MS (#4L)	60	Bilateral pulmonary M1	-	-	-
11	F	61	MS (#4R)	60	No progression	Negative reMS	Superior Bi-lobectomy	ypT0N0M0
12	M	63	MS (#4R and 7)	46	No progression	Negative reMS	RLL	ypT1aN0M0
13	F	69	MS (#4R)	60	No progression	reMS (post-operative death)	-	-

* lumbar puncture diagnosis
Abbreviations: N: number of patients; **RT**: radiotherapy; **CT**: computerized tomography; **PET**: positron emission tomography; **ypTNM**: post-induction phatologic TNM; **EUS**: trans-esophageal ultrasound guided puncture; **EBUS**: trans-bronchial ultrasound guided puncture; **MS**: mediastinoscopy; **reMS**: remediastinoscopy; **#7**: subcarinal station; **#4R**: right inferior paratracheal station; **#4L**: left inferior paratracheal station; **#5**: subaortic station; **RUL**: right upper lobectomy; **LLL**: left lower lobectomy; **RLL**: right lower lobectomy; **Pneum**.: Pneumonectomy; **M1**: metastases.

Conclusion: Induction treatment with ChT and high dose RT is feasible with a high rate of PCR and acceptable postoperative morbidity. Therefore, we can consider that ChT associated to high dose RT is a valid option in the preoperative treatment of locally advanced NSCLC.

Keywords: Radiotherapy, INDUCTION TREATMENT, Surgery

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.279 LONG-TERM RESULTS OF A PHASE II STUDY OF COMBINED MODALITY THERAPY WITH CONCURRENT RADIATION THERAPY PLUS DOCETAXEL AND CARBOPLATIN FOR UNRESECTABLE STAGE III NON-SMALL-CELL-LUNG CANCER

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Background: Concurrent chemoradiotherapy is emerging as standard treatment for patients with inoperable stage III non-small-cell lung cancer (NSCLC).
However, the optimal combination of chemotherapy and radiation therapy (RT) in patients with locally advanced NSCLC remains unknown. Docetaxel and carboplatin have demonstrated activity as radiation sensitisers in pre-clinical studies. Both drugs are active against NSCLC and can safely be combined with RT at effective systemic doses, making them attractive study agents against locally advanced NSCLC.
The objective of this phase II study was to document the activity and to evaluate the toxicity of concurrent docetaxel and carboplatin with thoracic RT in locally advanced stage III NSCLC.
Methods: Eligible patients had stage IIIA or IIIB NSCLC, baseline performance status of 0 to 1, forced expiratory volume in 1 second ≥1 L, and less than 5% weight loss. Carboplatin was administered at an AUC of 4 on days 1 and 29 of radiation therapy. Patients received docetaxel, 30 mg/m^2 intravenously (IV) on days 1, 8, 22, and 29, concurrently with three dimensional conformal thoracic RT to 60 Gy in 30 fractions (2 Gy per fraction, 5 fractions per week). The primary end point was to determine the overall response rate. The secondary endpoint was to evaluate survival and the safety profile.
Results: Patient characteristics (n = 48) were as follows: 48% female, 52% male; median age 67 years (range 40-84 years); 56% stage IIIA; and 44% stage IIIB. The overall response rate was 80.9%. The median survival time for all patients was 24 months (range 4-102 months), and the 1-year overall survival rate was 70.8%, while 5-year survival was 27.1%. Toxicity was moderate: grade 2 neutropenia was seen

in 4 patients, and grade 3 neutropenia in 1 patient. Grade 2 thrombocytopenia was seen in 2 patients, and grade 3 thrombocytopenia was not observed. Nonhaematological toxicities were moderate: grade 3 oesophagitis occurred in 2 patients. Grade 1 asthenia/fatigue was observed in 6 patients, and grade 2 asthenia/fatigue in 4 patients. Grade 3 pulmonary toxicity occurred in 1 patient.

Conclusion: In this single institution study, we have identified a well-tolerated and active chemoradiotherapy regimen in the treatment of patients with unresectable Stage III NSCLC. Concurrent docetaxel and carboplatin along with thoracic radiation therapy is feasible and tolerable. Survival results are promising and warrant further study in large randomised studies to document and confirm the effectiveness of this regimen.

Keywords: Non-small cell lung cancer, Stage III, concurrent chemoradiotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.280 A PROSPECTIVE PHASE I/II STUDY OF RECOMBINANT ENDOSTATIN (ENDOSTAR) COMBINED WITH CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH UNRESECTABLE STAGE III NON-SMALL CELL LUNG CANCER: A PRELIMINARY REPORT

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Background: More than 3000 patients with advanced non-small cell lung cancer (NSCLC) have been treated with recombinant endostatin (endostar) combined with chemotherapy in China. Recently our experimental study showed a synergistic effect between endostar and irradiation in xenografts of Lewis lung in mice. The critical mechanism of which is tumor vasculature normalization occurred in a certain duration. We designed this study to evaluate safety and efficacy of endostar combined with standard current chemoradiation therapy (CCRT) in patients with unresectable stage III NSCLC.

Methods: Patients were administered with endostatin 7.5mg/m^2 (week0, 2, 4, 6), docetaxel 65mg/m^2 (Day 1, 29) and cisplatin 65mg/m^2 (Day1, 29). Radiotherapy consists of 2.0 Gy in 30-33 fractions over 6-7 weeks to a total dose of 60-66 Gy. Tumor response was evaluated with thoracic CT scans performed 4 weeks after completion of treatment in accordance with RECIST criteria. Acute toxicities was evaluated with NCI-CTC AE version 3.0

Results: From March 2009 to December 2010, 37 patients completed treatment and were available for evaluation. Thirty-three patients remain alive. The median follow-up time was 9.5 months (1-22 months). Six (16.2%) patients achieved complete response (CR), 21 (56.8%) partial response (PR), 6 (16.2%) stable disease (SD), and 4 (10.8%) progressive disease (PD). Endostar did not increase toxicity to CCRT. Hematological and non-hematological toxicities were acceptable. No patient developed cardiovascular toxicity. Table 1. Acute Hematological toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Leucopenia	15(40.5%)	5(13.5%)	5(13.5%)	11(29.7%)
Neutropenia	4(10.8%)	3(8.1%)	4(10.8%)	10(27.0%)
Lymphocytopenia	2(5.4%)	3(8.1%)	19(51.4%)	12(32.4%)
Anemia	18(48.6%)	5(13.5%)	1(2.7%)	0
Thrombocytopenia	3(8.1%)	4(10.8%)	2(5.4%)	0

Table 2. Acute Non-hematological toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Esophagitis	2(5.4%)	31(83.8%)	4(10.8%)	0
Dermatitis	34(91.9%)	1(2.7%)	2(5.4%)	0
Alopecia	30(81.1%)	7(18.9%)	0	0
Pneumonitis	5(13.5%)	4(10.8%)	6(16.2%)	0
Anorexia	19(51.4%)	16(43.2%)	2(5.4%)	0
Nausea	18(48.6%)	6(16.2%)	0	0
Vomiting	7(18.9%)	3(8.1%)	2(5.4%)	0
Peripheral neuritis	2(5.4%)	0	0	0
Allergy	0	1(2.7%)	0	0
Fatigue	11(29.7%)	6(16.2%)	0	0
Cough	16(43.2%)	5(13.5%)	7(18.9%)	0
cardiovascular	0	0	0	0

Conclusion: The preliminary results showed that endostar combined with CCRT for unresectable stage III NSCLC was safe and the short term outcomes

were promising. Further investigation is warranted.
Keywords: Non-small cell lung cancer, recombinant endostatin, multi-modality treatment

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.281 PERSISTENT N2 DISEASE AFTER NEOADJUVANT CHEMOTHERAPY-NOW WHAT?

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Background: The optimal treatment for stage IIIA (N2) non-small cell lung cancer (NSCLC) is controversial. Neoadjuvant chemotherapy (ChT) followed by surgery is a common approach. Approximately 20-50% of patients achieve a mediastinal pathological complete response (pCR) with ChT alone. Several studies have shown that patients who clear their mediastinal lymph nodes have improved outcomes compared with patients with persistent N2 disease. How to manage those patients with persistent N2 disease after ChT is unclear. Whether surgery provides any benefit or whether definitive radiation therapy (RT) with further ChT should be pursued remains an unanswered question. We explored this further by evaluating our own experience at Duke University Medical Center.
Methods: All patients who initiated preoperative therapy for IIIA (N2) NSCLC between 1995 and 2008 were evaluated. Patients were excluded if they received preoperative RT, had evidence of distant progression after neoadjuvant ChT by imaging or intraoperative assessment, did not have pathologic documentation of mediastinal lymph node status, or achieved a mediastinal pCR with neoadjuvant ChT. Disease-free and overall survival was calculated using the Kaplan-Meier product-limit method and compared using a log-rank test. Clinical outcomes were measured from the date of diagnosis and disease-free survival was defined as interval between the date of diagnosis to the date of disease recurrence or death.
Results: 27 patients were identified who met the criteria. Median follow-up was 24 months (range, 8-151). Several neoadjuvant ChT regimens were utilized, most commonly carboplatin with paclitaxel (44%) or vinorelbine (30%). The median number of involved mediastinal lymph node stations at diagnosis was 1 (range, 1-3). An R0 resection was performed after neoadjuvant ChT in 20 (74%), consisting of lobectomy in 13, pneumonectomy in 2, and wedge/segmentectomy in 5. There were no postoperative deaths. Postoperative therapy (RT and/or further ChT) was administered to 11 (55%). The remaining 7 patients received definitive RT, with or without further ChT. Median survival for all patients was 22 months. Overall and disease-free survival at 1, 3 and 5 years was 78%, 38%, 38% and 63%, 37%, and 30%, respectively. Survival was similar between patients undergoing R0 resection (38%) and definitive RT +/- ChT (36%) (p=0.42).
Conclusion: Disease-free and overall survival was sufficiently high to warrant aggressive local therapy (surgery or RT) in patients with persistent N2 disease after neoadjuvant ChT.
Keywords: Induction Chemotherapy, Surgery, N2, combined-modality therapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.282 A PHASE II TRIAL OF NIMOTUZUMAB IN COMBINATION WITH CHEMORADIOTHERAPY IN LOCALLY ADVANCED LUNG SQUAMOUS CELL CARCINOMA

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Background: Concurrent chemoradiotherapy was the standard treatment for locally advanced

NSCLC. The aim of this study was to evaluate efficacy and toxicity of nimotuzumab in combination with concurrent chemoradiotherapy followed by consolidation chemotherapy for locally advanced lung squamous cell carcinoma.
Methods: During March 2009 and December 2010, 11 locally advanced (stage IIIB) lung squamous cell carcinoma patients were included in this prospective Phase II trial, included 9 male patients and 2 female patients, the median age was 54 (range 41-64). All patients received thoracic radiotherapy (6MV X-ray, IMRT) to involved-field with the median dose of 60Gy/30f (range 50Gy/25f-66Gy/33f), and concurrent with nimotuzumab (200mg, weekly) for the median of 6 weeks (range 6-8 weeks) plus docetaxel (60mg/m^2)/carboplatin (AUC=5) on day 1 administered intravenously every 21 days for 2 cycles, patients with stable disease or better after concurrent chemoradiotherapy received consolidation chemotherapy of docetaxel (75mg/m^2)/carboplatin (AUC=5) on day 1 administered intravenously every 21 days for 2 cycles.
Results: After a median follow-up of 11 months (range 2.5-23 months), confirmed responses included 2 CR, 6 PR, 1 SD and 2 PD, the best objective response rate (CR plus PR rate) was 72.7% (8/11). Median progression-free survival was 12 months (95%CI: 0.85-23.15 months), median survival was not reached (overall survival range 2.5-23 months), and six-month survival was 81.8%. At the end of follow-up, there were 6 patients had disease progression, included 3 patients of locoregional failure and 3 patients of distant metastases (1 with brain metastases, 1 with retroperitoneal lymph nodes metastases, 1 with brain and bone metastases), 2 disease progressions occurred during concurrent chemoradiation (both with distant metastases and died sooner after) and other 4 disease progressions occurred after consolidation chemotherapy. Grade 1 to 3 radiation pneumonitis were observed in 7 (63.6%); 2 (18.2%), 2 (18.2%) patients; grade 1 to 3 radiation esophagitis were observed in 2 (18.2%) , 7 (63.6%) and 2 (18.2%) patients; grade 1 to 2 radiation dermatitis were observed in 9 (81.8%) and 2 (18.2%) patients; grade 2 to 4 neutropenia were observed in 3 (27.2%), 4 (36.4%) and 4 (36.4%) patients; grade 1 to 3 thrombocytopenia were observed in 3 (27.2%), 1 (9.1%) and 2 (18.2%) patients, no skin rash or allergic toxicities appeared.
Conclusion: Although plus nimotuzumab to concurrent chemoradiotherapy followed by consolidation chemotherapy seemed not to take additional benefits or toxicities as compared to previous data with chemoradiotherapy alone, further follow-up and including more patients are necessary.
Keywords: nimotuzumab, chemoradiotherapy, Lung cancer

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P4.283 SIMULTANEOUS CHEMORADIOTHERAPY VERSUS SEQUENTIAL IN INOPERABLE NON-SMALL CELL LUNG CANCER.

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Background: Chemoradiotherapy with cisplatin-based chemotherapy is standard treatment for inoperable stage III non-small cell lung cancer (NSCLC). There has been conflicting evidence concerning the best sequence of radiotherapy (RT) and chemotherapy (CT) for locally advanced NSCLC. The aim of our study is to define the best sequence of radiotherapy and chemotherapy for inoperable stage IIB-IIIB NSCLC.
Methods: A nonrandomised retrospective trial in locally advanced non-small cell lung cancer, compared simultaneous and sequential regimens of chemoradiotherapy. 96 consecutive patients with histologically/cytologically proven NSCLC stage IIB-IIIB were enrolled. All patients were inoperable because of local spread, medical contraindications or refused surgery. Patients resieved radical course of radiotherapy by a CHART method with non-uniform crushing of a day dose (two daily fractions 1+1.5 Gy, the interval between fractions 5-6 hours) to a total dose 60 -70 Gy and 4 courses of chemotherapy (cisplatin+ethoposide). 35 patients received concurrent chemoradiotherapy (group A), 61 patients received sequential treatment (group B).
Results: The overall three-year survival rate in the group A - 37.5%, in the group B - 19%. Complete tumor response was observed in 45% in group A and 19% in the group B. Local recurrence developed in 32% patients with a sequential chemoradiotherapy and 25% in the simultaneous group. The incidence of

hematology and gastrointestinal toxicity was twice as high in simultaneous chemoradiotherapy group.
Conclusion: Simultaneous regimens of chemoradiotherapy are more effective then sequential regimens in locally advanced non-small cell lung cancer with low levels of toxicity. A higher potential of chemoradiation therapy might be reached by increasing the dose.
Keywords: Non-small cell lung cancer, chemoradiotherapy, sequential, simultaneous

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.284 FIRST REPORT: A PARALLEL PHASE I STUDY OF LBH589 IN COMBINATION WITH EXTERNAL BEAM RADIOTHERAPY OR CHEMORADIATION FOR LOCALLY ADVANCED NON SMALL CELL LUNG CANCER

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Background: The standard treatment for stage III Non small cell lung cancer is combined chemoradiation. However, not all patients are eligible. Limiting factors include large tumor size or radiation field constraints. LBH589 (panobinostat) is an oral histone deacetylase inhibitor (HDACi) drug that acts to hyperacetylate histones thus decondensing chromatin and activating expression of previously repressed genes such as pro-apoptotic genes. Major mechanisms of HDACi action include induction of apoptosis, promotion of cell differentiation and anti-angiogenesis. HDACi are potent radiosensitizers with potentially synergistic interactions with radiation. HDACi selectively kill tumour cells at concentrations that are 10-fold lower than those toxic to normal cells, which suggests that a favorable therapeutic window could be achieved. The HDACi drug, vorinostat, is approved for use in cutaneous lymphomas.
Methods: This is a parallel design, open label, phase I trial allocating patients to one of two treatment groups via dose-escalation cohorts of three subjects: Group I: Radiotherapy (40 Gy/20 fractions) plus study drug Group II: Chemoradiotherapy (60 Gy/30 fractions with cisplatin [50 mg/m^2 IVI d1 and 8, d29 and 36] and etoposide [50 mg/m^2 IVI d1-5, d29-33]) plus study drug The 3 dose cohorts of LBH589 are 20mg, 30 mg and 45 mg given as orally twice a week for duration of radiation starting the day before first radiation dose. Response assessment is at week 4 with CT and PET/CT scan. The primary objective of the study is to find DLT and MTD of LBH589 in combination with radiotherapy or chemoradiotherapy and the secondary objectives are response rate, progression free survival, and time to progression.
Results: Six patients have been treated so far. All 6 patients completed per protocol treatment. The treatment has been tolerated well so far. Transient thrombocytopenia was the commonest side effect (50%) (Table). Grade III or IV side effects included thrombocytopenia (33%) and syncope (16%). Other side effects were mainly Gr I or II and included nausea, vomiting, fatigue, chest pain, constipation, diarrhea, anemia and taste alteration. No dose limiting toxicity has been found so far. Best response was partial response (50%), together with stable disease (17%) and progressive disease (33%). The third cohort of radiation and LBH589 and first cohort of chemoradiation and LBH589 are currently open.

	LBH 589 dose (mg)	Radiation dose (Gy)	Gr III, IV toxicity	Nadir platelet count	Time to recovery	Best response
1	20	40	thrombocytopenia	46- D22	<7 days	PR
2	20	40	-	94- D25	-	PR
3	20	40	-	157- D25	-	SD
4	30	40	-	101- D18	-	PD
5	30	40	thrombocytopenia	60- D18	4 days	PR
6	30	40	thrombocytopenia	48-D11 19- D32	4 days	PD

Conclusion: The combination of radiation and LBH589 exhibited a tolerable toxicity profile with mechanism-related and transient thrombocytopenia as the dominant treatment-related side effect.
Keywords: chemoradiation, HDAC inhibitor

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P4.285 NEO-ADJUVANT CHEMOTHERAPY AND RADIATION THERAPY IN PATIENTS WITH STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER (NSCLC). A RETROSPECTIVE ANALYSIS WITH LESSONS LEARNED.

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Background: At the present time, there is no consensus for definitive treatment for patients presenting with stage IIIA (N2+) non-small cell lung cancer (NSCLC). We report twenty-six consecutive patients with stage IIIA NSCLC seen at our Interdisciplinary Clinic for Thoracic Malignancies treated with concomitant neo-adjuvant chemotherapy and radiation therapy followed by definitive surgery. This represents a community based, single-institution, retrospective analysis.

Methods: Twenty-six patients with stage IIIA (N2+) NSCLC received neo-adjuvant therapy included radiation; (4500 cGy) with concomitant weekly chemotherapy (paclitaxel + carboplatin), followed by definitive lung resection.

Results: Of the twenty-six patients selected for therapy, twenty-three patients completed surgical resection. Seventeen patients underwent lobectomy; six, pneumonectomy. The mean age of this group was 57.6 years (19 - 79 years). Two patients progressed after neo-adjuvant therapy and did not have surgery. One patient had unexpected pleural disease at surgery, resection was aborted. One patient who underwent surgery was lost to follow-up and is excluded from the analysis. For the twenty-two patients completing resection, median progression free survival (PFS), was 14.5 months and median overall survival (OS) was 19.5 months (analysis as of December 1, 2010). Review of pathology of the surgical resection identified eleven patients with fewer than 10% cancer cells admixed with fibrosis ("fibrosis" group). Eleven patients were characterized as having measurable viable tumor ("viable" group). Median PFS was 42 months in the "fibrosis" group vs. 9 months in the "viable" group (p=0.068). Median OS was 44 months in the "fibrosis" group vs. 19 months in the "viable" group (p=0.051). Of the patients who underwent resection, ten (45%) are still alive, seven with no evidence of disease (NED). Five of 11 (45%) patients with "fibrosis" remain NED vs. 2 of 11 (18%) "viable" patients. Ten patients (45%) relapsed distally (three with CNS as site of first relapse) and three (14%) relapsed locally. Two (9%) patients who died of unrelated causes were NED at the time of death. Seventeen patients (77%) had sterilization of mediastinal lymph nodes; five patients (23%) had residual nodal disease. Four of the five patients with lymph node involvement after neo-adjuvant therapy were in the "viable" group. There was minimal post-operative morbidity and the length of stay following surgery was under four days. When patients with adenocarcinoma were compared to patients with squamous cell carcinoma, there was no difference in either PFS or OS.

Conclusion: Neoadjuvant chemotherapy with concomitant radiation followed by surgery can safely be performed in selected patients. The presence of residual active tumor bodes poorly and these patients may not benefit from definitive resection. In moving forward we will utilize PET-CT to assess tumor response as well as pathologically stage the mediastinum before and after induction therapy with either endoscopic bronchoscopic ultrasound (EBUS) or mediastinoscopy. We anticipate that sterilization of mediastinal lymph nodes and a decrease in SUV on PET-CT will predict the pathologic response of the primary tumor and better select those patients who should complete surgical resection.

Keyword: Neo-adjuvant chemoradiation therapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.286 TREATMENT PATTERNS FOR LUNG CANCER IN SOUTH WESTERN SYDNEY, AUSTRALIA: DO PATIENTS GET TREATED ACCORDING TO GUIDELINES?

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Background: Australian patterns of care studies in lung cancer have previously shown that the management of patients is suboptimal, with significant under-utilization of radiotherapy and chemotherapy and a high proportion of patients receiving no anti-cancer therapy at all. However, most of these studies predated the publication of the Australian National Health & Medical Research Council (NHMRC) Guidelines for the management of Lung Cancer in 2004. The impact of these guidelines on lung cancer treatment in Australia has not been evaluated. We aim to evaluate the proportion of lung cancer patients in South Western Sydney (SWS) who were treated according to guidelines and to identify factors associated with receipt of such treatment in a contemporary population-based cohort.
Methods: Data on patients with newly diagnosed lung cancer from 2006 to 2008, who resided within SWS Local Government Area (LGA) postcodes at diagnosis, were gathered from the SWS Area Clinical Cancer Registry (CCR). Data investigated included tumour information, stage, initial treatment and performance status at diagnosis (ECOG). Patients with unknown stage and/or unknown ECOG performance status were excluded so that analysis was limited to patients for whom guideline therapy could be evaluated. Associations were tested using Chi Square and t-tests. Odds ratios were calculated using logistic regression.
Results: 815 new cases of Lung cancer were identified. 60% were male and the median age at diagnosis was 70 years. 86% of tumours were Non Small Cell Lung Cancer (NSCLC) and 14% were Small Cell Lung Cancer (SCLC). 10% of cases had no stage documented. Pre-therapy ECOG was documented in 64% of cases. Overall, 31% of patients received no initial anti-cancer therapy. The utilisation of guideline therapy by stage was 61% for Stage I&II NSCLC, 39% for Stage III NSCLC, 56% for Stage IV NSCLC, 22% for limited stage SCLC and 66% for extensive stage SCLC. Variables associated with the receipt of guideline therapy included age, stage, and ECOG status at diagnosis.
Conclusion: Adherence to national recommended guidelines has only been seen in approximately half of the population studied. Further investigation into the reasons for receipt of non-guideline therapy is required.

Keywords: guideline therapy, recommended treatment, cancer registry, australia

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Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.287 RADICAL PLATINUM-BASED SEQUENTIAL OR CONCURRENT CHEMORADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER. DIFFERENCES IN TOLERANCE, OPERABILITY, PATHOLOGIC RESPONSES AND SURVIVAL IN THE EXPERIENCE OF THE UNIVERSITY HOSPITAL ARNAU DE VILANOVA OF LLEIDA (SPAIN).

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Background: Chemoradiotherapy is the standard treatment for locally advanced N3 non-small cell lung cancer (NSCLC).
Methods: We retrospectively compared evolution of 23 patients diagnosed of stage II (T>5cm)-IIIB NSCLC and treated with neoadjuvant platinum-based chemotherapy (CT-RT N= 19) with or without concomitant radiotherapy to 50 Gy maximum (CTRT N= 33) that, after a second evaluation, were assumed N3 or non-resectable and received sequential radical radiotherapy (N= 7) or complete radiation dose to 60Gy (N= 16).
Results: Radiologic responses were 28.6% vs. 50.1% for stabilization, 57.1% vs. 25% for minor radiologic response, and 14.3% vs. 25.1 for bigger than 75% radiologic responses in the CT-RT and CTRT group, respectively (p= 0.5). There was no grade 3-4 toxicity neither in the CT-RT or the CTRT group. Medium relapse free survival (RFS) was 15.47 months in the CT-RT group and 11.3 months in the CTRT group (p= 0.4), and 6-month RFS were 71.4% and 82.4% respectively (p= 0.46). Overall survival was 25.76 months in the CT-RT group and 19.65 months in the CTRT. 1-year overall survival 71.4% and 58.8% (p= 0.47).

Conclusion: Neoadjuvant concurrent CTRT is a feasible and tolerable treatment for non-operable NSCLC. It seems to improve response rate and RFS over sequential CT-RT, with a similar toxicity.
Keywords: chemoradiotherapy, locally advanced, Non small cell lung cancer

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.288 NEOADJUVANT PLATINUM-BASED CHEMOTHERAPY WITH OR WITHOUT CONCURRENT RADIOTHERAPY. DIFFERENCES IN TOLERANCE, OPERABILITY, PATHOLOGIC RESPONSES AND SURVIVAL IN THE EXPERIENCE OF THE UNIVERSITY HOSPITAL ARNAU DE VILANOVA OF LLEIDA (SPAIN).

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Background: Neoadjuvant chemotherapy is a consolidated approach for locally advanced non-N3 non-small cell lung cancer (NSCLC), but it is not clear if to add concurrent radiotherapy to chemotherapy improves clinical benefits.
Methods: We retrospectively analyzed 53 cases of stage II (T>5cm)-IIIB NSCLC treated with neoadjuvant platinum-based chemotherapy (CT N= 19) with or without concurrent radiotherapy to 50 Gy maximum (CTRT N= 33), and their courses after a potential surgical resection.
Results: There were no significant differences in radiologic responses between neoadjuvant CT or CTRT group (Minor responses 84.2 vs. 69.7%; and bigger than a 75% radiologic responses 10.6 vs. 24.2%, p= 0.293). Twenty nine patients underwent surgery. There was no significant differences in operability between CT or CTRT group (63.2 vs. 50%, p= 0.2), but it was bias by a higher initial presence of stage IIIB in the CTRT group (21.1 vs. 50%). Pathologic responses were frankly better in the CTRT group (complete response 8.3% vs. 29.4%; minimal residual disease 0% vs. 23.5%; partial response 16% vs. 17.7%, p= 0.016). The presence of pathologic complete response o minimal residual disease trends to impact on relapse free survival (p= 0.1) and overall survival (p= 0.2). Anyway, no relapse was reported in the first 6 months after surgery. On depend of toxicity, grade 3-4 events were more common in the CTRT group (11.8% vs. 0%), but none pulmonary or esophageal adverse event was observed.
Conclusion: Neoadjuvant CTRT is feasible and tolerable. It obtains a similar survival benefit that neoadjuvant CT, but it is capable to increase the rate of major pathological responses. A longer follow-up is warranted to observe if increment of pathological response impact in survival.
Keywords: neoadjuvant chemorradiation, Non small cell lung cancer, locally advanced

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.289 NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY WITH PLATINUM AND VINORELBINE. RESULTS IN THE PROTOCOL OF THE ARNAU DE VILANOVA UNIVERSITY HOSPITAL OF LLEIDA (SPAIN).

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Background: Chemoradiotherapy (CTRT) is the standard treatment for N3 non-small cell lung cancer (NSCLC), and a promising approach for neoadjuvant therapy in non-N3 locally advanced NSCLC.
Methods: We retrospectively analyzed 27 male patients with stage II (T>5cm)-IIIB NSCLC and consecutively treated with 4 cycles of neoadjuvant Cisplatin (N= 21) or Carboplatin AUC 5 (N= 3) plus Vinorelbine with concurrent radiotherapy to 50 Gy during the third and fourth cycle since May, 2008 to May, 2010. Three patients received CBDCA AUC5 with concurrent radiotherapy only, due to comorbidity. After a second evaluation, operable cases underwent surgery and non-operable cases continued radiotherapy to 60 Gy.
Results: Mean age of the patients was 68.3 years

old, and initial ECOG was 0-1 (92.6%) or 2 (7.4%). There was a 3.7% of stage IIA tumors, a 44.4% of IIIA, and a 51.9% of IIIB in the initial evaluation. Clinical T4 tumor were a 37.1%, N2 a 51.9%, and N3 a 29.6%. Histological subtypes were: squamous carcinoma 77.8%, adenocarcinoma 11.1% and non-defined NSCLC 11.1%. Radiological responses appeared in a 92.6% of cases (stabilization 18.5%, partial response 70.3%, and bigger than 90% response 3.7%). Metabolic responses by PET-CT scan appeared in a 96.3% (stabilization 33.3%, partial response 51.9%, and bigger than 90% response 11.1%). An 81.22% of non-N3 NSCLC after CTRT underwent surgery (2 two atypical resections, 9 lobectomies, and 2 pneumectomies) with mediastinal lymph node dissection. Contraindications for surgery were initial N3 (50%), progression to CTRT (14.3%), bad respiratory function (7.1%), and persistence of T4-tumor (28.6%). Pathologic responses were: partial response 53.9%; minimal residual disease 23.1%; and complete pathological response 23.1%. Mean relapse free survival was 9.56 months, and 6-months RFS was 88.9%. 1-year OS was 65%. RFS was not related with metabolic (p= 0.49) nor pathological response (p= 0.41).

Conclusion: Neoadjuvant CTRT with platinum and vinorelbine is a feasible treatment for locally advanced NSCLC. Maybe a longer sample size and follow-up could allow appreciating differences in survival according tumor response.

Keywords: neoadjuvant chemoradiation, locally advanced, Non small cell lung cancer

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.290 INDUCTION CHEMORADIOTHERAPY IS NOT SUPERIOR TO INDUCTION CHEMOTHERAPY ALONE IN PATIENTS WITH STAGE IIIA(N2) NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The optimal treatment strategy for patients with stage IIIA(N2) non-small cell lung cancer (NSCLC) is uncertain. We performed a systematic review and meta-analysis to test the hypothesis that the addition of radiotherapy to induction chemotherapy prior to surgical resection does not improve survival compared to induction chemotherapy alone.

Methods: A systematic review and meta-analysis were performed by searching English articles in PubMed and the Cochrane Database over the years 1990-2010. Additional studies were identified by searching bibliographies of published review articles on lung cancer. All studies of stage IIIA(N2) NSCLC that reported outcomes on both patients treated with induction chemotherapy alone and patients treated with induction chemoradiotherapy were included in the overall systematic review. In addition, randomized controlled studies comparing induction chemotherapy and induction chemoradiotherapy that reported survival data were considered for use in the meta-analysis. The number of patients in each treatment group, survival data, and hazard ratios were extracted from each study.

Results: The initial database search yielded review 3276 potential studies, 205 of which were screened based on the inclusion and exclusion criteria. Six studies eligible for analysis were found, including 1 randomized control trial, 1 phase II study, 2 retrospective reviews, and 2 published abstracts of randomized controlled trials (Table). None of the studies demonstrated a survival benefit to adding radiation therapy to induction chemotherapy versus chemotherapy alone. There was inadequate survival data available to perform a meta-analysis specifically on stage IIIA(N2) patients. A meta-analysis was performed on randomized controlled trials (N=336 patients) with available survival data on stage III patients, which showed no benefit of the addition of radiation to induction chemotherapy (odds ratio 0.88, 95% confidence interval 0.56-1.36, P=0.55).

			Chemotherapy		Chemotherapy & Radiation		P
First Author	Study Design	Study Years	n	Survival	n	Survival	
Thomas[a]	Randomized Control Trial	1995-2003	154	33 (median)	142	32.4 (median)	0.54
Sauvaget	Randomized Control Trial (Abstract)	1991-2000	N/A	19 (median)	N/A	18.5 (median)	NS
Fleck[a]	Randomized Control Trial (Abstract)	N/A	15	17% (3yr)	25	23% (3yr)	NS
Girard	Phase II Trial	2003-2007	14	24 (median)	17[b]	13 (median)	0.29
Higgins	Retrospective Review	1995-2006	31	39% (3yr)	70	41% (3yr)	0.65
Pezzetta	Retrospective Review	1994-2003	36	40%[c] (5yr)	46	40%[c] (5yr)	NS

[a] includes all stage III patients [b] arm B. Arm C not chosen given lack of survival data [c] overall survival of both groups, which was not significantly different between groups

Conclusion: The use of radiation therapy in induction regimens for stage IIIA(N2) NSCLC is not supported by published evidence. Given the potential disadvantages of adding RT preoperatively, clinicians should consider using this treatment strategy only in the context of a clinical trial to allow better assessment of its effectiveness.

Keywords: neoadjuvant, Radiotherapy, stage IIIA(N2), Chemotherapy

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.291 VINORELBINE (VNR) IN CONCURRENT RADIATION THERAPY (TRT) IN NON SMALL CELL LUNG CANCER (NSCLC) STAGE III

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Background: A retrospective analysis was performed to evaluate Therapeutic Index of VNR with concurrent TRT in pts with stage III unresectable NSCLC in objective response or in stable disease after induction therapy with Platinum compounds and Gemcitabine.

Methods: Multimodality treatment consisted of induction therapy with Platinum (80 mg/m2/i.v.) or Carboplatinum (AUC 5) plus Gemcitabine (1200 mg/m2/i.v.)(GP) weekly day 1-8 every 21 days. In complete remission (CR), partial remission (PR) and stable disease (SD), patients, after induction therapy, were treated with Docetaxel (DCT) (25 mg/m2/i.v.) weekly and VNR os (12 mg/m2) or i.v. (5 mg/m2) three-times weekly 2 hours before concurrent TRT (2 Gy/day for 6 wks).

Results: From November 2002 to February 2011, 36 chemotherapy and radiotherapy-naive pts were treated: males/females 21/15; median age 58 years (range 18 to 77); median ECOG PS 0 (range 0-1); no weight loss: 10% in all pts; stage IIIA 8 pts (22%), stage IIIB 28 pts (78%). 21 Pts (85 cycles of chemotherapy) showed 6 WHO grade III toxic events (7%), mainly hematological (neuthropenia and thrombocytopenia) and 1 WHO grade IV (1.1%) hematological (neuthropenia). No toxic deaths have occurred. In 31 pts evaluable after induction therapy we observed: 11 partial responses (30,5%) and 20 stable diseases (55,5%); 5 pts (14%) were not evaluable for response (restaging not done). Toxicity observed was: 1 patient with dysphagia WHO grade III and 1 WHO grade IV, no toxic deaths have occurred. After concurrent radio-chemotherapy in 34 pts (because in 2 pts treatment not yet completed) clinical responses were: 14 partial response (41%), 15 stable disease (44%) and 5 progressive disease (15%). In all patients median survival was 14,9 months (range +1,3 to +81,1), median time to progression 10,3 months (range 2,9 to 51,6). By stratifying patients in stage IIIA and IIIB at diagnosis we observed that in stage IIIA median survival was 17,2 months (range 12 to +79,3 months) and median time to progression was 12.8 months (range 2,9 to 27,7 months). In stage IIIB median survival was 14,4 months (range +1,3 to +81,1 months) and time to progression 9,7 months (range 3.7 to 51,6 months). After the multimodality treatment of 34 pts evaluable 6 patients (17.6%) were submitted to thoracic surgery: at the diagnosis 4 patients were stage IIIA and 2 patients stage IIIB. Actuarial survival curve showed that at 1 year the probability was 74% and at 2 years 25% (stage IIIA 1 year 86% and at 2 year 37%: stage IIIB at 1 year 71% and at 2 year 25%). At this writing 6 pts (16,6%) were alive.

Conclusion: Preliminary results of this multimodality treatment are promising as concern activity, local control of disease, median and overall survival. Toxicity profile of this schedule was mild and reversible with a good patients compliance. A larger accrual will be required to verify these data.

Keyword: Vinorelbine

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.292 PHASE II TRIAL EVALUATING GEMCITABINE-IFOSFAMIDE-CISPLATIN AS INDUCTION TREATMENT FOR MEDIASTINOSCOPY PROVEN STAGE IIIA-N2 NON-SMALL CELL LUNG CANCER.

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Background: Induction chemotherapy is an option for the treatment of resectable locally advanced non-small cell lung cancer (LA-NSCLC). We evaluated the efficacy and safety of gemcitabine – ifosfamide – cisplatin (GIP) as an induction chemotherapy regimen.
Methods: Between October 2003 and October 2007, we prospectively treated 16 histologically proven LA-NSCLC (clinical stage T1-3 N2 M0) patients with three cycles GIP induction chemotherapy followed by attempted surgical resection. Each cycle consisted of gemcitabine 1000 mg/m^2 on days 1 and 8, ifosfamide 3 g/m^2 on day 8, and cisplatin 80 mg/m^2 on day 1. A CT scan was performed at baseline and after 3 cycles. The primary endpoint was objective response rate. Toxicity, mediastinal nodal downstaging, pattern of disease relapse and 3-year overall survival were secondary endpoints.
Results: Baseline characteristics of patients included were: median age 60 years (range 35-75); M/F ratio 11:5; histology adeno (n=7), squamous (n=7), large cell (n=1), mixed adenosquamous (n=1); single level N2 (n=11) and multilevel N2 (n=5) at mediastinoscopy; median lymph node size 15mm (range 9-34). Only 44% of patients received the planned full dose induction chemotherapy. Full dose cisplatin was administered in 88% of patients. Among the grade 3-4 toxicities, haematological toxicity was the most frequent (81% of patients) followed by gastrointestinal toxicity (nausea/vomiting) in 13% of patients. Ten patients (63%) obtained a partial remission after induction therapy (RECIST 1.0), five patients (32%) had stable disease and one patient had progressive disease. Surgical resection was performed in 12 patients. Mediastinal nodal downstaging occurred in 5 of 12 patients (42%), persistent N2 occurred in 5 of 12 (42%), while mediastinal disease progressed in 2 of 12. R0 resection rate was 92%. All patients without nodal downstaging received adjuvant postoperative radiotherapy. Locoregional radiotherapy only was performed in 4 patients: radical radiotherapy in 3 patients based on a multidisciplinary board meeting decision (one patient became medically inoperable after induction and two patients yielded a stable disease on CT considered as clinical trend to progression) and palliative radiotherapy in one patient with objective disease progression after induction. During 3 year follow-up, disease relapse occurred in 88%: one patient had an intrathoracic relapse only, while all other patients had distant relapses of whom a central nervous relapse occurred in 46% (67% with squamous histology). The ITT median survival was 19 months, with a 2- and 3-year overall survival rate of 50% and 31%, respectively.
Conclusion: While triplet GIP induction chemotherapy resulted in a high ORR of 63%, the mediastinal downstaging rate and median survival was moderate compared to specific cisplatin doublets, probably explained by the high grade 3-4 hematological toxicity rate responsible for impaired dose intensity in 56% of patients. Remarkably, we observed a high rate of central nervous relapse mainly in squamous cell histology.
Keywords: combined modality treatment, Non-small cell lung cancer, Induction Chemotherapy

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P4.293 LONG-TERM SURVIVAL OF NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH T4N0-N1 DISEASE TREATED WITH SEQUENTIAL OR CONCURRENT CHEMO-RADIATION.

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Background: The optimal treatment strategy for Stage IIIb NSCLC patients with a T4N0-1 tumor is a matter of debate. In prospective combined modality series including surgery, the median overall survival (OS) is approximately 24 months. As in most non-surgical series, multiple-level N2 or N3 disease are included, the outcome after chemo-radiation is unclear. We hypothetised that results comparable to regimens including surgery can be achieved with concurrent chemo-radiation in this patient group.

Methods: In our prospectively collected database of NSCLC patients, all patients with T4(mediastinal invasion) N0-1 NSCLC receiving concurrent or sequential chemoradiation (WHO-PS 0-2; FEV_1/DLCO >30%) were included. One patient had a recurrence after previous pneumonectomy. Patients were irradiated using an individualized accelerated prescribed total tumor dose (TTD) based on normal tissue dose constraints (maximal doses: mean lung dose (MLD): 19 Gy, spinal cord: 54 Gy, brachial plexus: 66 Gy) (van Baardwijk et al. J Clin Oncol 2010). In the sequentially irradiated patients a maximal dose of 79.2 Gy was prescribed, in the concurrently irradiated patients the maximal dose was 69 Gy. All patients were given 3 cycles of chemotherapy, radiotherapy (RT) was started at the 2nd course of chemotherapy (cisplatin-vinorelbine or -etoposide) or after chemotherapy. RT planning and staging was PET-CT based. OS was calculated from date of diagnosis (Kaplan-Meier method). Toxicity was scored according to CTCAEv3.0.
Results: 42 patients (8 female, 34 male) with a median age of 62.5 ± 9 years (44-80 years) were included from October 11th 2005 until December 30th 2009. Stage distribution: 86% T4N0 (n=36), 14% T4N1 (n=6). 16 patients received sequential chemoradiation, 26 patients received concurrent chemoradiation. The median dose delivered to tumor and nodes was 65.0 ± 10 Gy (21.6 -79.2 Gy) given in an overall treatment time of 30 (28-32) days. The median prescribed MLD was 15 ± 4.4 Gy (5.03 -19.9 Gy). Acute toxicity: 1 patient experienced grade 3 dyspnea during RT. Grade 3 dysphagia occurred in 5 patients (12%) during RT requiring tube feeding in 3 of these patients (7%). Dysphagia persisted later than 1 month after RT in 1 patient (2%). Grade 3 dysphagia only occurred in patients treated concurrently. Grade 3 cough occurred in 1 patient during RT, no patient experienced >= grade 3 cough 1 month after RT. 2 patients died within 3 months after start of RT, one due to myocardial infarction, one of unknown causes. Severe late toxicity was not present: no grade ≥3 complications more than 3 months after the end of radiotherapy. With a median FU of 42 months, the median OS for the whole group is 34 months (95% CI 24-43 months), 2-year survival is 55 %. The median OS for the sequential group is 27 months (95% CI 13-40 months), while the median OS for the concurrent group is not yet reached.
Conclusion: Concurrent accelerated chemoradiation using an individualized dose prescription is a valid treatment strategy for stage IIIb, T4N0-1 NSCLC patients yielding very promising OS results with low toxicity.
Keywords: NSCLC, Radiotherapy, Chemotherapy, T4

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P4.294 SURGERY IN PATIENTS WITH ADVANCED NSCLC FOLLOWING INDUCTION POLYCHEMOTHERAPY.

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Background: About 80% of primarily diagnosed patients with NSCLC were found to have non-operated stages and they are administered therapeutic or radiotherapy. Polychemotherapy administration before the operation in patients with NSCLC is to improve postoperative results.
Methods: From January 2003 to January 2009, 31 patients referred for neo-adjuvant (induction) therapy. Of those 14 patients were found to have non-resected tumore - Ð¢4 (five had bifurcation invasion, 3 SVS invasion, 4 apical tumors, in 2 cases tumor affected lobar bronchus and surrounding tissues, but pneumonectomy was contraindicated), in other 17 patients we noticed multiple invasion of mediastinal lymph nodes N2-3. Patients were diagnosed with videomediastinoscopy, VATS, transthoracic biopsy was taken in all cases before surgery. Functional status of patients corresponded to ECOG 0-2.
Results: After induction therapy we performed restaging and then we chose surgical or therapeutic treatment. Six patients (42%) with T 4 demonstrated response to the therapy – they were included to the surgical group. They underwent 2 pneumonectomies with resection of bifurcation and SVS plasty, in three cases we carried out pneumonectomy, in 1 – upper lobe resection with bronchoplasty. Of 17 patients with N2-3, surgery of various volume was indicated in five patients (29%). Postoperative complication rate was 9%, there were no cases of mortality. Survival rates in groups of operated and nonoperated patients were 7 months and 23 months, respectively.
Conclusion: Induction therapy was able to widen combined treatment modalities for NSCLC and

we carried out resections in cases which had been diagnosed as inoperable and performed restaging. Thus, overall rates of mortality and morbidity were decreased

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.295 A PILOT STUDY OF NEDAPLATIN PLUS DOCETAXEL AS ADJUVANT CHEMOTHERAPY IN PATIENTS WITH RESECTED NON-SMALL-CELL LUNG CANCER

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Background: Recent clinical trials have shown that adjuvant cisplatin-based chemotherapy improved survival for patients with completely resected stage II-IIIA non-small-cell lung cancer (NSCLC). In terms of toxicities, hematological or nonhematological toxicities are frequently observed in cisplatin-based chemotherapy. Adjuvant chemotherapy should be conducted safely, with potent activity. Thus, more suitable regimen with these criteria needs to be developed as adjuvant chemotherapy. Nedaplatin is a cisplatin derivative developed in Japan. It has similar activity to cisplatin in NSCLC when combined with vindesine, and causes less nausea/vomiting and nephrotoxicity compared with cisplatin. The purpose of this pilot study was to evaluate the safety of combination chemotherapy with nedaplatin plus docetaxel as adjuvant chemotherapy in patients with resected NSCLC.
Methods: In this pilot study, patients with resected NSCLC were received nedaplatin (64 mg/m^2) and docetaxel (48 mg/m^2) on day 1, every 4 weeks, 4 cycles. The primary end point was the feasibility. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (version 4.0).
Results: Between April 2009 and December 2011, 9 patients received combination chemotherapy of nedaplatin plus docetaxel. The demographics of patients were; mean age 60.6 years (range, 51-70 years), gender male/female 8/1 cases, stage I/II/III/IV 0/2/6/1, and histologic type adenocarcinoma/squamous cell carcinoma 4/5. Seven patients (78%) received four cycles of chemotherapy, and 2 patients (22%) did not complete four cycles. No treatment-related death was observed and the hematologic toxicities included grades 3-4 leukopenia (22%), neutropenia (44%), anemia (11%), and thrombocytopenia (0%). Nonhematologic toxicities included grade 3-4 nausea/vomiting, anorexia, and fever did not be observed.
Conclusion: Adjuvant chemotherapy of nedaplatin plus docetaxel was shown to be well tolerable in patient with resected NSCLC. On the basis of these results, phase II study of the combination of nedaplatin plus docetaxel as an adjuvant chemotherapy is required
Keywords: Nedaplatin, Docetaxel, Adjuvant chemotherapy, Non-Small-Cell Lung Cancer

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P4.296 PROGNOSTIC FACTORS IN THE RADICAL NON-SURGICAL TREATMENT OF STAGE IIIB NON-SMALL CELL LUNG CANCER

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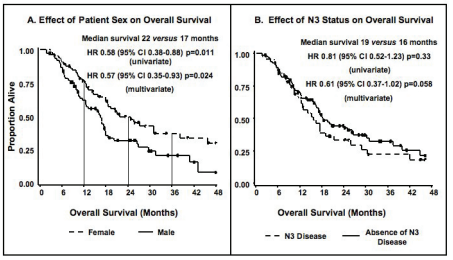
Background: Many patients diagnosed with Stage IIIb (AJCC 6th Edition; T4 and/or N3, no pleural effusion) non-small cell lung cancer (NSCLC) are treated with curative intent, despite a very low cure rate. Guidelines are required to help select patients for radical therapy, thus sparing many patients toxicities of aggressive treatment. We performed a retrospective analysis to investigate factors influencing outcomes in these patients.
Methods: From 2002-2009, all cases of stage IIIb NSCLC from our institution were identified. Patients treated with radical radiotherapy (minimum dose 50Gy), with or without chemotherapy, were included. With ethics approval, charts were

reviewed for patient demographics, baseline bloodwork, tumour factors, treatment factors and hospitalizations. The primary outcome was overall survival (OS), measured from time of diagnosis.
Results: Of 230 patients identified; we report results of the first 140 eligible cases reviewed. Baseline demographics are shown in the table. The median follow-up for all patients was 16 months. Median survival was 18 months, and OS was 69%, 40% and 28% at 1, 2 and 3 years respectively. Numerically longer median survival was seen in women (22 versus 17 months), good performance status patients (19 versus 13), patients without N3 disease (19 versus 16), patients who received ≥60Gy radiation (18 versus 11) and patients who received chemotherapy (18 versus 13). In multivariate analysis the most favourable characteristics were female sex (HR 0.57, 95% CI 0.35 – 0.93 , p=0.02), <5% weight loss (HR 0.65, 95% CI 0.40 – 1.05, p=0.08) and absence of N3 disease (HR 0.61, 95% CI 0.37-1.02, p=0.06). (See Figure).

Baseline Demographics		Percent (%)
Gender	Male	54
	Female	46
Performance Status (ECOG)	0,1	83
	2	11
	3,4	6
Weight Loss	≤5%	62
	>5%	38
Smoking Status	Current Smoker	60
	Ex-smoker	38
	Never Smoker	2
LDH	Normal	77
	Elevated	23
Calculated GFR (μmol/L)	< 60	27
	≥ 60	73
Hemoglobin (g/L)	< 100	16
	≥ 100	84
Stage IIIb Staging Subgroups	T4 disease (N0,1,2)	67
	N3 disease (T0,1,2,3)	26
	T4 and N3 disease	7
Treatment	Concurrent chemoradiation	70
	Sequential chemoradiation	11
	Radical radiotherapy without chemotherapy	19
Radiation Dosing (Gy)	< 60	14
	≥ 60	86



Conclusion: As in advanced NSCLC, overall survival was significantly longer in women than men. Additionally, patients with <5% weight loss and those without N3 disease, trended towards significantly longer survival. Good patient selection remains important in the radical treatment of stage IIIb NSCLC.
Keywords: Stage IIIb, NSCLC

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.297 A NOVEL APPROACH FOR FOLLOW UP OF RADICALLY TREATED LUNG CANCER PATIENTS -THE FEASBABILITY OF A PROSPECTIVE STUDY OF TELEPHONIC CONTACT AND SUBSEQUENT PHYSICAL FOLLOW UP

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Background: Patients of lung cancer, after their primary treatment are subsequently called for follow up visits to assess the disease status. Patients often have to travel long distances to report to the hospital and have to take care of other logistics as well. The present study deals with assessment of the utility of a telephonic conversation with the patient to assess the disease status before the patient's scheduled physical visit to the hospital.
Methods: 200 patients of lung cancer treated with a radical aim are being taken in this prospective study. A set of questions are asked to the patient in his /her vernacular during the telephonic interview. Based on this questionnaire an impression of clinical control/ recurrence/progression/uncertain is made. After the telephonic interview, the patients report to the cancer care specialist at the Tata Memorial Hospital for the due follow up visit.. This telephonic impression is corroborated with the physician impression when the patient physically reports to the hospital. The primary end point of the study is the concurrence between the telephonic interview and the subsequent physician final impression. Calculation of sensitivity, specificity, PPV and NPV shall be done using Hospital visit final impression as gold standard. Using Kappa statistics, the score of more than 80% shall be considered as good agreement.
Results: Till now 31 patients have been taken into this study. 18 patients have been called before their first follow up visits. The average time needed for each call was 3.51(SD 1.29) minutes. 14 patients

were reachable on the first attempt while 4 patients needed more than one attempt to be contacted. 15 patients deemed to be disease free in telephonic follow up were actually disease free during physical follow up. Only one patient was deemed to have local recurrence during telephonic follow up. Two patients were reported dead by the relatives during telephonic contact. This patient did not have a recurrence on physical examination. The average money spent by each patient for travel to hospital for the follow up visit was Rs 7148 (USD 142.9) and the average money spent on stay during the follow up visit was Rs 3971 (USD 79.4).
Conclusion: Telephonic follow up contact with lung cancer patients is a viable strategy and has the potential to save money, time and hospital resources as well. These preliminary findings need to be confirmed by mature results emerging from our study.
Keywords: Physcical follow up, Telephonic follw up, combined modality, Lung cancer

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P4.298 FINAL REPORT OF A PHASE I STUDY OF CONCURRENT THORACIC RADIOTHERAPY AND GEFITINIB IN PRE-TREATED PATIENTS WITH IIIB/ IV NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Preclinical data suggest that gefitinib (an epidermal growth factor receptor tyrosine kinase inhibitor) in combination with radiation resulted in additive to synergistic anti-proliferative effect against NSCLC. This study was designed to evaluate the safety and activity of radiotherapy (RT) with concurrent daily Gefitinib 250mg in Chinese patients with IIIB/IV of NSCLC after failure of platinum-based chemotherapy.
Methods: Patients with stage IIIB or stage IV, failure of platinum-based chemotherapy regimen NSCLC were eligible. Four Cohorts of eight patients each were planned to be treated with escalating doses from 54 to 60 Gy of conformal or intensity-modulated radiotherapy (2Gy/Fx) in combination with gefitinib 250mg daily during RT and 60 days after the completion of RT to determine the MTD (maximum tolerated dose). Toxicities are evaluated according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0).
Results: To Feb 2011, 4 cohorts, a total of 40 were enrolled with medium age of 55 yr (32-79): 28 male and 12 female;20 smokers and 20 nonsmokers;18 stage IIIB and 22 stage IV; 35 adenocarcinomas (86%), 4 squamous carcinomas and 1 poor differentiated carcinoma; Prior-chemotherapy regimen was consisted of NP, GP and TP for a median of 3 cycles (95% CI:, 1-6). With a median follow-up of 13.7 months (95% CI:2.7-28.1 months), 35 patients progressed, 5 patients remained progression-free to date. Median progression-free survival time was 6.2 months (95% CI: 3.4-8.9 months). Median overall survival time was 14.2 months (95% CI: 11.7-16.7 months).1-year survival rate was 60%.One patient developed acute ILD in both lungs one week after the completion of radiation therapy,and died of respiratory failure 30 days after. Except of this patient, other adverse events were generally mild to moderate. 29 (73%) experienced grade 1 to 2 pulmonary infiltrates/ pneumonitis (grade 1 33%,grade 2 40%).Otherwise, the most common grade 1 - 2 toxicities were rash (60%), and esophagitis (40%).
Conclusion: Thoracic radiotherapy up to 60 Gy concurrent with gefitinib 250 mg daily was feasible and clinically active in this group of pre-treated patients with NSCLC. Close monitoring for pulmonary toxicity remains necessary, as serious complication of ILD was observed in one patient (2.5%). Otherwise, adverse events were well tolerated. (NCT00497250)
Keywords: Radiotherapy, gefitinib, Non-small cell lung cancer

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P4.299 IMPACT OF NEOADJUVANT THERAPY ON TUMOR RESECTABILITY AND SURVIVAL OF PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Surgery is the treatment of choice in patients with early stage non small cell lung cancer (NSCLC). It is also used in some cases of locally advanced tumors, but with a low cure rate. Therefore, preoperative treatment is seeking to improve survival in these patients. The aim of this study was to evaluate tumor resectability and survival in patients with locally advanced stage (IIIA and IIIB) NSCLC treated with chemotherapy (CT) or chemotherapy and radiotherapy (CT-RT) neoadjuvant.
Methods: This was a cross-sectional observational study that evaluated patients with locally advanced NSCLC in a university hospital during 2000 and 2006, that received induction therapy. The collected variables were anthropometric values, lung function, histology, stage of the tumor, neoadjuvant treatment and therapeutic response. Kaplan-Meier curve was used to evaluate survival. T-Test was used when variables accomplished normal criteria and analysis of variance to compare values among groups. Differences were considered significant when p values were < 0.05.
Results: A total of 32 patients were included; 9 subjects (28.1%) were diagnosed with stage IIIA and 23 (71.9%) stage IIIB, being the IIIB the most common indication for induction therapy. All patients were treated with CT, showing a treatment response in 80% of cases and only 7 were also required radiotherapy. Surgical resection was indicated in 31 patients and only in 6 subjects exploratory thoracotomy was performed for mediastinal invasion, seeing a downstaging in 46.9% of all the cases Over-all 5 year survival was 27.8% with a median of 52.9 months (95% CI 38.1-67.6). This survival is dependent on the response to neoadjuvant treatment (responders: 55.7 months on average and non-responders: 30.5 months on average, p<0.05).
Conclusion: Neoadjuvant treatment reduces tumor size resulting in a downstaging and improving the resectability of locally advanced NSCLC. The neoadjuvant therapy could be a viable therapeutic option to improve survival of these patients.
Keywords: Lung cancer, neoadyuvant

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.300 A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING SURVIVAL AFTER INDUCTION TREATMENT IN PATIENTS WITH N2 DISEASE RANDOMISED TO EITHER SURGERY OR RADIOTHERAPY.

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Background: Chemotherapy and radiotherapy is often considered to be the "standard of care" in the management of patients with N2 disease. The aim of this study is to ascertain the treatment effect on overall survival using meta-analysis.
Methods: A literature search was conduction from 1966-2009 for all studies of patients with N2 disease who received either induction chemotherapy or induction chemo-radiotherapy and randomised to surgery or radiotherapy. Fixed and random effects meta-analysis were performed.
Results: In all, 5 randomised trials were identified (Johnstone, Shepherd, Van Meerbeck, Stephens and Albain et al), consisting of 674 patients. The study groups were broadly comparable for age and gender. In three trials, patients received induction chemotherapy and in one trial, patients received induction chemo-radiotherapy. There

was no evidence of heterogeneity with I2 as 0% (P=0.770). The overall hazard ratio comparing patients randomised to post-induction surgery versus was 0.942 (95% CI 0.813 to 1.090) in favour of surgery, although this was not statistically significant (P=0.421).
Conclusion: In the randomised studies of N2 disease, after induction treatment, radiotherapy was not found to be superior to surgery. Published evidence does not support the premise that chemotherapy and radiotherapy should be considered the standard of care, surgery is an acceptable alternative.
Keywords: Non-small cell lung cancer, meta-analysis, survival, treatment

A revised/updated abstract may be included in the Late Breaking Abstract Supplement, available at the 14th World Conference on Lung Cancer.

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P4.301 A PHASE II TRIAL OF PEMETREXED IN COMBINATION WITH WHOLE BRAIN RADIATION THERAPY (WBRT)

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Background: The treatment of patients with non-small cell lung cancer (NSCLC) with brain metastases (BM) is a frequent clinical problem. Patients frequently require WBRT for treatment of the brain metastases initially. While patients are receiving WBRT, patients may experience extra-cranial disease progression and/or decline in performance status, and consequently not be candidates for systemic therapy. Earlier initiation of systemic therapy and improvements in local control of BM could extend survival.
Methods: We performed a single arm, two-stage phase II trial of pemetrexed in combination with WBRT. Eligibility criteria included: histologically or cytologically proven NSCLC, computed tomography or magnetic resonance imaging evidence of BM, Karnofsky Performance Status (KPS) of ≥70, adequate end organ function, and ability to provide informed consent. Patients received premedication with folic acid, vitamin B12, and dexamethasone and pemetrexed 500 mg/m2 IV every 21 days starting within 5 days of the WBRT. Patients received WBRT with 2.5 Gy, 5 days a week, for 3 weeks to a total dose of 3750 cGy. The initial 5 patients were enrolled and treated sequentially to monitor for toxicity. After the trial initiated the trial was amended, and eligibility was restricted to treatment naïve patients with a KPS of 70 or age ≥70 years. The primary-endpoint was response to intra-cranial lesions according to RECIST. The null hypothesis was the response rate would 30% and a response rate of >50% would be determined as clinically meaningful. If ≤4 of 15 patients responded the trial would be stopped for lack of efficacy, and if ≥10 of 15 patients responded then the trial would be stopped and the response rate would be considered >50%. If 5-9 patients responded the trial would proceed to the second-stage and enrollment would continue to 30. The trial was stopped for poor accrual.
Results: Between May 2005 and April 2008 10 patients were enrolled and treated on trial. The median age was 62.5 (range 46 to 82), the majority of patients were white (white (n=8), Native America (n=1), and African American (n=1)) and most patients had a good performance status (KPS of 90-100 (n=3), KPS of 70-80 (n=6), and the KPS unknown (n=1)). The median number of cycles was 3 (range 1 to 6). Of the 10 patients, 6 patients were evaluable for intra-cranial response; 2 patients experienced progressive disease, 1 patient experienced a partial response and 3 patients experienced stable disease. Four patients were unevaluable due to extra-cranial disease progression or decline in performance status prevent re-evaluation. The median progression-free survival was 3.4 months (95% CI, 1.4 to 6.0), and the median overall survival was 6.0 months (95% CI, 1.7 to 8.3). The toxicities observed were grade 1 or 2. Grade 2 toxicities observed were dry skin (n=1), fatigue (n=1), anemia (n=2), pulmonary infection with grade 1 or 2 neutropenia (n=1), and nausea (n=2).
Conclusion: Treatment with patients with NSCLC with brain metastases remains a challenge. The combination of pemetrexed and WBRT appears to have been well tolerated in this limited trial, but both extra-cranial and intra-cranial disease control remain problematic.
Keywords: Pemetrexed, brain metastases, chemoradiotherapy, whole brain radiation therapy

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P4.302 PHASE II STUDY OF ERLOTINIB WITH CONCURRENT WHOLE-BRAIN RADIATION THERAPY FOR PATIENTS WITH BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER

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Background: Brain metastasis is a leading cause of death from non-small cell lung cancer (NSCLC). Because some patients with NSCLC have mutations in the epidermal growth factor receptor (EGFR) and because EGFR inhibition plus irradiation has clinical benefit in head and neck cancer, we developed a phase II clinical trial to test whole-brain radiation therapy (WBRT) with the anti-EGFR agent erlotinib for patients with NSCLC and brain metastases.
Methods: This study opened in February 2006 and enrolled 40 patients with brain metastases from NSCLC. Patients were given erlotinib 150 mg PO/day ï,´ 1 wk, then erlotinib concurrently with WBRT, followed by erlotinib only until disease progression. Dose reduction was allowed but all patients had to remain on erlotinib until completion of radiation to be evaluable. EGFR mutation status was assessed in primary tumor samples from 18 patients by DNA sequencing at MD Anderson's core facility.
Results: All 40 enrolled patients (median age 59 y; 19 male, 21 female; median 20 pack-y smoking) completed erlotinib+WBRT. Six patients had grade 3 dermatologic toxicity requiring dose reduction; 2 patients had grade 3 diarrhea; and 2 patients had grade 3 neurotoxicity (one at 12 and the other at 18 months). At a median follow-up of 21 months, the median survival time (10.9 months) compared favorably to historical outcomes and to the most recent phase III trial of WBRT (RTOG 0118; median survival time 3.9 months). Nine of the 18 patients for whom EGFR mutation status was known (50%) had mutations; most (77%) of the patients with mutations were female (odds ratio 0.036, P=0.012). Survival was related to dermatitis severity (3.7 mo grade 0, 10 months grade 1, and 17 months grade > 2).
Conclusion: Early findings from this study suggest that erlotinib+WBRT may prolong survival among patients with NSCLC and brain metastases. Our unexpected finding of a high rate of EGFR mutations in primary tumors in this group suggests that patients with NSCLC and mutated EGFR may be at higher risk of brain metastases. Longer term follow-up is needed to assess local control, survival, and neurotoxicity.

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P4.303 ALSO ELDERLY PATIENTS (75 YEARS OR OLDER) WITH STAGE III NON-SMALL CELL LUNG CANCER (NSCLC) HAVE SURVIVAL GAINS WITH RADICAL TREATMENT: A PROSPECTIVE POPULATION-BASED STUDY

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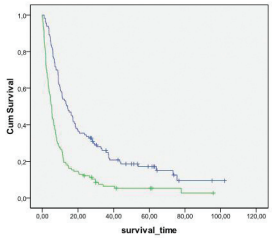
Background: Randomised studies with palliative systemic treatment have shown a survival benefit in favour of active therapy in elderly patients, this is still unclear in stage III NSCLC. We hypothesised that active treatment should lead to improved overall survival (OS) rates in the elderly.
Methods: All patients with a pathological diagnosis of NSCLC in South- and Middle Limburg (Maastricht Cancer Registry, MCR), The Netherlands, and with stage III (UICC 6th Edition) from 2002 to 2008 were included. MCR covers >

98 % of all lung cancer cases. Patients were staged with a whole body FDG-PET scan and a CT or MRI of the brain and treated according to standard regional protocols: Period 1: 2002-2005 3 cycles of cisplatin or carboplatin-gemcitabine followed by chest radiotherapy (60 Gy/ 30 fractions/ 6 weeks); Period 2: 2006-2007 the same 3 cycles of induction chemotherapy, but followed by individualised accelerated radiotherapy (INDAR) (mean dose 64.8 Gy/ 36 fractions/ 3.6 weeks = biological equivalent 82 Gy/ 41 fractions/ 8.2 weeks); Period 3: 2008 concurrent cisplatin-vinorelbine and INDAR (mean dose 65 Gy/ 40 fractions/ 5.5 weeks = biological equivalent 74 Gy/ 36 fractions in 7.4 weeks). The minimal follow-up of all patients is 2 years.
Results: 1002 patients with stage III were diagnosed, of which 545 were less than 70 years, 220 between 70 and 74 years and 237 75 years or older. 51.4 % were treated with curative intent; in the >= 75 years 47.7 % were treated with curative intent. In the >= 75 years group, no significant difference in Charlson co-morbidity, age or gender was found between patients referred for curative or palliative treatment. In all age groups, treatment with curative intent increased OS: < 70 years: median OS 19.1 vs. 8.0 months, 2-year OS 42.7 % vs. 19.6 %; 70-74 years: median OS 16 vs. 5.7 months (5.3-4.6), 2-year OS 32.9 % vs. 13.7 %; >= 75 years: median OS 14.2 months vs. 5.2 months, 2-year OS 35.5 % vs. 12.1 % (all differences p<0.001) (Fig. OS of => 75 years). Patients younger than 75 years had a better OS with more intense treatment (p<0.001), **but not the >= 75 years (p>0.40).**



Conclusion: In this prospective series a clear increase in survival occurred in all age groups with curative intent treatment. Patients of 75 years or older do not seem to benefit from more intensive treatment.
Keywords: Elderly, combined modality treatment, Non-small cell lung cancer

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P4.304 LONG TERM FOLLOW-UP OF CONSOLIDATION CHEMOTHERAPY AFTER CHEMORADIOTHERAPY FOR STAGE III NSCLC

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Background: The place of adjuvant chemotherapy for resected early stage NSCLC has been established in several randomised trials. However there is no proven role for adjuvant consolidation chemotherapy (CC) after radical combined modality chemoradiotherapy (CRT) despite the high risk of relapse over five years. This likely reflects the inadequacy of currently available cytotoxic agents and the variable natural history of NSCLC . Following encouraging phase II data using consolidation taxane therapy, our institution explored this approach. This practice was abandoned after publication of Hoosier Oncology Group's negative phase III trial. We present initial characteristics and outcome of patients treated with CC. Comparison is made with patients treated during the same time period who were not considered by their treating oncologist as candidates for consolidation docetaxel therapy.
Methods: All patients treated between January 2005 and June 2007 had data available. Thirty-eight consecutive patients were treated for stage III NSCLC during this time. All patients received CRT with weekly carboplatin (AUC2) and docetaxel (25mg/m2) and concurrent radiotherapy (60Gy in 30 fractions). Fourteen patients of the thirty-eight then received CC with two cycles of carboplatin (AUC5) and docetaxel (75mg/m2) given three weekly.
Results: Despite no predetermined randomisation, the two patient groups (CRT vs CRT/CC) were found to be equivalent with regard to stage, histology, biochemical measurements of organ function and ECOG score. Overall, 1 and 2 year survival were improved in the CRT/CC arm. Grade 3 or 4 toxicities were not significantly more frequent in the CRT/ CC group (35.7% vs 29.1%) and the solitary fatal toxicity was seen with CRT

	CRT/CC (n=14)	CRT Alone (n=24)
Mean Age (yrs)	62	69
ECOG		
0	35.7%	33.3%
1	50.0%	62.5%
2	14.3%	4.2%
Pathology		
SCC	28.6%	29.2%
Adeno	35.7%	37.5%
Large Cell	28.6%	29.2%
Mixed	7.1%	4.2%
Stage		
IIIA	50.0%	50.0%
IIIB	50.0%	50.0%
Ever Smoker	92.9%	95.8%
Survival		
1 year survival	85.7%	54.2%
2 year survival	35.7%	25.0%
Median Overall Survival (mo.)	**16.60**	**9.43**

Conclusion: Patients selected for consolidation chemotherapy had significantly better overall survival, but did not show more favourable prognostic features. This data suggests a subset of patients benefited from more aggressive treatment or alternatively that clinicians intuitively selected a better prognostic group not defined by usual clinical characteristics. More sophisticated prognostic and predictive markers are required.

Keywords: Consolidation Chemotherapy, Stage III unresectable Non Small cell lung Cancer

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P4.305 INDUCTION CONCURRENT CHEMORADIOTHERAPY FOLLOWED BY SURGICAL RESECTION FOR STAGE III NON-SMALL CELL LUNG CANCER: A FEASIBILITY STUDY

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Background: S-1 consists of tegafur and uracil at a 1:4 molar ratio concentration (5-FUprodrug), and has been clinically used in Japan. Based on the favorable result in response rate and treatment safety of concurrent chemoradiotherapy using combination chemotherapy of S-1 and cisplatin (SP) for unresectable non-small cell lung cancer (NSCLC) confirmed by multicenter Phase II trial in Japan, we conducted a feasibility study for concurrent chemoradiotherapy using SP (SP-RTx) as an induction treatment followed by surgery for Stage III NSCLC.
Methods: A single institutional feasibility study. Patients with stage III NSCLC, ECOG PS 0–1, age 20 to 80 year-old and preserve adequate pulmonary and other organ function for pulmonary resection were eligible. S-1(40 mg/m^2/dose b.i.d) was taken orally twice a day on days 1-14 and cisplatin (60mg/m^2) was administered on day 1. The combination chemotherapy with SP was repeated twice with a 3 week-interval concurrently with thoracic radiation (2Gy/fraction, once a day, total 40Gy). At 2 to 4 weeks after the completion of the concurrent chemoradiotherapy, curative-intent pulmonary resection was planned.
Results: 30 patients between July 2005 and April 2009 were reviewed, and 28 patients were underwent surgical resection. Median follow-up time was 22.4 months. The mean age was 58 (range 47-77) year-old, 23 men and 7 women, 16 Stage IIIA and 14 IIIB. Histologically: 13 adenocarcinoma (Ad), 9 squamous cell carcionoma (Sq), and 8 others. Twenty-seven patients (90.0%) completed SP-RTx. Grade 3/4 toxicities during SP-RTx consisted mainly of leukopenia (10.0%/ 0%), neutropenia (3.3%/ 0.0%) and anemia (6.6%/ 0%). There was one febrile neutropenia (3.3%). Objective tumor response was obtained in 50.0 % (95% CI: 29-71%) after SP-RTx: 15 PR cases and 15 SD cases. Lobectomy was performed in 15 cases and pneumonectomy in 13 cases. Twelve cases experienced comorbidity: 3 arrhythmias, 3 excessive pleural effusion, 2 chylothorax, 2 postoperative bleedings, and each 1 pneumothorax, pulmonary edema, empyema and spinal cord injury. However, no bronchial fistula was observed. One patient died due to bleeding from empyema lesion on 136th postoperative day. During the follow-up period, 11 cases experienced recurrence. The first recurrence site was distant lesion in 10 cases and one in mediastinal lymph node. The 3-year disease free survival rate was 58.8 and 3-year over all survival rates was 64.6%, respectively.
Conclusion: SP-RTx as an induction treatment followed by surgery for Stage III NSCLC might be feasible. However, careful patient selection would be warranted, and phase III study would be necessary to confirm survival benefit of this strategy.

Keywords: S-1 and cysplatine, surgical resection, stage III NSCLC, Induction concurrent chemoradiotherapy

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P4.306 BIMODALITY AND TRIMODALITY THERAPY IN STAGE III NSCLC: ANALYSIS OF TOXICITY AND PATTERNS OF RECURRENCE.

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Background: Concurrent chemoradiotherapy (CT-RT) is the standard of care in fit patients with stage III NSCLC. A previous phase III study suggested that patients with small-volume disease who could undergo a lobectomy, may still benefit from surgery after induction CT-RT. Until 2008, selected patients at our center who had 'downstaged' mediastinal nodal disease after 46-50Gy CT-RT were operated upon. After 2008, delivery of 66Gy was routinely possible as intensity modulated radiotherapy (IMRT) became available. In order to assess the role of surgery after high-dose CT-RT, we retrospectively evaluated toxicity and outcomes in all stage III lung cancer patients who received CT-RT to a dose of either 46-50Gy or 60-66Gy.
Methods: Between 2004-2010, 204 NSCLC patients with stage III disease received involved-field concurrent platinum-based CT-RT at a single center. Pancoast tumors were excluded from analysis (n=26). Median follow-up of the entire group was 29.9 months. In total, 30 patients underwent surgery after concurrent CT-RT and all were operated by the same operating team. Patients were selected by the multidisciplinary team if they had partial response to preceding CT-RT, limited co-morbidity, and when a pneumonectomy could be avoided. A total of 46 patients were treated to 46-50Gy, of which 15 (32.6%) subsequently underwent surgery (CT-RT-S). In the group treated to 60Gy or higher, 15 (10.9%) out of 137 patients underwent CT-RT-S. Median follow-up was 50 months in the 46-50Gy group, and 21.7 months in the 60-66Gy group.
Results: The CT-RT-S group was significantly younger than CT-RT only patients (P=.001), and had less co-morbidity according to the Charlson Comorbidity Index (P=.009). No patients with cN3- disease underwent surgery. Grade III radiation pneumonitis was recorded in 2.4% of the 46-50Gy CT-RT compared to 9.5% in the 60-66Gy CT-RT (p=.31). Half of all operated patients (46.7%) had ≥1 major post-operative complication, but this did not differ between the two dose levels (p=.14). Two patients (6.7%) died within 90-days after surgery. Median disease free survival was 13.6 months and was not significantly different between groups (p=.052). In multivariate analysis, prognostic indicators for local control were better performance status (p=.006) and absence of cN3-nodes (p=.045). Locoregional control was similar between CT-RT-S and CT-RT (13% for CT-RT versus 25.4% for CT-RT-S; p=.42). Brain metastasis was the first manifestation of distant failure in 13.7% of the entire cohort. Median time to local and distant failure was 17.1 months and 8.3 months, respectively in total cohort (p=.27). A median overall survival of 25.8 months was attained in all patients and did not differ significantly between surgery versus non-surgery groups (p=.124).
Conclusion: Despite careful selection to identify favorable stage III NSCLC patients for surgery, no significant differences in disease free survival were observed in this retrospective, single-institution analysis, between patients who were operated (CT-RT-S) compared to only CT-RT.
Keywords: NSCLC, trimodality, advanged stage

Poster Session 4 – Combined Modality Thursday, 7 July 2011 10:00-12:30

P4.307 LONG-TERM SURVIVAL OF NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH SINGLE STATION N2 DISEASE TREATED WITH CONCURRENT CHEMO-RADIOTHERAPY.

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Background: The optimal treatment strategy for Stage III NSCLC patients with a single involved nodal site is heavily debated. In prospective surgical series median survival is approximately 24 months. As in most non-surgical series, multiple-level N2 or N3 disease are included, outcome after chemo-radiation in single-station N2 disease is unclear. We hypothetised results comparable to surgery can be achieved with concurrent accelerated individualized chemo-radiation.

Methods: In our prospectively collected database of NSCLC patients, all patients with stage III NSCLC receiving concurrent chemoradiation (WHO-PS 0-2; FEV_1/DLCO >30%) with N2 disease at 1 single location (Mountain Dressler) were included. A total tumor dose (TTD) between 51 and 69 Gy was prescribed in 1.5 Gy fractions twice daily up to 45 Gy, followed by once daily fractions of 2 Gy up to an individualized TTD based on normal tissue constraints (maximal doses: mean lung dose (MLD): 19 Gy, spinal cord: 54 Gy, brachial plexus: 66 Gy) (van Baardwijk et al. J Clin Oncol 2010). Radiotherapy (RT) was started at the 2nd course of chemotherapy (cisplatin-vinorelbine or cisplatin-etoposide). RT planning was 4D-PET-CT based. Nodal staging was PET-CT based, and confirmed by pathology whenever posible. Overall Survival (OS) and Progression Free Survival (PFS) were calculated from date of diagnosis (Kaplan-Meier method). Toxicity was scored according to CTCAEv3.0.

Results: 30 patients (12 female, 18 male) with a age of 65 years (44-77 years) were included from April 1st 2006 until December 31st 2009. Stage distribution: 10% T0N2 (n=3), 23% T1N2 (n=7), 30% T2N2 (n=9), 20% T3N2 (n=6), 17% T4N2 (n=5). 2 patients (T0N2) had recurrent disease post-lobectomy. Nodal stations involved: station 7 in 12 patients (40%), 4R in 7 patients (23%), region 5 in 8 patients (27%) and region 4L, 8 and 2R in 1 patient (3%) each. The median dose delivered to the PTV was 65.0 ± 4.9 Gy (52.5-69.0 Gy) given in an overall treatment time of 35 days. The median MLD was 15.2 ± 3.55 Gy (8.3-19.66 Gy). Acute toxicity: no patients experienced grade 3 dyspnea, 1 patient had grade 4 dyspnea during RT. 1 month after radiotherapy no grade 3 dyspnea was found. Grade 3 dysphagia occurred in 6 patients (20%) during RT, requiring tube feeding in 5 of these patients (17%), but subsiding to grade 1 at 1 month after RT in all patients. No patients died within 3 months after start of RT. Late toxicity was infrequent: 1 patient experienced a thoracic empyema and 1 patient had radiation pneumonitis 3 months after radiotherapy. At a median FU of 34 months, the median OS was 33 months (95% CI 25-40 months). Median PFS is 26 months (95% CI 16.5-35.5 months) with an estimated survival at 2 years of 57%.

Conclusion: Concurrent individualized accelerated chemoradiotherapy is a valid treatment strategy for stage III, N2 NSCLC patients with single station disease yielding very promising overall and progression free survival results with low toxicity, even in this patient group with 40 % station 7 involvement.

Keywords: NSCLC, Concurrent, Radiotherapy, Chemotherapy

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John, William (Employment; Eli Lilly and Company)
Johnson, Bruce (Consultant; Boehringer-Ingelheim (Uncompensated))
Johnson, Bruce (Consultant; Genentech (Uncompensated))
Johnson, Bruce (Consultant; KEW Group (Diagnostics) (Uncompensated))
Johnson, Bruce (Consultant; Millenium (Uncompensated))
Johnson, Bruce (Stock Ownership; Celgene)
Johnson, Bruce (Patent reviewed for EGFR testing; Genzyme)
Johnson, Bruce (Consultant; Astrazeneca (Uncompensated))
Johnson, Bruce (Consultant; Pfizer)
Johnston, Mary (Employment; GTx,Inc. (Director of Medical Affairs))
Jones, Kirk (Planner)
Jullien, Anne (Employment; Biosystems International)
Jung, Laura (Employment; Roche Molecular Systems)
Kadas, Janos (Employment; Biosystems International)
Kalemkerian, Gregory (Research Support; Lilly Oncology)
Kallen, Karl-Josef (Employment; CureVac)
Kanivets, Yana (Employment; Eli Lilly and Company)
Katz, Terry (Employment; Eli Lilly and IMClone)
Kazakin, J. (Employment; ArQuLe, Inc)
Keats, Jeffrey (Employment; ARIAd Pharmaceuticals)
Keith, Robert (Intellectual property-Patent for Prostacyclin to prevent lung ca; University of Colorado)
Kerns, B. (Employment; HTG Molecular, Inc.)
Kerr, Keith (Consultant; Merck Serono)
Kestin, Larry (Research Support; Elekta)
Khamar, Baukulesh (Employment; Cadila Pharmaceuticals, Ltd)
Khuri, Fadlo (Planner)
Kieffer, yann (Employment; Biosystems International)
Kim, Dong-Wan (Consultant; Pfizer)
Kim, Dong-Wan (Honorarium; Pfizer (Pfizer Oncology Symposium, APLCC))
Kim, Dong-Wan (Research Support; Pfizer (Outcome Research Service Agreement))
Kim, Joo-Hang (Honorarium; Roche)
Kim, Joo-Hang (Honorarium; GlaxoSmithKline)
Kim, Joo-Hang (Honorarium; Astra Zeneca (And consultancy))
Kim, Joo-Hang (Honorarium; Eli Lilly and Company)
Kindler, Hedy Lee (Consultant; AstraZeneca)
Kindler, Hedy Lee (Planner)
Kishi, Yoshiro (Employment; Ina Institute/Med& Bio Laboratories, Co. Ltd. (No role in collection/analysis of data; writing/approval of abstract.))
Kiura, Katsuyuki (Honorarium; SANOFI AVENTIS)
Klimovsky, Judith (Employment; Novartis)
Klomp, Houke (Planner)
Klughammer, Barbara (Employment; F. Hoffmann-La Roche)
Knuth, Alexander (Advisory Board; CureVac (Scientific Advisory Board))
Koch, Sven (Employment; CureVac GmbH)
Köhler, Jens (Honorarium; BI Pharma GmbH & Co. KG)
Koning, Caro (Planner)
Koustenis, Andrew (Employment; Eli Lilly and Company (Stock))
Kratz, Johannes (Consultant; Pinpoint Genomics)
Kremer, A (Employment; Eisai Inc)
Kris, Mark (Consultant; Boehringer Ingelheim)
Kris, Mark (Consultant; Pfizer)
Krivoshik, Andrew (Employment; Abbott)
Kulig, Kimary (Major Stockholder; Pfizer)
Kulig, Kimary (Employment; Pfizer)
Kumar, Ravindra (Employment; Acceleron Pharma)
Kurucz, Istvan (Employment; Biosystems International)
Kwak, Eunice (Research Support; Pfizer)
Laack, Eckart (Consultant; Eli Lilly and Company)
Lacouture, Mario (Consultant; Amgen)
Lacouture, Mario (Consultant; Bayer)
Lacouture, Mario (Consultant; BMS)
Lacouture, Mario (Consultant; Boehringer Ingelheim)
Lacouture, Mario (Consultant; Genentech)
Lacouture, Mario (Consultant; Genzyme)
Lacouture, Mario (Consultant; GSK)
Lacouture, Mario (Consultant; Hara)
Lacouture, Mario (Consultant; ImClone)
Lacouture, Mario (Consultant; Lilly)
Lacouture, Mario (Consultant; Onyx)
Lacouture, Mario (Consultant; Pfizer)
Lacouture, Mario (Consultant; Roche)
Lacouture, Mario (Consultant; Wyeth)
Lacouture, Mario (Honorarium; Amgen)
Lacouture, Mario (Honorarium; Bayer)
Lacouture, Mario (Honorarium; BMS)
Lacouture, Mario (Honorarium; Boehringer Ingelheim)
Lacouture, Mario (Honorarium; Genentech)
Lacouture, Mario (Honorarium; Genzyme)
Lacouture, Mario (Honorarium; GSK)
Lacouture, Mario (Honorarium; Hara)
Lacouture, Mario (Honorarium; ImClone)
Lacouture, Mario (Honorarium; Lilly)
Lacouture, Mario (Honorarium; Onyx)
Lacouture, Mario (Honorarium; Pfizer)
Lacouture, Mario (Honorarium; Roche)
Lacouture, Mario (Honorarium; Wyeth)
Lafrate, A (Consultant; Abbott Molecular)
Lafrate, A (Consultant; Pfizer)
Lagerwaard, Frank J. (Honorarium; BrainLab AG (honorarium for presentations))
Lagerwaard, Frank J. (Research Support; Varian medical systems (Departmental research agreement))
Lagier, Robet (Employment; Celera)
Lahaye, M. (Employment; Janssen-Cilag B.V.)
Lam, Stephen (Planner)
Lander, Thomas (Consultant; CureVac GmbH)
Langenfeld, Merel (Employment; AstraZeneca)
Langer, Corey (Advisory Board; Genentech)
Langer, Corey (Advisory Board; Lilly)
Langer, Corey (Grant; Genentech (advisor))
Langer, Corey (Grant; OSI (advisor))
Langer, Corey (Grant; Sanofi-Aventis (advisor))
Langer, Corey (Research Support; Bristol Myers Squibb (advisor))
Langer, Corey (Research Support; Genentech)

Langer, Corey (Research Support; Imclone (advisor))
Langer, Corey (Research Support; Lilly)
Langland, Rachel (Employment; Roche Molecular Systems)
Lara, Primo (Consultant; Novartis)
Laurie, Scott (Advisory Board; Eli Lilly)
Lavialle, Sebastien (Employment; sanofi-aventis)
Lavolé, Armelle (Honorarium; Lilly)
Lawrence, Jeffrey (Employment; Roche Molecular Systems)
Lazarov, Mirella (Employment; Genentech)
Le, Quynh-Thu (Planner)
Le Caer, Herve (Honorarium; ROCHE)
Le Caer, Herve (Honorarium; LILLY)
Le Pechoux, Cecile (Planner)
Lee, Hyun Jung (Employment; Eli Lilly)
Lee, J (Research Support; Quintiles)
Lee, Jin Soo (Planner)
Lenk, Thomas (Employment; Celera)
Leonard, Pauline (Honorarium; Lilly (Two presentations for Lilly))
Leonard, Pauline (Advisory Board; Lilly)
Letrent, Stephen (Major Stockholder; Pfizer)
Letrent, Stephen (Employment; Pfizer)
Liang, Jane (Stockholder (minor); Pfizer Inc)
Liang, Jane (Employment; Pfizer Inc)
Lipkind, Marina (Employment; Genentech)
Liu, Li (Employment; GlaxoSmithKline)
Liu, Lian (Employment; Roche)
Liu, Zhixin (Employment; Eli Lilly & Company)
Liyanage, Hema (Employment; Sequenom (Worked as collaborator on assay development only.))
Loo, Billy (Honorarium; GE Medical Systems (Lecture))
Loo, Billy (Honorarium; Varian Medical Systems (Lecture))
Lopes, Jr., Gilberto (Honorarium; AstraZeneca)
Lopes, Jr., Gilberto (Research Support; Roche)
Lopes, Jr., Gilberto (Honorarium; Roche)
Lopes, Jr., Gilberto (Research Support; AstraZeneca)
Lopez-Rios, Fernando (Research Support; Roche Molecular System)
Lopez-Rios, Fernando (Research Support; Ventana Medical Systems)
Lorence, Robert (Employment; Boehringer Ingelheim Pharmaceuticals)
Lu, Brian (Employment; Merck & Co., Inc.)
Ludwig, Heinz (Research Support; Celgene)
Ludwig, Heinz (Honorarium; Sandoz)
Ludwig, Heinz (Honorarium; Celgene)
Ludwig, Heinz (Honorarium; Ortho Biotech)
Ludwig, Heinz (Consultant; Celgene)
Ludwig, Heinz (Consultant; Ortho Biotech)
Ludwig, Heinz (Research Support; Mundipharma)
Luecke, John (Employment; HTG Molecular, Inc.)
Lufkin, Joelle (Employment; Synta Pharmaceuticals)
Lüftner, Diana (Expert Testimony; Amgen)
Lüftner, Diana (Honorarium; Amgen)
Mabry, Mack (Employment; Abbott)
Mack, Philip (Planner)
MacManus, Michael (Planner)
Madsen, ida (Grant; Roche)
Maeda, Hiroshi (Employment; Kyowa Hakko Kirin Co., LTD.)
Magallanes, Manuel (Honorarium; Eli Lilly and Company (Honoraria received for consultancy services))
Magliocco, Anthony (Honorarium; Astra Zeneca)
Magliocco, Anthony (Consultant; Astra Zeneca)
Maguire, Joe (Consultant; Pierre Fabre)
Majnesjö, Karin (Employment; Fujirebio Diagnostics AB)
Maki, Robert (Research Support; Pfizer)
Maki, Robert (Consultant; Pfizer)
Malderez-Bloes, Carole Carole (Employment; Biosystems International)
Malik, Rajesh (Employment; Agennix)
Maneatis, Thomas (Employment; Genentech)
Manegold, Christian (Honorarium; Eli Lilly and Company)
Mango, Jason (Employment; Genentech)
Mann, Michael (Major Stockholder; Pinpoint Genomics (Minor ownership interest))
Märten, Angela (Employment; BI Pharma GmbH & Co. KG)
Martinez, Betzaida (Employment; Eli Lilly & Company)
Martins, Renato (Grant; Eli Lilly)
Martins, Renato (Honorarium; Eil Lilly)
Martins, Renato (Research Support; Pfizer)
Massuti, Bartomeu (Consultant; ROCHE)
Mather, Cecile (Employment; Pfizer, Inc.)
Mazières, Julien (Honorarium; Lilly)
McCoy, Sheryl (Minor stockholder; Amgen Inc.)
McCoy, Sheryl (Employment; Amgen Inc.)
McIntosh, Donna (Employment; Aveo Pharmaceuticals)
McKeage, Mark (Honorarium; Novartis, Antisoma)
McKeage, Mark (Consultant; Novartis, Antisoma)
McKee, Mark (Employment; Abbott Laboratories)
Mckeegan, Evelyn (Employment; Abbott)
McNally, Richard (Major Stockholder; Celgene Corporation)
McNally, Richard (Employment; Celgene Corporation)
Meech, Sandra (Employment; Pfizer, Inc.)
Meetze, Kristan (Employment; Aveo Pharmaceutical)
Melemed, Allen (Employment; Eli Lilly and Company)
Melemed, Symantha (Employment; Eli Lilly and Company)
Mellemgaard, Anders (Advisory Board; Roche)
Meshref, Mohamed (Employment; Eli Lilly & Company)
Messersmith, Wells (I serve as PI of the clinical trial; GlaxoSmithKline)
Mettinger, Karl (Employment; Oncolytics Biotech Inc)
Meyer, Michael (Employment; VisionGate)
Michiels, Stephan (Planner)
Middleton, Gary (Honorarium; Eli Lilly and Company)
Middleton, Gary (Consultant; Eli Lilly and Company)
Miller, Daniel (Research Support; Deep Breeze LTD)
Miller, Vincent (Consultant; ArQule)
Miller, Vincent (Consultant; Boehringer-Ingelheim)
Miller, Vincent (Consultant; Genetech Oncology)
Miller, Vincent (Consultant; Pfizer)
Miller, Vincent (Consultant; Roche)
Miller, Vincent (Honorarium; Boehringer Ingelheim)
Miller, Vincent (Honorarium; Genentech)
Miller, Vincent (Honorarium; OSI)
Miller, Vincent (Honorarium; Pfizer)
Miller, York (intellectual property; University of Colorado)

Miller, York (Intellectual property-Patent for Prostacyclin to prevent lung ca; University of Colorado)
Milleron, Bernard (Honorarium; Eli Lilly)
Milleron, Bernard (Honorarium; Roche)
Mills, Gordon (Advisory Board; Aushon)
Millward, Michael (Planner)
Miret, Juan (Employment; ARIAD Pharmaceuticals)
Modiano, M (Research Support; Arizona Clinical Research Center)
Mohan, Sankar (Employment; Genentech)
Mohemmad, Qurish (Employment; ARIAD Pharmaceuticals)
Mok, Tony (Advisory Board; AstraZeneca, Roche, Eli Lilly, Pfizer, Merck-Serono, BI)
Mok, Tony (Advisory Board; AVEO)
Mok, Tony (Advisory Board; Eisai)
Mok, Tony (Advisory Board; Taiho)
Mok, Tony (Consultant; AstraZeneca, Roche, Pfizer, Eli Lilly, Taiho, Merck-Serono, Eisai)
Mok, Tony (Consultant; AVEO)
Mok, Tony (Consultant; BMS Elsai)
Mok, Tony (Consultant; Taiho)
Mok, Tony (Grant; Astra-Zeneca)
Mok, Tony (Honorarium; AstraZeneca, Roche, Pfizer, Eli Lilly, Taiho, Eisai)
Mok, Tony (Honorarium; BI)
Mok, Tony (Honorarium; Merck Serono)
Mok, Tony (Myself - compensated; AstraZeneca)
Mok, Tony (Myself - compensated; BMS)
Mok, Tony (Myself - compensated; Eisai)
Mok, Tony (Myself - compensated; Eli Lilly)
Mok, Tony (Myself - compensated; Merck-Serono)
Mok, Tony (Myself - compensated; Pfizer)
Mok, Tony (Myself - compensated; Roche)
Mok, Tony (Myself - compensated; Taiho)
Mok, Tony (Research Support; AstraZeneca)
Mok, Tony (Speaker's Bureau; Astrazenece (speaker and consultancy))
Mok, Tony (Speaker's Bureau; BMS (speaker and consultancy))
Mok, Tony (Speaker's Bureau; Eisai (speaker and consultancy))
Mok, Tony (Speaker's Bureau; Eli Lilly (speaker and consultancy))
Mok, Tony (Speaker's Bureau; Merck-Serono (speaker and consultancy))
Mok, Tony (Speaker's Bureau; Pfizer (speaker and consultancy))
Mok, Tony (Speaker's Bureau; Roche (speaker and consultancy))
Mok, Tony (Speaker's Bureau; Taiho (speaker and consultancy))
Mok, Tony (Planner)
Moran, Lauren (Employment; ARIAD Pharmaceuticals)
Morant, Rudolf (Consultant; AstraZeneca)
Morice, Rodolfo (Research Support; Deep Breeze LTD)
Moro-Sibilot, Denis (Honorarium; AstraZeneca)
Moro-Sibilot, Denis (Honorarium; Eli Lilly)
Moro-Sibilot, Denis (Honorarium; AstraZeneca)
Morris, Peter (Research Support; Agennix)
Mundayat, Rajiv (Employment; Pfizer (Director of Statistics; owns Pfizer stock options/restricted stock units))
Myers, Thomas (Employment; Roche Molecular Systems)
Nakagawa, Kazuhiko (Advisory Board; Eli Lilly Japan K.K.)
Nakagawa, Kazuhiko (Honorarium; Bristol-Myers Squibb)
Nakagawa, Kazuhiko (Speaker's Bureau; Eli Lilly Japan K.K.)
Nakagawa, Kazuhiko (Honorarium; Taiho Pharmaciutical)
Nakanishi, Yoichi (Research Support; CHUGAI PHARMACEUTICAL CO., LTD)
Narasimhan, Narayana (Employment; ARIAD Pharmaceuticals)
Nederlof, Petra (Planner)
Nelson, Alan (Employment; VisionGate)
Neumann, Thomas (Employment; VisionGate)
Newton, Nick (Employment; Roche Molecular Systems)
Nicolson, Marianne (Honorarium; Lilly)
Nicolson, Marianne (Research Support; Lilly)
Nicolson, Marianne (Advisory Board; Lilly)
Nielsen, Henrik (Grant; Roche Denmark)
Nilsson, Mats (Major Stockholder; Olink AB)
Ning, yaoyu (Employment; ARIAD Pharmaceuticals)
Nogami, Naoyuki (Advisory Board; Eli Lilly Japan K.K.)
Nogova, Lucia (Other Remuneration; Bayer)
Nogova, Lucia (Other Remuneration; Novartis)
Noguchi, Masayuki (Planner)
Nolan, Catherine (Employment; Abbott)
Nowak, Anna (Planner)
Obasaju, Coleman (Employment; Eli Lilly and Company (Stock))
O'Brien, Mary (Advisory Board; Celgene Corporation)
O'Brien, Mary (Honorarium; Celgene Corporation)
O'Brien, Mary (Research Support; Celgene Corporation)
O'Byrne, Ken (Planner)
O'Byrne, Kenneth (Research Support; Merck Serono)
O'Byrne, Kenneth (Advisory Board; Merck Serono)
O'Byrne, Kenneth (Advisory Board; Lilly)
O'Byrne, Kenneth (Honorarium; Merck Serono)
O'Connell, Joseph (Employment; Pfizer Inc)
O'Donnell, Patrick (Employment; Roche Molecular Systems)
Okamoto, Hiroaki (Speaker's Bureau; Eli Lilly Japan K.K.)
Okamoto, isamu (Honorarium; Eli Lilly)
Okamoto, isamu (Honorarium; Chugai Pharmaceutical)
O'Reilly, Michael (Research Support; AstraZeneca)
Orlando, Mauro (Employment; Eli Lilly and Company (Full-time employee with Lilly shares (clinical research physician)))
Orlov, Sergey (Consultant; Eli Lilly and Company)
Orlov, Sergey (Research Support; Genentech)
Ossa, Diego (Employment; Novartis Pharma AG)
Otterson, Gregory (Research Support; Pfizer)
Otterson, Gregory (Research Support; Genentech (Advisory Panel))
Otterson, Gregory (Research Support; Tragara)
Palmer, Mike (Consultant; Boehringer Ingelheim)
Pandita, Ajay (Employment; Genentech)
Pao, William (Consultant; AZ)
Pao, William (Consultant; Bristol-Myers Squibb)
Pao, William (Consultant; MolecularMD)
Pao, William (Consultant; Symphony Evolution)
Pao, William (Rights to testing EGFR T790M licensed on my behalf/others-MSKCC to MolecularMD; MolecularMD)
Parab, Vaishali (Employment; Genentech)
Park, Jennifer (Employment; GlaxoSmithKline)

Park, Keunchil (Advisory Board; Astra-Zeneca)
Park, Keunchil (Advisory Board; Boheringer Ingelheim)
Park, Keunchil (Advisory Board; Eli Lilly)
Park, Keunchil (Advisory Board; GSK)
Park, Keunchil (Advisory Board; Lilly)
Park, Keunchil (Advisory Board; Merck & Co)
Park, Keunchil (Advisory Board; Pfizer)
Park, Keunchil (Advisory Board; Roche)
Park, Keunchil (Consultant; Amgen Inc.)
Park, Keunchil (Consultant; Pfizer)
Park, Keunchil (Consultant; Roche)
Park, Keunchil (Honorarium; AstraZeneca)
Park, Keunchil (Honorarium; Eli Lilly)
Park, Keunchil (Honorarium; Pfizer)
Pass, Harvey (Research Support; Response Genetics Inc.)
Pass, Harvey (Owns patent for Plasma OPN discovery of Mesothelioma; Harvey Pass)
Pass, Harvey (Planner)
Pastorino, Ugo (Planner)
Patel, P (Employment; Genentech)
Patel, Premal (Employment; Genentech)
Patel, Rajesh (Employment; Genentech)
Patel, Taral (Consultant; Genentech)
Patten, Florence (Employment; VisionGate)
Patterson, Scott (Minor stockholder; Amgen Inc.)
Patterson, Scott (Employment; Amgen Inc.)
Patz, Edward (Planner)
Paul, Rick (Planner)
Paz-Ares, Luiz (Planner)
Pearsall, R. (Employment; Acceleron Pharma)
Peddareddigari, Vijay (Employment; GlaxoSmithKline)
Pellicioli, Erica (Employment; AstraZeneca)
Peltz, Gerson (Employment; Eli Lilly & Company)
Peng, Guangbin (Employment; Eli Lilly and Company (Stocks))
Pennella, Eduardo (Employment; Eli Lilly & Company)
Penuel, Elicia (Employment; Genentech)
Peters, Matthew (Planner)
Petersen, Jennifer (Employment; Pfizer (Health Economics and Outcomes Research Department))
Petersen, Judith (Employment; Nexcura)
Peterson, Amy (Employment; Genentech)
Pignon, Jean-Pierre (Planner)
Pirker, Robert (Speaker's Bureau; Merck Serono)
Pirker, Robert (Advisory Board; Merck Serono)
Pirker, Robert (Honorarium; Merck Serono)
Pohl, Gerhardt (Employment; Eli Lilly & Company)
Polli, Anna (Stocks; Pfizer)
Polli, Anna (Employment; Pfizer)
Port, R (Employment; Genentech)
Postmus, Pieter (No personal fee for related topic; fee for chairing session PILC 2010; depart grants; Roche)
Postmus, Pieter (Planner)
Pouget, Jean-Christophe (Employment; Pierre Fabre Médicament Biometrie)
Pujol, Jean-Louis (Speaker's Bureau; Eli Lilly and Company)
Qi, Jiwei (Employment; ARIAD Pharmaceuticals)
Quoix, Elisabeth (Honorarium; Roche)
Quoix, Elisabeth (Honorarium; Lilly)
Rabin, Michael (Advisory Board; Genentech)
Radwan, Rachel (Employment; Fujirebio Diagnostics, Inc)
Raja, Rajiv (Employment; Genentech)
Rajan, Narayan (Employment; Eli Lilly and Company)
Ramakrishan, Vanitha (Employment; Genentech)
Ramalingam, Suresh (Advisory Board; Astellas)
Ramalingam, Suresh (Advisory Board; Genentech)
Ramalingam, Suresh (Advisory Board; OSI)
Ramalingam, Suresh (Advisory Board; Pfizer)
Ramalingam, Suresh (Advisory Board; Roche)
Ramsey, Scott (Consultant; Novartis Pharma AG)
Ranger-Moore, James (Employment; Ventana Medical Systems)
Ray, Joshua (Employment; F. Hoffmann-La Roche, Ltd.)
Reck, Martin (Advisory Board; AstraZeneca (Compensated))
Reck, Martin (Advisory Board; Bristol Myers Squibb (Compensated))
Reck, Martin (Advisory Board; Hoffmann La-Roche (Compensated))
Reck, Martin (Advisory Board; Lilly (Compensated))
Reck, Martin (Advisory Board; Pfizer (Compensated))
Reck, Martin (Advisory Board; Roche)
Reck, Martin (Consultant; Lilly, Hoffman La Roche, Astra Zeneca, Pfizer, BMS)
Reck, Martin (Honorarium; Lilly, Hoffman La Roche, Astra Zeneca,)
Reck, Martin (Honorarium; Merck)
Reckamp, Karen (Consultant; Amgen)
Reckamp, Karen (Consultant; Tragara Pharmaceuticals)
Reckamp, Karen (Speaker's Bureau; Genentech)
Reckamp, Karen (Speaker's Bureau; Lilly)
Reckamp, Karen (Research Support; Pfizer (Clinical trial research support))
Reisman, Arlene (Stockholder; Pfizer)
Reisman, Arlene (Employment; Pfizer)
Renschler, Markus (Major Stockholder; Celgene Corporation)
Renschler, Markus (Employment; Celgene Corporation)
Reuter, David (Employment; Abbott Laboratories)
Reyes, Carolina (Employment; Genentech Corporation)
Richardson, Frank (I will be leaving OSI on May 31; OSI Pharmaceuticals)
Ricker, Justin (Employment; Abbott Laboratories)
Riely, Gregory (Advisory Board; Ariad)
Riely, Gregory (Advisory Board; Chugai)
Riely, Gregory (Consultant; Ariad)
Riely, Gregory (Consultant; Astra Zeneca)
Riely, Gregory (Consultant; Boehringer Ingelheim)
Riely, Gregory (Consultant; Chugai)
Riely, Gregory (Research Support; Merck)
Riely, Gregory (Research Support; Pfizer)
Rigas, James (Consultant; Boeheringer Ingelheim)
Riggi, Marcello (Employment; Pierre Fabre Medicaments)
Rivera, Victor (Employment; ARIAD Pharmaceuticals)
Robertson, John (Major Stockholder; Oncimmune Ltd)
Robinet, Gilles (Honorarium; Roche)
Roder, Heinrich (Major Stockholder; Biodesix)
Roder, Heinrich (Employment; Biodesix)
Roder, J (Employment; Biodesix)

Roder, Joanna (Employment; Biodesix)
Rogerio, Jaqueline (Employment; Novartis Oncology (Stock Ownership))
Rolss, Patrick (Honorarium; Axcan Pharma)
Rosery, Hubertus (Research Support; F. Hoffmann-La Roche)
Roughley, Adam (Research Support; F. Hoffmann - La Roche Ltd.)
Roy, Hemant (Co-Founder; American BioOptics)
Ruben, Steve (Employment; Celera)
Saito, Hiroshi (Honorarium; Taiho Pharmaciutical)
Sandler, Alan (Consultant; Roche)
Sandler, Alan (Speaker's Bureau; Genentech)
Sandler, Alan (Research Support; Genentech)
Sandler, Alan (Consultant; Genentech)
Sarashina, Akiko (Employment; Nippon Boehringer Ingelheim)
Sathyanarayanan, Sriram (Employment; Merck & Co., Inc.)
Satram-Hoang, Sacha (Employment; Genentech Corporation)
Scagliotti, Giorgio (Consultant; Eli Lilly & Company (Honoraria))
Scagliotti, Giorgio (Honorarium; AstraZeneca)
Scagliotti, Giorgio (Honorarium; Eli Lilly and Company)
Scagliotti, Giorgio (Honorarium; Roche)
Schaunberg, John (Employment; Agennix)
Scheel, Birgit (Employment; CureVac)
Schiller, Joan (Research Support; Genentech)
Schiller, Joan (Consultant; Roche)
Schiller, Joan (Consultant; Genentech)
Schirmacher, Peter (Honorarium; AstraZeneca)
Schirmacher, Peter (Consultant; AstraZeneca)
Schloesser, Axel (Employment; Novartis Pharma AG)
Schnaars, Yvonne (Employment; Merck KGaA)
Schneider, Bryan (Speaker's Bureau; Genentech)
Schnyder, Judy (Employment; Gemin X Pharmaceuticals)
Schoenbrunner, Nancy (Employment; Roche Molecular Systems)
Schramel, Franz (Consultancy fee; AstraZeneca)
Schuler, Martin (Research Support; BI Pharma GmbH & Co. KG)
Schuler, Martin (Research Support; Lilly)
Schumacher, Karl-Maria (Employment; Merck KGaA)
Schwartz, Brian (Employment; ArQuLe, Inc)
Schwartzberg, Lee (Honorarium; Eisai Inc.)
Sebastian, Martin (Advisory Board; Lilly)
Segal, Marc (Consultant; Pinpoint Genomics)
Segel, Joel (Research Support; AstraZeneca)
Sehdev, Sandeep (Advisory Board; AstraZeneca)
Seki, Yoko (Employment; Nippon Boehringer Ingelheim)
Sekiguchi, Risa (Employment; Eli Lilly Japan K.K.)
Selaru, Paulina (Major Stockholder; Pfizer)
Selaru, Paulina (Employment; Pfizer)
Senan, Suresh (Advisory Board; Varian medical systems)
Senan, Suresh (Speaker's Bureau; Varian Medical Systems)
Senan, Suresh (Research Support; Varian Medical Systems)
Senan, Suresh (Honorarium; Varian medical systems (Speakers fee))
Senan, Suresh (Planner)
Sennello, Regina (Employment; OSI Pharmaceuticals)
Sequist, Lecia (Advisory Board; GlaxoSmithKline)
Shafren, Darren (Consultant; Viralytics)
Shahidi, Mehdi (Employment; Boehringer Ingelheim)
Shakespeare, William (Employment; ARIAD Pharmaceuticals)
Shapiro, Geoffrey (Research Support; Pfizer)
Sharma, Sunil (Research Support; Acceleron Pharma)
Shaw, Alice (Advisory Board; Ariad)
Shaw, Alice (Consultant; Ariad)
Shaw, Alice (Consultant; Millenium)
Shaw, Alice (Consultant; Pfizer)
Shaw, Alice (Honorarium; Millenium)
Shaw, Alice (Research Support; Astrazeneca)
Shaw, Alice (Research Support; Novartis)
Shelton, David (Planner)
Shepherd, Frances (Honorarium; Eli Lilly)
Shepherd, Frances (Honorarium; Celgene Corporation)
Shepherd, Frances (Advisory Board; Eli Lilly)
Shepherd, Frances (Advisory Board; AstraZeneca)
Shepherd, Frances (Consultant; Celgene Corporation)
Sherman, Matthew (Employment; Acceleron Pharma)
Shi, Hong (Employment; GlaxoSmithKline)
Shimodaira, Shigetaka (Advisor; Tella, Inc)
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