KEYNOTE LECTURES

1IN

TOBACCO CONTROL-WHAT IS IMPORTANT FOR ONCOLOGISTS TO KNOW

C. Dresler *Tobacco Prevention and Cessation Program, Arkansas Department of Health, Little Rock/USA*

The known relationship between tobacco and lung cancer goes back to the 1950s. Despite this knowledge, lung cancer remains the leading cause of cancer deaths in developed countries, and is becoming so in developing economies. This increase in lung cancer death rates can be related to economic development – due to the fact that tobacco industries have increased their marketing in these developing economies. We know the causative agent for a significant majority of lung cancers and we know the vector – the tobacco transnational oligopolies. Fortunately there has been tremendous growth in the strength and impact of the tobacco control movement globally. Europe, in many ways, has been a leader in promulgating effective policies. It is fascinating to look at the cross-disciplinary concepts between the generally more advocacy based tobacco control movement and the basic and clinical science of the treatment of lung cancer. Although there is often little cross-talk, the science between the two is converging. Examples would include the studies performed to ascertain the effective chemotherapeutic agent and/or dose depending on whether the lung cancer patient smokes tobacco or not; or, the constituents either in or created by combustion and inhaled in the cigarette and how they impact the initiation, histology or growth of a lung cancer; or the genetic determinants that lead to nicotine addiction and/or susceptibility to lung cancer. It is critical that the disparate research fields are aware of developments in each other's area of expertise. For example, as the various countries implement regulations that limit or eliminate certain constituents, such as nitrosamines, there will be changes in the epidemiology of the growing proportion of adenocarcinomas, and the related biomarkers associated with adenocarcinomas. Similarly, knowledge of such changes may impact the treatment, and the studies performed to determine appropriate treatment for the potentially shifting proportions of histologic types of lung cancer. Thus, practitioners and researchers will need to be cognizant of the continual changes occurring in the tobacco control environment. It is an exciting time to observe the growth of knowledge and impacts in both tobacco control and lung cancer treatment.

Disclosure: The author has declared no conflicts of interest.

2IN

FUTURE DIRECTIONS IN THE TREATMENT OF NSCLC

P.A. Bunn, Jr. *Medicine-Oncology, University of Colorado Cancer Center, Aurora/USA*

The most striking advances in NSCLC have been the recognition that tumors with activating mutations in the EGFR gene are likely to be addicted to this signal pathway, are likely to respond to EGFR TKIs and are likely to develop resistance to EGFR TKIs through secondary resistance mutations that inhibit TKI binding to the receptor and the recognition that EML4/ALK fusion genes predict response to ALK TKIs. Mutations in known oncogenes are present in at least 50% of NSCLC tumors.

What are the challenges and limitation to this molecular approach? 1) A significant minority of patients will have intrinsic resistance and will not respond, 2) all responding patients will develop acquired resistance. 3) mutations in genes such as KRAS for which there are no known therapies, new agents need to be developed. 4) we need to develop a way to deliver tumor suppressor genes. 5) we need to distinguish between "driving" mutations and "passenger" mutations. 6) we need to be able to develop validate and receive regulatory approval of mutation and other biomarker tests. 7) we need predictive biomarkers for patients with wildtype tumors. We must recognize that EGFR TKI such as erlotinib can improve DFS and OS even in EGFR wt tumors.

There has been limited study of EGFR TKIs in patients with Stage I-III NSCLC. These agents have the potential to improve the cure rate in the early stage patients. Oncogenes can be activated by fusion with other genes as well as by mutation in NSCLC. The EML4/ALK fusion gene is present in about 4% of lung adenocarcinomas essentially limited to never smokers. Patients whose tumors harbor these fused genes have high ALK expression and had high response rates to the ALK TKI term PF1066 in a phase I trial of this agent. These results have led to a phase II/III randomized trial in these patients. Many of these oncogenic transformations lead to activation of downstream signal proteins such as MAPK, AKT, mTOR and others. Use of therapies directed at these downstream targets used alone and in combination will occur in the next several years. Thus, screening of NSCLC tumor for multiple mutations is likely to be a common occurrence in the future.

There are a host of other targets that are under investigation and the list of these is too long for this presentation but is available in other publications. Prominent among these targets are PARP inhibitors; inhibitors of other growth factor pathways (eg. FGF, IGF-1); inducers of apoptosis such as DR4 and DR5 agonists; Bcl-2 inhibitors and IAP inhibitors; vaccines; SMAC mimetics; vascular disruption agents, angiogenesis inhibitors; mitotic check point inhibitors; and others. The potential for these new therapies to improve the outcome in NSCLC patients is large and the hope is that predictive biomarkers will develop along with each of these classes of agents.

Disclosure: The author has declared no conflicts of interest.

MEET THE EXPERT

3IN

THE EMERGING ROLE OF IMMUNOTHERAPY IN LUNG CANCER

J. Vansteenkiste *Respiratory Oncology Unit, University Hospital Gasthuisberg, Leuven/BELGIUM*

For patients with resectable NSCLC, resection is the standard approach, resulting in a 5-year survival of about 40%, with a further absolute increase of 5-10% with adjuvant chemotherapy (IALT, NEJM 2004). Patients with unresectable stage III NSCLC are treated with chemotherapy and radiotherapy, with 5-year survival rates of about 20% with a concurrent approach (Fournel, JCO 2005). So, despite complete resection or radical dose of radiotherapy, many patients still die of their cancer, because NSCLC cells remaining after a radical approach cause tumour relapse. In these patients, the aim of immunotherapy is to eliminate as much as possible the cancer cells remaining after radical treatment, in order to delay relapse, or even avoid relapse and increase cure rate. For that purpose, a well defined tumour target and a strong adjuvans to boost immune response are mandatory as – after all – the tumour initially developed in a failing immune environment. We will mainly discuss approaches in this setting which are in phase III testing. In the postoperative setting, effective adjuvant strategies with better tolerability than cisplatin-based chemotherapy are needed. The MAGE-A3 antigen might be a good target: it is expressed on tumours only (35 to 50% for NSCLC, depending on the stage), not on normal tissues. The MAGE-A3 immunotherapy consists of a recombinant protein combined with a potent GSK proprietary immunological adjuvant. Pilot studies demonstrated humoral and cellular responses, and clinical responses in metastatic melanoma (Kruit, Int J Cancer 2005). In the proof-of-concept double-blind randomised phase II study, patients with completely resected MAGE-A3 positive NSCLC who received MAGE-A3 immunotherapy had a hazard ratio (HR) of 0.76 for disease-free survival and 0.81 for overall survival, figures similar to the benefit with adjuvant chemotherapy (Vansteenkiste, JTO 2008). Immunotherapy with liposomal BLP25 (Stimuvax®) is a promising adjuvant approach after chemoradiotherapy in stage III NSCLC. In a phase II randomised study, the subgroup of patients with stage IIIB had a HR of 0.52 for overall survival (Butts, JCO 2005). In both

studies, the immunotherapy was well tolerated with very little grade III/IV toxicity. Both strategies are in phase III testing.
Disclosure: J. Vansteenkiste: Advisory function for GSK Bio

4IN
RESTAGING TECHNIQUES

P.E. Van Schil, M. De Waele, J.M. Hendriks, P. Lauwers *Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem/ BELGIUM*

Downstaging after induction therapy is an important prognostic factor in locally advanced stage III non-small cell lung cancer with N2 or N3 involvement. Patients with persisting mediastinal involvement will not benefit from surgical resection. For this reason, accurate restaging is of utmost importance and a histological proof of downstaging should be obtained before considering surgical resection. The different restaging techniques are summarized in table 1. They all have distinct advantages and disadvantages. The non-invasive modalities computed tomography (CT) and magnetic resonance imaging are not accurate enough to predict response. Integrated CT-PET (positron emission tomographic) scanning performs better but as well false-positive as false-negative cases occur and the precise technical modalities remain to be determined. Minimally invasive techniques as transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) are promising but only provide a cytological diagnosis and the false-negative rate remains high. Repeat mediastinoscopy is an invasive staging technique which is less accurate than an initial procedure and technically more difficult. However, it provides a histological proof of mediastinal downstaging, determines prognosis and guides further therapy. VATS has not been extensively investigated for restaging at the present time. As minimally invasive staging techniques are gradually improving, especially in patients with enlarged mediastinal lymph nodes, there is currently a tendency to use these techniques for initial staging. Mediastinoscopy is reserved for restaging providing a thorough superior mediastinal evaluation at that time. Patients with mediastinal downstaging are considered for subsequent surgical resection, especially when a complete resection can be obtained by lobectomy with systematic nodal dissection.

Table. Techniques for Mediastinal Restaging

Noninvasive
Computed tomography (CT)
Magnetic resonance imaging (MRI)
Positron emission tomography (PET)
Integrated CT-PET
Minimally invasive
Transthoracic fine-needle aspiration (FNA) biopsy
Transbronchial needle aspiration (TBNA)
Endobronchial ultrasound (EBUS) with FNA
Endoscopic ultrasound (EUS) with FNA
Invasive
Redo, second or repeat mediastinoscopy (reMS)
Video-assisted thoracic surgery (VATS)

Disclosure: All authors have declared no conflicts of interest.

5IN
THE MANAGEMENT OF PLEURAL EFFUSION

G. Rocco *Department of Thoracic Surgery and Oncology, National Cancer Institute, Naples/ITALY*

The management of suspicious pleural effusions in a patient with a history of cancer is aimed at establishing the diagnosis, evacuating the pleural collection, and, obliterating the pleural space in order to avoid recurrences. The crucial issue is the presence of a trapped lung, either by cancer or by long standing fibrinous exudates. Failure to re-expand the lung is the single most adverse predictor against the success of pleurodesis. Despite due to breast and lung cancer in the majority of patients, in almost 11% of the cases the origin of the effusion is unknown. The overall efficacy of pleurodesis is about 66% but the likelihood of success is higher with thoracoscopic instillation of talc (failure rate 0 to 7%) than with chest tube (11 to 24% failure rate). The available pleurodetic agents are grouped into categories including mineral agents (talc), antibiotic (doxycycline,quinacrine), antiseptic (iodopovidone, silver nitrate), anticancer drug (bleomycin, mitoxantrone, cisplatin), bacterial product or component (corynebacterium parvum, staphylococcus aureus superantigen, OK432), and, cytokine (interferon alpha-2 ß). A success rate of 95-100% has been reported for talc, quinacrine, silver nitrate, staphylococcus aureus, interferon alpha. Talc is to be favoured as a single agent for pleurodesis instilled through VATS rather than as slurry, especially for pleural effusion resulting from breast or lung cancer. Slurry should be reserved to fragile, cachectic patients. Talc is the least expensive agent but it is reported to cause respiratory failure and empyema. Maximum benefit from talc is obtained in women with re-expandable lung, acceptable performance status (>60% according to Karnofsky), and, in patients with a BMI greater than 25. Management of trapped lung is one of the most challenging issues the clinician is faced with. Domiciliary care with self managed chest drains ($Pleur_x$) have proved to be beneficial for symptom relief albeit the percentage of completely controlled effusions vas reported to be around 60%. An implantable access system to the pleural has also been described to facilitate home care. However, several reviews have demonstrated a high level of compliance with the chronically indwelling tube by patients with malignant, recurring pleural effusions.
Disclosure: The author has declared no conflicts of interest.

6IN
NOVEL TARGETED THERAPIES FOR SPECIFIC SUBGROUPS OF NSCLC WITH SPECIFIC GENE MUTATIONS

D. Costa *Hematology Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston/USA*

Non-small-cell lung cancers (NSCLCs) are heterogeneous cancers. A major paradigm shift in understanding and treating this disease has occurred in the last years as new oncogenes have been identified and subsequently targeted in patients. In 2004, the identification of epidermal growth factor receptor (EGFR) somatic mutations provided the first glimpse of a clinically-relevant NSCLC oncogene. Over 70% of NSCLCs with EGFR mutations (exon 19 deletions or the exon 21 L858R) attain responses to EGFR TKIs (gefitinib and erlotinib), with improved response rate (RR), progression-free survival (PFS) and in some reports overall survival (OS) when compared to EGFR wild-type (WT) cases. Randomized phase III trials of gefitinib versus chemotherapy in stage IV NSCLC have consistently demonstrated better RR and PFS for EGFR mutated patients treated with gefitinib. IPASS reported a RR of 71.2% for gefitinib and 47.3% for carboplatin-paclitaxel ($p<0.001$), with PFS HR of 0.48 ($p<0.001$) favoring gefitinib; and WJTOG3405 reported a RR of 62.1% for gefitinib and 32.2% for cisplatin-docetaxel

($p<0.001$), with PFS HR of 0.489 ($p<0.001$) favoring gefitinib. Novel irreversible EGFR TKIs (BIBW2992, XL647, PF00299804) show similar activity in EGFR mutated patients. A translocation involving the anaplastic lymphoma kinase (ALK) gene with echinoderm microtubule-associated protein-like 4 (EML4) is the most recent oncogene found in NSCLC. Rarer ALK fusion partners (TGF-ALK and KIF5B-ALK) also exist. PF-02341066, a novel ALK TKI, has shown impressive activity against ALK translocated NSCLC in an expanded cohort of a phase I trial (NCT00585195). Over 60 patients have been treated and the RR exceeds 60%. Due to short follow-up the median PFS has not been reached, however many patients have been on study drug for over 6-10 months. A registration phase III trial of PF-02341066 versus second line chemotherapy (pemetrexed/docetaxel) is underway (NCT00932893). KRAS, EGFR mutations and ALK translocations are usually mutually exclusive and few KRAS mutated, EGFR WT or ALK translocated NSCLC respond to EGFR TKIs. The promising results of EGFR and ALK TKIs in molecular subgroups of NSCLC herald a new age of drug and clinical trial development for patients with NSCLC.

Disclosure: The author has declared no conflicts of interest.

7IN
CHEMOTHERAPY FOR THE ELDERLY

E. Quoix *Pneumology Service, Nouvel Hopital Civil, Strasbourg/FRANCE*

Incidence of advanced Non-Small Cell Lung Cancer in the elderly is increasing with a median age at diagnosis around 65 years, a third of the pts being more than 70 years old. After a nihilistic period during which elderly were under represented in clinical trials, more interest for these pts has emerged during the previous decade with publication of clinical trials devoted to them and expert meetings leading to some treatment recommendations. The Elvis trial, a phase III study, published in 1999, compared in 161 pts aged 70 and more best supportive care to vinorelbine alone. There was a significant benefit of survival with a relative risk of 0.65 (95% CI O.45; 0.93) in the vinorelbine arm. In a randomized study comparing in japanese pts vinorelbine to docetaxel there was a significant advantage for docetaxel concerning response rate (22.2% vs 9%) and progression-free survival (5.5 vs 3.1 months) and a non significant trend for longer survival (10.3 vs 6.4 months). The next step was to compare single agents with a doublet. The Miles trial performed in 698 pts compared vinorelbine or gemcitabine alone to a doublet (vinorelbine + gemcitabine) with no improvement in survival. Another study was in favor of the doublet but included only 120 patients.In a phase III trial comparing in elderly or poor PS pts weekly docetaxel to combined docetaxel and gemcitabine, there was a modest improvement in time to progression with no impact on overall survival (5.55 months versus 5.1 months). The role of platin salts is still debated. It has been investigated mostly through trials not devoted to elderly and thus there is obviously a selection bias. In those trials, toxicity was more important in elderly but the outcomes were generally speaking similar. The only published trial comparing a platin salt doublet (carboplatin + paclitaxel versus paclitaxel alone) devoted to poor performance status pts concluded in a significant benefit of the doublet in young and older pts. The results of the IFCT phase III study comparing in pts aged 70 to 89 years vinorelbine or gemcitabine alone to carboplatin and paclitaxel are awaited for this year. Bevacizumab in addition to chemotherapy seems to be of no interest in elderly. In conclusion, specific trials for elderly need to be implemented to improve the outcome at the expense of lower toxicity.

Disclosure: E. Quoix: Travel grants for congresses: Roche, Lilly, Merck Honoraria for advisory boards : Merck, Lilly, Roche, Astra Zeneca, Mundipharma, Novartis.

8IN
THYMOMAS

N. Girard *Respiratory Medicine, Reference Center for Orphan Pulmonary Diseases, Louis Pradel Hospital, Lyon/FRANCE*

The treatment of thymic malignancies is a paradigm of cooperation for the management of rare tumors between clinicians, surgeons, and pathologists from establishing the diagnosis to organizing the therapeutic strategy and evaluating the prognosis. Given the rarity of thymic tumors, only few randomized trials have been available and current recommendations are mostly based upon small-size cohorts, retrospective data, and expert consensus. The current histologic classification of thymic epithelial tumors distinguishes thymomas (types A, AB, B1, B2, B3) and thymic carcinomas. These subtypes are based upon the morphology of epithelial cells (with an increasing degree of atypia from type A to thymic carcinoma), the relative proportion of the non-tumoral lymphocytic component (decreasing from types B1 to B3), and resemblance to the normal thymic architecture. Beyond histology, treatment recommendations are mostly based upon the Masaoka staging system, which integrates the degree of tumor invasion and represents the most significant prognostic factor of overall survival. Surgery is the cornerstone of the management of thymic tumors, both ensuring the initial histopathologic diagnosis and staging, and the first step of the therapeutics. At least 10 different surgical approaches to the thymus have been described. Robotic surgery is currently under evaluation for small-size thymomas. Radiotherapy is mostly used as adjuvant treatment, and currently integrates the use of multi-field arrangement and three-dimensional treatment planning. Postoperative radiotherapy is recommended in incompletely resected thymomas, but is controversial for completely resected stage II-III tumors. Thymomas are sensitive to chemotherapy including combinations of cisplatin either with adriamycin and cyclophosphamide or etoposide and ifosfamide. Chemotherapy is indicated both as an induction treatment for marginally-resectable tumors and as the exclusive treatment for non-resectable, metastatic, and recurrent tumors. An alternative option may be the use of octreotide and prednisone in octreoscan-positive lesions. Targeted therapies also represent a promising approach in specific molecular subsets of tumors.

Disclosure: The author has declared no conflicts of interest.

9IN
IMPROVING SURVIVAL IN LS-SCLC AND ES-SCLC WITH RADIOTHERAPY

C. Faivre-Finn *Department of Clinical Oncology, Christie Hospital NHS Trust, Withington, Manchester/UNITED KINGDOM*

Small-cell lung cancer (SCLC) constitutes 10-15% of all newly diagnosed lung cancers. At the time of diagnosis, approximately 30% of patients with SCLC will have limited-stage disease (LS-SCLC or stage I-III according to the new TNM classification), and most long-term disease-free survivors come from this group. Whilst the incidence of small cell lung cancer has reduced over the last twenty years, the prognosis of the disease remains poor. Major advances include improvements in RT techniques, the use of prophylactic cranial irradiation (PCI) for all stages of SCLC and the improved association of chemotherapy (CT) and RT. It is unlikely that future advances in the treatment of SCLC will relate to standard CT. It is crucial that patients with SCLC are given the opportunity to participate in clinical research in order to continue to improve the survival of this disease. Ongoing clinical trials addressing RT related questions include the CONVERT and the CREST studies. CONVERT is a European phase III trial in LS-SCLC comparing twice daily thoracic RT (45 Gy in 30 fractions starting with the second cycle of cisplatin and etoposide) to a higher dose of conventional radiation (66 Gy in 33 daily fractions over 6.5 weeks starting with the second cycle of cisplatin and etoposide). The aim is to establish a standard of care in good performance status LS-SCLC. A similar study is ongoing in the US.

CREST is a Dutch Phase III trial randomising patients with ES-SCLC responding to CT between thoracic RT and no thoracic RT followed by PCI if appropriate. Molecular studies are ongoing aiming to gain improved insight into the molecular biology of SCLC, discover and/or validate candidate biomarkers for response, resistance to or toxicity of systemic treatment and radiation. There is now a concerted effort within the research community to understand the molecular mechanisms that underpin the molecular pathways in cancer. It is hoped that this understanding will lead to the development of targeted therapies that will not only prove efficacious but also less toxic than more conventional CT treatments. In combination with newer techniques such as conformal RT and better imaging, it is hoped that the rates of long term survivors will increase significantly in the future.
Disclosure: The author has declared no conflicts of interest.

10IN
CIRCULATING LUNG CANCER CELLS

J. Mazières *Department of Pneumology, Larrey Hospital, CHU Toulouse, Toulouse/FRANCE*

Tumor molecular characteristics are becoming crucial for determining the better treatment for lung cancer patients. These data are usually obtained from resected tumor or biopsies. Data are thus collected at the beginning of the disease whereas many genetic abnormalities that can lead to acquired drug resistance may emerge during treatment. Tumor sampling cannot be repeatedly proposed during treatment to monitor changes in tumor characteristics. Moreover most of the tumor samples are issued from the lung primitive tissue and do not give complete information about the metastatic potential of the tumor. Tumor cells are known to circulate in the blood of patients with metastatic cancer suggesting that their detection might be useful to obtain tumor-derived biological markers. Potential interest of the isolation of lung cancer circulating cell are the following: -Diagnosis of lung cancer by a non invasive method in high risk patients -Prognostic marker as the presence of CTC is associated with shortened survival -Marker of treatment efficacy by monitoring the blood tumor cell count during the treatment -Analysis of tumor characteristics by performing cell and molecular biology on isolated cells. There is no consensus on the optimal protocol for isolation of circulating tumor DNA. Different procedure have been studied and recently published recently: - magnetic beads conjugated antibodies against epithelial-cell adhesion molecule (EpCAM). - microfluidic-based device (called the CTC-chip) that can isolate, quantify, and analyze circulating tumor cells from a blood sample. -ISET based on tumoral cell size. We will focus on the potential role of CTC isolation for treatment optimization and particularly on the monitoring of EGFR mutation during lung cancer evolution before and after treatment. We will develop different devices available for CTC isolation and the perspectives concerning this very promising and timely topic.
Disclosure: The author has declared no conflicts of interest.

11IN
PRINCIPLES OF MODERN RADIOTHERAPY FOR THE NON-RADIATION ONCOLOGIST

M. Brada *The Royal Marsden NHS Foundation Trust, The Institute of Cancer Research, Sutton/UNITED KINGDOM*

European Lung Cancer Conference Principles of Modern Radiotherapy for the non radiation oncologist. Professor Michal Brada The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, UK Radiotherapy (RT) remains an effective curative and palliative treatment for localised lung cancer and is generally delivered as photons (x-rays) by linear accelerator. The standard technique is described as 3 dimensional conformal radiotherapy (3DCRT) which aims to concentrate high dose to the tumour with minimum dose to surrounding normal tissues and this is achieved by using multiple shaped beams conforming to the shape of the tumour. The principle of advanced techniques is better avoidance of normal tissues to allow dose escalation without increasing treatment toxicity particularly to the lung. Intensity modulated radiotherapy (IMRT), a variant of 3DC RT can shape radiation to avoid adjacent critical normal structures and deliver differential doses to various parts of the tumour ("dose painting"). Proton therapy can be considered as potentially more conformal RT having the same biological effect. Visualisation of the tumour close to the actual treatment with image guided techniques (IGRT) and the use of "adaptive" RT improve the accuracy of treatment further. One of the main challenges for NSCLC RT is tumour motion and this can be dealt with using gating or tracking techniques sparing more normal lung. Small localised tumours can currently be treated to higher doses with more accurate often gated treatment techniques and this is described as stereotactic body radiotherapy (SBRT) which achieves excellent local control. The principles of the new techniques, their application and the clinical results will be illustrated. Lung cancer RT is currently at the forefront of innovation of RT technology with a great potential for improved results combining novel techniques with dose escalation and with biological targeted agents modifying radiation response.
Disclosure: The author has declared no conflicts of interest.

12IN
SCLC: DRUGS AND TARGETED THERAPIES

P. Baas *Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam/NETHERLANDS*

Small Cell Lung Cancer (SCLC) represents about 15% of all lung cancers diagnosed annually. It is characterized by early dissemination; good initial response to chemotherapy and its aggressive growth. SCLC is considered to be a systemic disease since 60-7-% of the patients present with metastatic disease. SCLC is responsive to many different chemotherapeutics and new, targeted agents but rapidly develops drug resistance. For LS the standard in Europe and the US is still the combination of concurrent chemo-radiotherapy. Key is to keep the overall treatment time as short as possible to prevent repopulation of the tumor cells and development of resistance to chemotherapy. To improve outcome in SCLC many studies have examined the addition of a third agent to the cisplatin-etoposide backbone. Drugs like taxanes, thalidomide, vaccins BEC2 and topotecan have unfortunately not resulted in an improved survival but only added more toxicity. Since many patients will have recurrence of the disease, many different schedules of new drugs and targeted agents have been tested in second line. Of these topotecan is the only drug approved by the FDA for this indication. One of the new approaches is to test promising drugs in a "window of opportunity". The EORTC lung cancer group is testing a multi-target tyrosine kinase inhibitor agent (sunitinib) in patients with ES disease. The drug is given as single agent in the first line with close follow-up to find early responses or patients who progress. It is postulated that inhibition of multiple signaling pathways in cancer cells might lead to quick responses and limited toxicity. Other groups (CALGB) are combining sunitinib with cisplatin-etoposide to determine optimal dose en response rate. Since SCLC has a high degree of vascularization and VEGF expression, monoclonal angiogenesis inhibitors like bevacizumab have been tested in phase II setting with cisplatin-etoposide. The response observed were interesting (1-year OS 49%) and has resulted in a randomized phase 3 study. During the presentation on overview of all recently tested drugs (amrubicin; Hedgehog inhibitors; pemetrexed; irinotecan etc) and new approaches will be given.
Disclosure: P. Baas has been advisor for Merck Sharp Dohme and Hospira

13IN

THE MANAGEMENT OF BRAIN METASTASES

R.O. Mirimanoff *Radiation Oncology, Centre Hospitalier University Vaudois, Lausanne/SWITZERLAND*

Brain metastases occur in 20-50% of NSCLC and 50-80% of SCLC. In this review, we will look at evidence-based medicine data and give some perspectives on the management of BM. We will address the problems of multiple BM, single BM and prophylactic cranial irradiation. Recursive Partitioning Analysis (RPA) is a powerful prognostic tool to facilitate treatment decisions. Dealing with multiple BM, the use of corticosteroids was established more than 40 years ago by a unique randomized trial (RCT). Palliative effect is high (>80%) as well as side-effects. Whole brain radiotherapy (WBRT) was evaluated in many RCTs with a high (60-90%) response rate; several RT regimes are equivalent, but very high dose per fraction should be avoided. In multiple BM from SCLC, the effect of WBRT is comparable to that in NSCLC but chemotherapy (CXT) although advocated is probably less effective than RT. Single BM from NSCLC occurs in 30% of all BM cases; several prognostic classifications including RPA are very useful. Several options are available in single BM: WBRT, surgery (SX), radiosurgery (RS) or any combination of these. All were studied in RCTs and will be reviewed: the addition of WBRT to SX or RS gives a better neurological tumour control, has little or no impact on survival, and may be more toxic. However omitting WBRT after SX alone gives a higher risk of cerebro-spinal fluid dissemination. Prophylactic cranial irradiation (PCI) has a major role in SCLC. In limited disease, meta-analyses have shown a positive impact of PCI in the decrease of brain relapse and in survival improvement, especially for patients in complete remission. Surprisingly, this has been recently confirmed also in extensive disease. Experience with PCI for NSCLC is still limited, but RCT suggest a reduction of BM with no impact on survival. Toxicity of PCI is a matter of debate, as neurological or neuro-cognitive impairment is already present prior to PCI in almost half of patients. However RT toxicity is probably related to total dose and dose per fraction. Perspectives : Future research should concentrate on : 1) combined modalities in multiple BM. 2) Exploration of treatments in oligo-metastases. 3) Further exploration of PCI in NSCLC. 4) Exploration of new, toxicity-sparing radiotherapy techniques (IMRT, Tomotherapy etc).

Disclosure: The author has declared no conflicts of interest.

14IN

TARGETING LUNG CANCER INVASION AND METASTASIS: LESSONS FROM THE PAST, CURRENT STATUS AND NEW DIRECTIONS

O. Gautschi *Medical Oncology, University Hospital, Bern/SWITZERLAND*

Many cases of cancer death are related to metastasis. Therefore, pharmacological inhibitors of cancer cell metastasis have substantial clinical potential. One of the earliest steps in the process of metastasis is cancer cell invasion into surrounding normal tiussue and into the blood stream. Invasion is mediated by many different factors, including matrix metalloproteinases (MMP), focal adhesion kinases (FAK), and Src family kinases (SFK). All these molecular drug targets are currently under clinical investigation. MMP inhibitors have already been tested in phase III trials, including patients with lung cancer. One of the largest trials was BR.18, testing the MMP inhibitor BMS-275291 in combination with carboplatin and paclitaxel in patients with advanced NSCLC. An update on more recent clinical data with MMP inhibitors will be provided at the meeting. Members of the SFK regulate adhesion and migration by cooperation with FAK and integrin receptors. In humans, the SFK include c-Src, Yes, Fyn, Lyn, Lck, Hck, Fgr, and Blk. Whereas c-Src, Yes and Fyn are ubiquitously expressed, other SFK members are expressed predominatly in hematopoetic cells. c-Src is frequently expressed and activated in primary SCLC and NSCLC. Several Src inhibitors, including dasatinib, saracatinib, bosutinib, and KX2-391, are currently investigated in clinical trials. These compounds, as well as other Src inhibitors, will be discussed in detail at the meeting. Additional topics will include the potential mechanisms of drug sensitivity and/or resistance, the interaction between Src and EGFR, as well as the current knowledge of combination therapies, including Src inhibitors, radiation and chemotherapy. At last, the current status of FAK inhibitors in the clinic will be summarized. (Grant support: Swiss Cancer League and Bernese Cancer League).

Disclosure: O. Gautschi: Advisory boards by Amgen, Astrazeneca, Bayer, Eli Lilly, Merck Serono, Novartis and Roche

15IN

THE NEW FRONTIERS IN SURGERY IN T4 TUMORS AND METASTATIC DISEASE, INCLUDING SUPERIOR SULCUS

D. Grunenwald *Thoracic Surgery, University of Paris Hôpital Tenon, Paris/FRANCE*

The 7th edition of the TNM staging system for lung cancer, edited under the auspices of the International Association for the Study of Lung Cancer (IASLC) carries several critical breakpoints. Among them, an improved specificity of T4 component, and a better definition of metastatic disease should affect the medical practice. New frontiers in surgery have been established since T4 tumors associated with N0-N1 nodal disease henceforth become stage IIIA, thus opening new perspectives, particularly for superior sulcus tumors. Regarding the T4 descriptors from the 7th edition of the TNM staging system for lung cancer, consistent series of extended resections have been reported in different situations. Proximal tumors from the lower lobe developed around the inferior pulmonary vein may involve the atrial wall of the heart. In some cases a left atrial resection can be performed. Low stages in nodal status were associated with increased survival ($p = 0.0013$). Invasion of the SVC by a T4 tumor in the right upper lobe led surgical teams to attempt lobectomies or pneumonectomies extended to the vena cava. A multicentric international review of prosthetic replacement after superior vena cava resection for non small cell lung cancer in 28 patients (N2 involvement in 50%) showed morbidity and mortality rates of 39% and 14%, respectively. Overall 5-year survival rate was 15%. A bronchial carcinoma from the right lung extended to the lower part of the thoracic trachea, and/or the tracheal carina can be resected in selected patients. Long-term survivals have been observed in 15 to 23% of the cases. The best local control for resectable tumors is achieved by surgical operation, provided the resection is complet and respecting oncologic principles. Recently reported experiences of enbloc vertebrectomy demonstrate feasability of these challenging procedures.

Conclusion: Recent advances in patient's care and surgical techniques allowed surgeons to become more aggressive, and to propose extended resections in locally advanced non-small cell lung cancer, with favorable long-term survival rates. The 7th edition of TNM staging system adapted to these progress, by classifying T4N0-1 tumors in a "surgical" category, stage IIIA.

Disclosure: The author has declared no conflicts of interest.

CONTROVERSY SESSION – STAGE III N2 NSCLC

16IN

SURGERY STILL HAS A ROLE TO PLAY IN STAGE III NSCLC

P. De Leyn *Departmentof Thoracic Surgery, University Hospital Leuven, Leuven/BELGIUM*

Most patients with stage III have mediastinal lymph node (LN) involvement. For stage IIIA-N2 disease a combination of chemotherapy with surgery and/or radiotherapy will be the best strategy. There remains controversy on the role of surgical multimodality treatment due to the lack of fully convincing randomized trials and the diversity of phase II studies. The main reason for this

controversy can be explained by the fact that N2-disease is a very heterogeneous entity with a broad spectrum of metastatic LN involvement. The two randomized trials failed to show a survival benefit for the surgical treated cohort. In the Intergroup trial, potentially resectable N2-disease was included. In the EORTC study, patients with irresectable N2-disease were included. In this study, induction chemotherapy did not convert unresectable disease into resectable disease as illustrated by the low complete resection rate (50%) in the surgery arm – and, not unexpectedly, did not result in better outcome compared with radiotherapy. However, in the Intergroup trial disease free survival was significantly higher in the surgical cohort and the 5-year survival was doubled (36%) compared to the radiotherapy arm when pneumonectomy could be avoided. Moreover, both trials observed substantial long-term survival in patients with mediastinal downstaging. Prediction of complete resection and downstaging seems to be essential in the setting of combined surgical multimodality. Baseline, patients with stage IIIA should be evaluated by a multidisciplinary team including an experienced thoracic surgeon in thoracic oncology assessing baseline resectability. Bulky, extracapsular and/or multilevel disease are contraindicating surgical multimodality treatments. After induction treatment, restaging should be performed. Mainly patients with evidence of response in the primary tumor and LNs will benefit from surgical exploration. PET-CT and invasive mediastinal techniques are indicated. Patients should be carefully reassessed including new pulmonary function tests with diffusion capacity. We believe that in experienced centers, selected patients with N2-disease may benefit from surgical multimodality treatment.

Disclosure: The author has declared no conflicts of interest.

17IN

SURGERY STILL HAS A ROLE TO PLAY IN STAGE III NSCLC

No abstract received at time of going to press.

18IN

SURGERY HAS NO ROLE TO PLAY IN STAGE III NSCLC

B. Putnam *Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville/USA*

Given: Surgery has no role to play in stage III (N2) NSCLC. The management of clinically staged IIIA (N2) NSCLC challenges the clinician with the heterogeneity of the local disease and the variable incidence of regional and systemic metastasis. Patients with cStage IIIA (N2) NSCLC should be preferentially entered into a prospective clinical trial. In the absence of such a trial, chemoradiotherapy would be considered standard. The North American Intergroup 0139 phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs. CT/RT followed by surgical resection (S) for stage IIIA (pN2) NSCLC was designed to evaluate the role of resection after chemotherapy and radiation therapy. Pneumonectomy accounted for 14/15 postoperative deaths and may have compromised overall survival. The study showed that no significant survival advantage CT/RT + S compared to CT/RT alone. Although progression free survival was better with resection after CT/RT, morbidity and mortality were excessive. S might be considered in fit patients; however, the survival with resection is no different than with CT/RT alone, and the potential extent of the resection cannot be predicted. Patients with persistent biopsy-proven N2 disease after induction therapy have poor survival and are not operative candidates. Down-staging with CT/RT (changing from cN2 to cN0) may identify patients with the potential for better survival who would not need resection. The role of resection after CT/RT for more limited stage IIIA is unclear and probably unsafe. Resection following CT/RT over and above that achieved with CT/RT alone, may improve local control, but the resection itself would carry significant operative and perioperative risk for the general population of patients so treated. Subset analysis of INT 0139 suggests lobectomy after CT/RT may carry survival advantage, but the analysis is underpowered and may subject patients to unnecessary surgery and significant perioperative morbidity. Future treatment for stage IIIA (N2) NSCLC requires consistent excellent clinical staging, identification of specific biological characteristics for more directed therapy, and consideration of the risk and benefit ratio of all therapeutic modalities.

Disclosure: The author has declared no conflicts of interest.

19IN

SURGERY HAS NO ROLE TO PLAY IN STAGE III (N2) NSCLC

J. Jassem *Oncology and Radiotherapy, Medical University, Gdansk POLAND*

The role of surgery in stage III NSCLC has long been debated. Stage III lung cancer is the most heterogeneous subset of patients, as it ranges from T3N1 category, generally amenable to surgery, to T4N3 tumors, where surgery has definitely no role. The most controversial category is that including patients with ipsilateral mediastinal nodal metastases (IIIA-N2). Whereas surgery is technically feasible in some of these patients, most of them will relapse despite apparently curative resection. Strategies that have been hoped to improve prognosis in N2 patients include induction chemotherapy or chemoradiotherapy. However, despite early positive studies, no large randomized trial demonstrated improved survival with these approaches as compared to surgery alone or surgery followed by chemotherapy. Results of studies investigating the role of postoperative chemotherapy are inconsistent; nevertheless this method is currently considered the standard of care in patients with regional lymph node involvement. Two large phase III studies compared directly multimodality treatment including surgery versus non-surgical approaches in stage IIIA (N2) patients. In the first study, patients were assigned to surgery or radiotherapy after response to induction chemotherapy[1]. Both disease-free survival and overall survival did not differ between the two study arms. The second study compared concurrent chemotherapy and radiotherapy followed by resection versus definitive concurrent chemotherapy and radiotherapy without resection[2]. Despite increased disease-free survival in the surgery arm, there was again no survival benefit of resection in the intent-to-treat analysis. This negative outcome was partly attributed to increased treatment-related deaths of respiratory causes in patients subjected to surgery. It is expected that the introduction of new staging system for lung cancer may better select candidates for various therapeutic strategies in NSCLC patients. Currently, given lower toxicity of radiotherapy, there is however no strong rationale for using surgery in patients with proven stage IIIA N2 disease.

References

1. Albain KS, et al. *Lancet* 2009;374:379.
2. van Meerbeeck JP, et al. *J Natl Cancer Inst* 2007;99:442.

Disclosure: The author has declared no conflicts of interest.

CONTROVERSY SESSION

20IN

STAGE IV: TARGETED THERAPY AS FIRST LINE TREATMENT - YES

R. Pirker *Department of Internal Medicine I, Medical University of Vienna, Wien/AUSTRIA*

Systemic chemotherapy is established in all stages of NSCLC. Further improvement in the systemic therapy is anticipated through targeted therapies, either as single modality or in combination with chemotherapy. Targeted therapies currently focus on inhibition of both growth factor receptor

systems and angiogenesis. Several targeted agents have been shown to improve outcome in patients with advanced NSCLC. Cetuximab added to chemotherapy increased survival of patients with advanced NSCLC in the FLEX trial. A meta-analysis of randomized trials confirmed the benefit of cetuximab. In selected patients with advanced non-squamous NSCLC, bevacizumab added to chemotherapy increased progression-free survival (PFS) in two trials and survival in one of these trials. EGFR-directed tyrosine kinase inhibitors (erlotinib, gefitinib) have shown efficacy in patients with advanced NSCLC previously treated with chemotherapy. In the first-line setting in advanced NSCLC, gefitinib administered until disease progression resulted in superior PFS compared to up to 6 cycles of carboplatin plus paclitaxel in patients with EGFR activating mutations. Erlotinib was also shown to improve PFS and survival when given as a maintenance therapy in selected patients with advanced NSCLC. Thus targeted therapies have resulted in clinically relevant improvements in the management of patients with advanced NSCLC. These improvements have to be seen in the context of both a difficult to treat disease and the high frequency of NSCLC. Targeted therapies active in advanced NSCLC also lend themselves for evaluation in earlier stages of NSCLC with the primary aim of cure. Future research will focus on the characterization of biomarkers for selection of those patients who benefit most, the optimal scheduling of targeted agents with chemotherapy, and the characterization of new targets. Targeted therapies eventually will allow an individualized therapy based on patient characteristics, molecular tumor features, convenient administration, costs and patient preference. In conclusion, targeted therapies have been shown to benefit patients with advanced NSCLC, have led to a better understanding of the biology of lung cancer, and will continue to stimulate both basic and clinical research.

Disclosure: R. Pirker: Honoraria for Consultant/Advisory Board: Merck Serono, Astra Zeneca, Roche, Eli Lilly Speaker's fee: Merck Serono, Astra Zeneca, Roche, Eli Lilly.

21IN
STAGE IV: TARGETED THERAPY AS FIRST LINE TREATMENT - NO

G.V. Scagliotti *Thoracic Oncology Unit, University of Turin, Orbassano/ITALY*

Targeted agents are extremely active to treat homogeneous cancer patient population which harbour a specific molecular abnormality or profile, or express a specific receptor or antigen. In advanced NSCLC phase III studies, collectively including more than 20.000 unselected patients, in which targeted therapies were added to platinum-based doublets, in the vast majority of these studies no progression-free (PFS) or overall survival (OS) improvement was observed. The anti-VEGF monoclonal antibody bevacizumab was the first targeted agent to prolong survival when added to a first-line doublet in advanced NSCLC. However grade ≥ 3 adverse events occurred at a significantly higher rate in the bevacizumab-containing arm including bleeding, hypertension and proteinuria. A total of 15 treatment-related deaths occurred in the bevacizumab/chemotherapy arm, including 5 from pulmonary hemorrhage. A second bevacizumab study demonstrated an improvement in response rate and progression-free survival (PFS) but no statistically significant improvement in OS. More recently in phase III studies a detrimental activity in squamous cell carcinoma of the lung of two VEGFR multiple tyrosine kinase inhibitors, sorafenib and motesanib, has been demonstrated when added to carboplatin and paclitaxel. The anti-EGFR monoclonal antibody cetuximab when added to cisplatin and vinorelbine and in maintenance after chemotherapy improved modestly OS but not PFS. Any attempt to identify through molecular markers or specific a molecular profile patients which can most benefit from bevacizumab and cetuximab have failed. Two papers reported about the use of EGFR-TKIs as first-line therapy in selected patients with advanced NSCLC. Both studies showed significant improvements in response rate and PFS in patients whose tumors had EGFR mutations. A Spanish group screened over two thousands patients for the presence of EGFR mutations, that were more frequent in females, adenocarcinomas and non-smoking patients. Patients who presented an EGFR mutation were treated with upfront erlotinib with median survival of 27 months but, more importantly, OS in EGFR mutated tumors did not vary if patients received EGFR-TKIs front- or second-line.

Disclosure: G.V. Scagliotti: honoraria from AstraZeneca, Eli Lilly, Sanofiaventis and Roche.

22IN
STAGE III: COMBINED TREATMENT - SEQUENTIAL

R. Dziadziuszko *Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND*

A combination of chemotherapy and radiation has become the standard management in locally advanced inoperable (stage III) non-small cell lung cancer (NSCLC). Available evidence indicates higher efficacy of concomitant versus sequential chemo-radiation. However, the magnitude of benefit is relatively modest (4.5% absolute survival benefit at five years) and achieved at the expense of increased toxicity, particularly acute esophagitis. Given large tumor bulk, frequent comorbid conditions and advanced age in a proportion of stage III patients, the choice of concomitant versus sequential treatment should be well balanced. Precise and uniformly adopted criteria of patient evaluation for either treatment strategy are lacking. Recent report indicates that approximately 60% of stage III NSCLC patients under the age of 75 would not be candidates for concurrent approach. These patients may clearly benefit from sequential treatment as compared to radiotherapy alone. Recent clinical trials exploring dose, fractionation, volume and technique of radiation delivery in stage III NSCLC will be discussed, with emphasis on choice of concurrent versus sequential chemoradiotherapy in the study designs. Issues of patient selection based on molecular predictive factors and incorporation of targeted therapies into treatment strategy are poorly studied and warrant more attention.

Disclosure: The author has declared no conflicts of interest.

23IN
STAGE III: COMBINED TREATMENT - CONCURRENT

D. De Ruysscher *Department of Radiation Oncology (Maastro Clinic), Maastricht University Medical Center + GROW Research Institute, Maastricht/NETHERLANDS*

After having established the superiority of induction chemotherapy followed by radiotherapy (RT) over RT alone, several randomized studies and two meta-analyses have clearly demonstrated a superior survival with concurrent chemo-radiation compared to sequential administration. The survival at 5 years increased from about 10 % with sequential chemo-radiation to approximately 15 % with the concurrent approach. This improved survival has been attributed to improved local tumour control (LC) without affecting distant metastases. This improved survival is at the expense of a higher incidence of severe, though reversible oesophagitis, occurring in 20-30 % of the patients for 3-6 weeks. No increased lung toxicity was observed. Also in concurrent chemo-radiation it is of utmost importance to avoid treatment delays. In a large series of the Radiation Therapy Oncology Group (RTOG), it was demonstrated that each day of treatment prolongation beyond about 6.5 weeks resulted in a 2 % decrease of survival. Concurrent chemotherapy and radiotherapy is only safe in patients with no or limited co-morbidities, who are relatively young and have adequate organ functions. In a prospective, population-based study, we could estimate that only about 40 % of the patients with stage III lung cancer are suitable for the concurrent approach. For the other, sequential chemotherapy and radiotherapy remains a reasonable alternative. Because of the still high local tumour recurrence rates in non-surgical series, patients with resectable N2 disease were randomized between surgery and definitive chemo-radiation after induction concurrent

chemo-radiation in the Lung Intergroup Trial 0139. Survival was similar in both arms, although local tumour progression was approximately reduced by 50 % by the addition of surgery. Ongoing research focuses on the integration of concurrent chemo-radiation with targeted agents, the possibility to deliver full-dose chemotherapy with radiotherapy, increasing the radiotherapy dose, patient selection to individualise therapy and the role of prophylactic cranial irradiation (PCI) to decrease the incidence of brain metastases.

Disclosure: The author has declared no conflicts of interest.

IMPLICATIONS OF THE NEW STAGING SYSTEM

24IN

HOW SHOULD WE USE T?

R. Rami-Porta *Thoracic Surgery, Hospital Mutua de Terrassa, Terrassa/SPAIN*

The seventh edition of the tumour, node and metastasis (TNM) classification for lung cancer introduced several changes in the T component: T1 is divided into T1a (2 cm or less in greatest dimension) and T1b (more than 2 but not more than 3 cm); T2 is divided into T2a (more than 3 but not more than 5 cm) and T2b (more than 5 but not more than 7 cm); T2 greater than 7 cm is reclassified as T3; T4 by additional nodule(s) in the same lobe of the primary tumour is reclassified as T3; and M1 by additional nodule(s) in another ipsilateral lobe is reclassified as T4. Malignant pleural effusion is now under the M1a category. Tumour size has much more relevance than it had in the previous editions. Five tumour-size groups with significantly different prognosis are defined in contrast to the previous two-size groups. Because tumour size has an important prognostic impact, its measurement is essential to classify the tumour correctly. Patients who are potential candidates for radical treatment have a computed tomography (CT) scan of the chest and upper abdomen. Tumour size is measured on the CT scan and the greatest dimension recorded. This is usually done on the two-dimension axial slices, but if the CT has software with possibilities for coronal and sagital reconstructions, the craneo-caudal size should be checked as it may be the greatest and the one that should count to determine tumour size. Atelectasis and pneumonitis that comprise less than the entire lung and reach the hilum are T2 descriptors, and if they comprise the entire lung, T3 descriptors. Tumour size is not easy to measure in these cases. Integrated CT and positron emission tomography (PET) is useful to differentiate tumour from collapsed lung, and may help to record the precise tumour size and the extent of atelectasis. Unless the endobronchial tumour is clearly visible on CT scan, distance from the carina is best determined at bronchoscopy. This is an important measurement performed during the clinical phase of staging, and it is likely to be the most reliable, because the pathologist will not be able to measure it unless the surgical specimen includes the carina, too. Within the possibilities of each multidisciplinary team, the most accurate and reliable methods should be applied in the clinical staging of lung cancer to determine the T component of the classification.

Disclosure: The author has declared no conflicts of interest.

25IN

MULTIPLE NODULES IN THE LUNGS

P.E. Postmus *Pulmonary Diseases 4a50, VU University Medical Center, Amsterdam/NETHERLANDS*

The revison of the classification of lung cancer – UICC 7 – has brought a number of changes for classifying patients with nodules in the lungs. Based on the large database of the IASLC it became clear that patients with a nodule or nodules in the same lobe as the primary tumor have a better prognosis that is better than of patients with T4 tumors (old classification) and more or less identical to patients with T3 tumors. Comparable changes were implemented for patients with a nodule or nodules in the same lung as the primary tumor but in a different lobe. These patients have a better prognosis than M1 (old classification) cases and behave more like T4 tumors. Furthermore of all patients with signs of metastases outside the affected lung the ones with nodules in the contralateral lung have a slightly better outcome than other case with M1 disease, therefore this group was split up in M1a and M1b. Staging of patients is especially useful for defining the prognosis of a case and can as such be of help in making clinical decisions on potential valuable treatments for the individual patient. As the UICC 7 classification is based on retrospective analysis of a large number of cases from all kinds of databases it was impossible to fine-tune this aspect of staging of lung cancer. For example it was impossible to differentiate between single and multiple nodules in the same or in the contralateral lung. In this session cases will be demonstrated with multiple nodules in the lung of lungs and potentially approaches will be discussed.

Disclosure: The author has declared no conflicts of interest.

26IN

STAGING OF SMALL CELL LUNG CANCER

F.A. Shepherd *Department of Medicine, Division of Medical Oncology and Hematology of the University Health Network, Princess Margaret Hospital and University of Toronto, Toronto/CANADA*

The first staging system for small cell lung cancer (SCLC), introduced by the Veterans' Administration Lung Study Group (VALSG) divided SCLC into two subgroups termed "Limited" and "Extensive" Disease. Limited Disease (LD) was characterized by tumors confined to one hemi-thorax, although local extension and ipsilateral, supra-clavicular nodes could also be present if they could be encompassed in the radiation field of the primary tumor. All other patients were classified as extensive disease (ED). In 1989, the International Association for the Study of Lung Cancer (IASLC) recommended that LD should be expanded to include patients with tumors limited to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal and ipsilateral and contralateral supra-clavicular nodes. They also recommended that patients with ipsilateral pleural effusion (cytology positive or negative) should be considered to have LD in the absence of extra-thoracic metastases. The TNM (tumor, node, metastasis) staging systems of the American Joint Committee on Cancer Staging (AJCC) and the Union Internationale Contre le Cancer (UICC) are also applicable to SCLC, but are used less frequently, particularly in the non-surgical setting. The IASLC database contained 12,620 eligible cases of small cell histology with TNM staging available for 8088 patients. Clinical staging: Increasing clinical T and N categories, using the 6th edition TNM system are associated with progressively lower survival. In the IASLC proposal for the 7th edition, the presence of a pleural effusion will be considered as M1 disease. In the SCLC database, the survival of LD patients with effusion (cytologically negative or positive) was intermediate between that of LD patients without effusion and ED patients, and the survival of LD patients with cytologically positive effusions was superior to that of ED patients ($p<0.0001$). Surgical Staging: Of the 12,620 eligible SCLC cases, 349 had undergone surgical resection and full pathologic TNM staging was available for 262 patients. Increasing T and N categories were associated with worsening survival. TNM classification: The proposals made by the IASLC for the 7th edition of the TNM staging system also appear to have relevance to SCLC. The Small Cell Lung Cancer Subcommittee of the IASLC Lung Cancer Staging Committee has recommended that TNM staging be applied in SCLC and that stratification by TNM stage be incorporated into clinical trials in Stage I-III SCLC. For prospective staging validation studies, more information must be collected to define the N category more clearly and to determine whether there is a difference in

prognosis for patients with cytology negative or positive pleural effusions and for patients with pericardial effusions.
Disclosure: The author has declared no conflicts of interest.

27IN

CONSEQUENCES OF THE NEW STAGING SYSTEM

J-P. Sculier *Soins Intensifs et Oncologie Thoracique, Institut Jules Bordet, Bruxelles/BELGIUM*

The new system proposed by the IASLC staging project has introduced multiple changes in the TNM classification of lung cancer, taking into account tumour size in the T descriptors, site of other lung nodules, introduction of a new M1a category and a better grouping of the TNM subsets, proposing a new thoracic lymph node map, extending its application to other histological type than non-small cell lung cancer (small cell lung cancer, carcinoid tumours). All those changes have practical operational and prognostic consequences. Operational consequences consist in a better approach of the therapeutic management of lung cancer patients with the following considerations. For stage I, whatever the histological type, the main treatment will be surgery; the role of adjuvant chemotherapy in non-small cell lung cancer remains to be defined. For stage II, treatment will be based on surgery and adjuvant cisplatin-based chemotherapy; in case of stage IIB by satellite nodule in the same lobe, the role of adjuvant chemotherapy has to be assessed. For stage III, treatment will be multimodal, combining, surgery, radiotherapy and/or chemotherapy; the new system does not allow selecting the therapeutic approach on the only basis of the TNM, particularly concerning thoracic irradiation; it requires a multidisciplinary discussion. The role of the new universal mediastinal lymph node map and the concept of nodal zones have to be validated. For stage IV, medical treatment (chemotherapy, biological agents) will be proposed; sites of metastases such as brain involvement have to be considered in some patients and, in the future, molecular tests such as EGFr mutations might be other important operational factors. In term of prognosis, the new staging system is applicable for all types of histology, including carcinoid tumours. In addition, non-anatomical prognostic factors have been validated in the very large series of cases provided by the data basis. Those are performance status, sex, age and histological subtype. Other potential useful factors are some routine biological tests and the SUVmax measured on the primary tumour on PET scan; they require prospective validation by adequate studies with multivariate models taking into account the other known independent prognostic factors.
Disclosure: The author has declared no conflicts of interest.

NOVEL THERAPEUTIC AGENTS

28IN

TARGETING THE M-PHASE: FOCUS ON PLK-1 AND AURORA B

F. Solca, D. Rudolph, U. Guertler *Department of Pharmacology, Boehringer-Ingelheim, RCV GmbH & Co KG, Vienna/AUSTRIA*

Tubulin-binding anti-mitotic agents (e.g. taxanes and vinca alkaloids) represent established treatment modalities in cancer therapy. Some of their limitations, in particular side effects such as neuropathy, are based on their effects on microtubule function in interphase cells. Non-structural components of the mitotic machinery, such as Aurora kinases or Polo-like kinase 1 (Plk1), which are exclusively expressed in dividing cells, are therefore considered to be attractive drug targets for cancer therapy. Plk1 regulates multiple steps in mitosis including centrosome maturation and separation, bipolar spindle formation and cytokinesis. Inhibition of Plk1 leads to the formation of monopolar spindles, prolonged mitotic arrest in prometaphase followed by apoptotic cell death due to activation of the spindle assembly checkpoint (SAC), a mitotic checkpoint that delays the onset of anaphase until all chromosomes have attached to a bipolar spindle and are ready for segregation. BI 6727 is a potent and selective Plk1 inhibitor (IC_{50} = 0.8 nM). It inhibits proliferation of a broad panel of cancer cell lines irrespective of their oncogenome signature (EC_{50} = 11-37 nM) and shows excellent anti-tumor activity in multiple xenograft models of human cancer. Its distinct pharmacokinetic profile characterized by a high volume of distribution and a long terminal half-life indicates sustained tissue exposure. BI 6727 is currently in Phase II clinical trials. While Plk1 inhibitors, Aurora A inhibitors as well as tubulin binders lead to activation of the SAC, Aurora B inhibitors have a distinct mode of action. Inactivation of Aurora B abrogates the SAC and causes premature mitotic exit without cytokinesis, resulting in polyploid cells that eventually stop further DNA replication. BI 811283, a potent inhibitor of Aurora B kinase (IC_{50} = 9 nM), blocks proliferation in various human cancer cell lines (EC_{50} = 2-14 nM) and induces the characteristic polyploid phenotype. Hallmarks of senescence as well as a slow onset of apoptosis in a small fraction of cells have been observed. Excellent in vivo activity of BI 811283 has been demonstrated in multiple cancer xenograft models in nude mice. Phase I clinical trials with this inhibitor are currently ongoing.
Disclosure: F. Solca: Boehringer Ingelheim employee; D. Rudolph: Boehringer Ingelheim employee; U. Guertler: Boehringer Ingelheim employee

29IN

GLI INHIBITORS/HEDGEHOG PATHWAY INHIBITORS

D. Jablons *Thoracic Surgery, UCSF Helen Diller Family, San Francisco/USA*

Hedgehog (Hh) and Wnt signaling pathways play key roles during embryonic development and postembryonic stem cell regulation. Aberrant activation of Hh and Wnt signaling is thought to arm normal stem cells with proliferative and anti-apoptotic armor, setting the stage for carcinogenesis with its hallmark of destructive processes: invasion, progression and distant micrometastatic spread. Targeted inhibition of aberrantly activated Hh signaling may lead to the suppression or killing of cancer stem cells awakened from biological dormancy by aberrant Hh activation and propelled forward by deranged Hh signaling. Targeted inhibition at cell membrane level of Hh pathway has shown promising preclinical and clinical anti-cancer activity in basal-cell carcinoma (BCC) and medulloblastoma suggesting its potential clinical applications in the treatment of multiple cancers through possible suppression of cancer stem cells. However, recent reports about noncanonical Gli activation through alternative pathways such as RAS or TGFβ suggest the potential importance of Gli function as a therapeutic target. We hypothesize that blockade of Gli function results in inhibition of Hh pathway downstream activity, which in turn halt the proliferation of Gli-activated cancer cells. We screened a set of compounds based on their ability to interfere the Gli dependent transcription activity in an in vitro system. We demonstrate that the identified hit compound efficiently inhibits Gli dependent transcription activity. More importantly, the hit compound suppressed cancer cell proliferation in a Gli-dependent manner compared to the less effectiveness of upstream Hh inhibitor cyclopamine in such situations in vitro and inhibited tumor growth in vivo, suggesting a more effective cancer therapeutic strategy of blocking Gli function, a key control point of downstream oncogenic pathway activation.
Disclosure: The author has declared no conflicts of interest.

30IN
FORETINIB: A MULTIKINASE AXL/MET INHIBITOR

L. Liu *Translational Research, GlaxoSmithKline, King of Prussia/USA*

MET and AXL are membrane-bound receptor tyrosine kinases (RTKs), whose frequent deregulation in human cancer is associated with poor prognosis and an aggressive cancer phenotype. Activation of MET promotes cellular proliferation, migration and invasion and confers resistance to HER-targeted agents in a subset of tumors including lung and breast. Foretinib (GSK1363089) is an RTK inhibitor with potent activity (IC_{50} values ≤8 nM) against MET, AXL and VEGFR2 that is currently in phase I/II clinical trials for gastric, papillary renal and hepatocellular carcinomas. Foretinib demonstrated potent antitumor activity in MET-amplified tumor lines and tumor xenograft models. In MET amplified MKN45 gastric tumor cells and xenografts, foretinib inhibited phosphorylation of MET and suppressed phosphorylation of AKT and ERK in a dose-dependent manner. Foretinib alters expression of genes involved in RTK cross-talk, PI3K and MAPK signaling, cell motility and survival both in vitro and in vivo, and exhibits a gene expression profile similar to that of a MET-selective inhibitor. In addition, HER1/2 amplified tumor cell lines with MET-amplification or over-expression that were resistant to HER-targeted agents lapatinib and erlotinib were sensitive to combination therapy with either of these agents and foretinib. AXL contains a kinase domain closely related to MET and an extracellular domain resembling that of neural cell adhesion molecules. AXL overexpression is associated with poor prognosis and increased invasiveness of breast, lung, ovarian, renal, glioma and other cancers. Foretinib potently inhibited AXL phosphorylation and restored lapatinib and trastuzumab sensitivity in multiple HER2-positive, ER-positive breast cancer cell lines overexpressing AXL. Furthermore, treatment of these cells with siRNA to AXL or HER2 restored sensitivity to lapatinib or foretinib, respectively, suggesting cross-talk between AXL and HER2. These data demonstrate that foretinib is a potent inhibitor of MET and AXL that may be an effective therapy for cancers with MET and/or AXL overexpression. Additional clinical studies of foretinib as a single agent and in combination with lapatinib and erlotinib are warranted.

Disclosure: L. Liu: The author is a stock holder and employee of GlaxoSmithKline

31IN
TARGETING ALK-REARRANGED NON-SMALL CELL LUNG CARCINOMA

A.J. Iafrate[1], E. Kwak[2], Y. Bang[3], B. Solomon[4], A. Shaw[2], D.R. Camidge[5], S.H. Ou[6], R. Maki[7], R. Salgia[8], J. Clark[2] *[1]Department of Pathology, Massachusetts General Hospital, Boston/USA, [2]Cancer Center, Massachusetts General Hospital, Boston/USA, [3]Internal Medicine, Seoul National University Hospital, Seoul/KOREA, [4]Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne/AUSTRALIA, [5]Medical Oncology, University of Colorado Health Sciences Center, Denver/USA, [6]Medicine-Hematology/Oncology, Chao Family Comprehensive Cancer Center, UC Irvine Medical Center, Orange/USA, [7]Medicine, Memorial Sloan Kettering Cancer Center, New York/USA, [8]Medicine, University of Chicago, Chicago/USA*

Rearrangement of the ALK gene has recently been described in a subset of non-small cell lung carcinoma (NSCLC), resulting in oncogenic fusion genes most commonly partnering with the EML4 gene. ALK-positive cases possess a distinct profile, with the majority of cases occurring in never or light smokers, and being associated with a younger age (median age 55 vs. 65 in ALK-negative cases), and associated with distinct histologic characteristics, including signet ring cell morphology in many cases. The overall prevalence of ALK-positive cases is approximately 4%, but is significantly higher in populations enriched in younger non-smoking patients. Rejecting both KRAS and EGFR-mutant cases, which appear mutually exclusive of ALK-positivity, allows further enrichment of ALK-positive cases.

The effectiveness of targeting ALK in these patients has been tested in a phase I trial of PF-02341066, a small molecule inhibitor of the ALK and MET receptor tyrosine kinases. Prospective screening of NSCLC samples with an ALK FISH break-apart probe has allowed the enrollment of a molecularly defined cohort, treated at the recommended Phase 2 dose (orally at 250mg BID). Clinical responses were determined using RECIST with radiographic studies repeated every 8 weeks. Approximately 1,000 NSCLC patients have been screened to identify >70 ALK-positives. With few exceptions, patients had adenocarcinoma histology and were never or former smokers. The median number of prior lines of therapy was 3 (range, 0-7). To date, the response rate (complete + partial responses) is approximately 65%; the median progression-free survival has not been reached. Radiological responses typically were observed at the first or second restaging CT scan.

Based on the promising results of this trial, a Phase 3 study has been initiated with PF-02341066 in ALK-positive cases. Prospective identification of molecularly defined cohorts can be achieved in the setting of a phase 1 clinical trial, and thereby expedite the development of targeted cancer therapies.

Disclosure: J. Iafrate: I have been a paid consultant to Pfizer in the development of companion diagnostics for PF-02341066 (<$10,000). I have been a member of the Pfizer advisory board in the development of PF-02341066; B. Solomon: Research funding to laboratory to study ALK in NSCLC from Pfizer; All other authors have declared no conflicts of interest.

EARLY NSCLC STAGE I/II: STATE-OF-THE-ART

32IN
HOW TO MANAGE STAGE I DISEASE

P. Van Houtte *Department of Radio-oncology, Institut Jules Bordet, Brussels/BELGIUM*

Surgery is considered to be the cornerstone in treating patients with stage I NSCLC. Indeed, a lobectomy or an anatomical segmentectomy in selected cases coupled with a lymph node dissection is considered to be the reference. Nevertheless, stage I NSCLCL is a more complex issue: there is a wide range of clinical situation related to the tumor extent, size or location and the patient co morbidities. Today, there are several alternatives to surgery for occult lung cancer: cryosurgery, endoluminal brachytherapy or phototherapy. For larger tumors, stereotactic body radiotherapy (SBRT) or radiofrequency are two modalities challenging surgery for high-risk patients. What are their advantages and drawbacks? Surgery allows having a pathological diagnose and may include a lymph node dissection; its limit is mainly related to the patient physiological status. A wedge resection is less optimal with a higher rate of local relapse. Radiofrequency is an invasive procedure with the risk of pneumothorax. SBFRT has the advantage to be a non-invasive approach. Tumor location and size are the limits of SBRT and radiofrequency (not to close to the mediastinal structures). Two arguments often presented against SBRT is the absence of histological diagnosis and nodal sampling. In the PET-CT era, the rate of positive nodes is less than 10% in the absence of mediastinal uptake; the number of isolated nodal relapse is relatively low in the different published series confirming the observation of conventional external radiotherapy with limited field. In the absence of tissue confirmation, there is a risk treating benign disease but using strict criteria, positive PET-CT, history of tobacco smoking, successive CT enlargement, this probability is very low and the outcome of patients with or without tissue diagnosis is very similar in the different published series. The current data for the different modalities yields very similar results but we must be aware of the limitations of many reported series: short follow-up, wide varieties of cases (recurrent disease, primary tumor, second primary and even metastatic

deposit). In the absence of phase III trials, treatment decision should be individualized base taking into account patient condition, tumor location and the local expertise.
Disclosure: The author has declared no conflicts of interest.

33IN
HOW IMPORTANT IS LYMPH NODE DISSECTION IN STAGE I AND II?

P. De Leyn *Department of Thoracic Surgery, University Hospital Leuven, Leuven/BELGIUM*

Accurate staging in patients with non-small cell lung cancer (NSCLC) is critical since it provides prognostic information and guides the choice of treatments. There are international followed guidelines on preoperative lymph node (LN) staging. However, it is remarkable how much variability there exists in intra-operative LN evaluation. For intra-operative LN evaluation different techniques are used, ranging from simple visual inspection of the unopened mediastinum to an extended bilateral LN dissection. In 2006, the European Society of Thoracic Surgeons made guidelines on intraoperative lymph node staging for NSCLC (Lardinois, 2006). For complete resection of NSCLC, a systematic nodal dissection (SND) is recommended in all cases. The mediastinal, hilar and (in case of lobectomy or segmentectomy) interlobar LNs are dissected and put in different vials with separate labeling. The highest removed mediastinal LN should be identified. Despite the systematic use of PET-CT and invasive techniques as indicated by recent guidelines (De Leyn, 2008) systematic nodal dissection will detect positive N1 and N2 nodes in 19% of patients with clinical stage I NSCLC (Cerfolio, 2009). It remains unclear whether SND on itself improves survival. In a meta-analysis, mediastinal LN dissection was associated with improved survival (pooled hazard ratio 0.78 [confidence interval: 0.65 to 0.93]) compared to nodal sampling in patients undergoing resection for early stage I-IIIA NSCLC (Wright, 2006). A subgroup analysis by stage was not conducted due to the possibility of stage migration in the complete mediastinal LN dissection group (Will Rogers phenomenon). A recent meta-analysis on the use of adjuvant chemotherapy after complete resection of NSCLC showed clear benefit in patients with N1 and N2-disease. So, by performing SND, more patients will be accurately staged and treated. Nowadays, VATS lobectomy combined with SND is performed for early stage NSCLC.
Conclusion: SND is important in stage I – II NSCLC. A meta-analysis showed better survival over nodal sampling. Moreover, SND refines staging allowing identification of patients that will benefit from adjuvant chemotherapy. The beneficial role of SND is not available with other local therapies such as radiofrequency ablation or stereotactic radiotherapy.
Disclosure: The author has declared no conflicts of interest.

34IN
NEOADJUVANT VERSUS ADJUVANT CHEMOTHERAPY

E. Felip, P. Martínez *Medical Oncology, Vall d'Hebron University Hospital, Barcelona/SPAIN*

Approximately one-third of NSCLC patients are diagnosed with early-stage disease. For these patients surgery is the most effective treatment. However, a high percentage of patients relapse and die of their disease. Adjuvant platinum-based chemotherapy is now standard treatment in completely resected patients with stage II and III, with a 5-year absolute survival benefit of approximately 5%. The role of neoadjuvant chemotherapy remains unclear in early-stage disease. Several trials have assessed the use of neoadjuvant chemotherapy, but none of these trials were conclusive to demonstrate a benefit in survival. In a systematic review, which included 1,507 patients randomized to neoadjuvant chemotherapy or surgery alone, there was a trend to improve survival with neoadjuvant chemotherapy in a range of benefit similar to adjuvant approach. The NATCH trial is a phase 3 randomized, multicenter trial which compares surgery alone (S arm), or 3 cycles of neoadjuvant carboplatin/paclitaxel followed by surgery (Neo arm), or surgery followed by the same chemotherapy regimen (Adj arm). This trial is the first to have Adj and Neo chemotherapy arms in its design, and to allocate patients to the Adj arm before surgery. Eligible patients had to have clinical stage IA with tumor size>2 cm, IB, II or T3N1 NSCLC considered resectable by the attending thoracic surgeon. The primary end point was DFS. A total of 624 patients were randomized (S=212, Neo=201 and Adj=211 patients); 75% of patients had clinical stage I. Only 66% of the patients allocated to Adj arm received the planned treatment as compared to 97% of the patients in the Neo arm. Patients in the Neo arm had a non-significant trend toward longer DFS than those assigned to S arm (5-year DFS 38.3% vs. 34.1%; HR 0.92; P=0.176). Five-year DFS rates were 36.6% in the Adj arm vs. 34.1% in the S arm (HR 0.96; P=0.74). Median OS was 48.8, 55.2 and 50.3 months for S, Neo and Adj arms, respectively. In summary, in clinically-staged resectable NSCLC, more patients are able to receive neoadjuvant than adjuvant chemotherapy. The NATCH trial was not powered to address the benefit of adjuvant chemotherapy in resected patients. In the trial neoadjuvant chemotherapy yields a trend toward improved disease-free survival when compared to surgery alone.
Disclosure: All authors have declared no conflicts of interest.

35IN
FITNESS FOR RADICAL TREATMENT. ERS-ESTS GUIDELINES

A. Charloux *Service de Physiologie et d'Explorations Fonctionnelles, NHC, University Hospital of Strasbourg, Nouvel Hopital Civil BP 426, Strasbourg/ FRANCE*

The objective of the task force was to develop up-to-date clinical guidelines on fitness for surgery and chemo-radiotherapy. Evidence supporting each recommendation was graded according to the Scottish Intercollegiate Guidelines Network Grading Review Group. Regarding the preoperative evaluation of the lung resection candidate, all available information was integrated in a functional algorithm (Eur Respir J 2009; 34: 17–41). The first step is a cardiologic assessment based on validated index estimates of patient's risk. Patients at low cardiologic risk or with an optimized cardiologic treatment could proceed with pulmonary evaluation. Spirometry and diffusion capacity of the lung for carbon monoxide (DLCO) assessment is recommended in all patients. All patients with either forced expiratory volume in one second (FEV1) or DLCO or both below 80% of predicted should ideally undergo a formal cardiopulmonary exercise test (CPET) with peak oxygen consumption (VO2) measurement. However, since many centres may have logistic problems in systematically performing this test, a low-technology exercise test, preferentially stair climbing test (or shuttle walk test) may be used as a screening test. Patients showing low performance at these tests should perform a formal CPET. Patients with peakVO2 lower than 35% of predicted value or 10 ml/kg/min and those with predicted post-operative (ppo) FEV1 or ppoDLCO or both lower than 30% of predicted values in association with ppoVO2peak lower than 35% of predicted value or 10 ml/kg/min are regarded at prohibitive risk for major lung resection (lobectomy or pneumonectomy) and other therapeutic options should be considered. The ppo values calculation is based on the number of segments to be resected before lobectomy, and on scintigraphic or quantitative CT studies before pneumonectomy. After a careful selection based on cardiac and pulmonary parameters, patients unable to perform exercise tests should be regarded as high-risk patients and monitored in advanced care management setting. Contrary to lung resection, we were unable to recommend any specific test, cut-off value, or algorithm before radiochemotherapy due to the lack of data.
Disclosure: The author has declared no conflicts of interest.

EARLY NSCLC STAGE I/II: INVITED PAPERS

36IN
BIOLOGICAL MARKERS FOR SELECTING PATIENTS FOR CHEMOTHERAPY

No abstract received at time of going to press.

37IN
HOW FAR CAN WE MINIMISE SURGERY FOR STAGE I?

H. Asamura *Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo/JAPAN*

The history of lung cancer surgery is that of "down-sizing" of the extent of pulmonary parenchyma which are to be removed together with a primary lung cancer lesion. The evolution of lung cancer surgery has been well described with several important surgical epochs. These included the first successful pneumonectomy by Graham at the Barnes Hospital in St. Louis, the concept of "radical pneumonectomy" [1] and "radical lobectomy" [2] by Cahan at the Memorial Hospital in New York, and the randomized, phase III study comparing the surgical outcome of lobectomy and sublobar resections by North American Lung Cancer Study Group [3]. Through these, lobectomy with lymph node sampling/dissection has been respected as the present-day gold standard for the resection of lung cancer. The randomized study by North American Lung Cancer Study Group is the only one randomized study in the thoracic surgical community that directly compared the prognosis and postoperative pulmonary function between lobectomy and sublobar resections for patients with T1N0M0 lung cancer less than 3 cm in diameter. The results of the study showed that the prognosis of patients undergoing sublobar resection was significantly worse than those undergoing lobectomy, and the local recurrence rate for sublobar resection was also three times higher. Although the following retrospective studies have suggested at least the equivalent outcome after sublobar resection, there has been no definitive demonstration of non-inferiority of sublobar resections by a fair, non-biased, randomized study. On the other hand, owing to the advent of refined chest CT images with higher resolution and CT screening programs, smaller lung cancers are being encountered in our practice more frequently [4, 5]. Furthermore, the preoperative work-up for the surgical candidates has been sophisticated together with new technologies such as PET scan. In these situations, we have become able to deal with patients with the "true" early stage lung cancers, and therefore, the clinical significance and importance of sublobar resection need to be revised by definitive clinical trials. For these reasons, two large scaled studies are underway across the ocean in US and Japan. Both studies are targeting peripheral lung cancers less than 2 cm in diameter without nodal involvement, and the accrual of more than 1,000 patients is planned with primary endpoint of over-all survival and secondary endpoint of postoperative pulmonary function. The future international/regional collaboration must be encouraged to draw meaningful conclusions from these studies. The down-sizing of the extent of lymph node dissection is another aspect of the issues in minimizing the lung cancer surgery. The extent of the lymph node dissection generally has included the ipsilateral pulmonary hilum and mediastinum. However, the recent studies have suggested that the more efficient dissection could be achieved according to the location of the primary tumor [6]. According to the definition by ESTS (European Society of Thoracic Surgeons), such selective lymph node dissection is called as "lobe-specific systematic node dissection", where it reads "The mediastinal tissue containing specific lymph node stations are excised, depending on the lobar location of the primary tumor" [7]. The future studies should focusing upon more precise demonstration and larger accumulation of the evidence that indicate the prognostic equivalence between lobectomy and sublobar resection as well as between systematic and lobe-specific lymph node dissection for lung cancer.

REFERENCES

1. Cahan WG, Watson WL, Pool JL. Radical pneumonectomy. *J Thorac Surg* 1951;22:449–73.
2. Cahan WG. Radical lobectomy. *J Thorac Cardiovasc Surg* 1960;5:555–72.
3. Lung Cancer Study Group, Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. *Ann Thorac Surg* 1995;60:615–23.
4. Adler B, Padley S, Miller RR, Muler NL. High-resolution CT of bronchioloalveolar carcinoma. *Am J Radiol* 1992;159:275–7.
5. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, Kondo H, Shimosato Y. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995; 75:2844–52.
6. Asamura H, et al. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas based on a retrospective study of metastasis and prognosis. *J Thorac Cardiovasc Surg* 1999; 117:1102–11.
7. Lardinois D, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardio-Thorac Surg* 2006;30:787–92.

Disclosure: The author has declared no conflicts of interest.

38IN
STEREOTACTIC RADIOTHERAPY: THE NEW STANDARD?

B.J. Slotman[1], F.J. Lagerwaard[2], C.J.A. Haasbeek[3], S. Senan[4] *[1]Department of Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS, [2]Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS, [3]Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS, [4]Department of Radiation Oncology, VU University Medical Centre, Amsterdam/NETHERLANDS*

Background: Based on our experience with stereotactic radiotherapy (SRT) in >600 treated NSCLC pts, the role of SRT as the preferred treatment in inoperable pts and as an alternative treatment for operable pts will be discussed.
Methods: This analysis pertains to 457 Stage I NSCLC pts, referred from 70 Dutch centers, treated between 2003 and 2009. Pts treated for double or recurrent tumors were excluded. Evaluations before and regularly after SRT included CT-scans and QoL evaluation. There were 287 T1N0 (63%) and 170 T2N0 (37%) tumors. Mean age was 73 years. All underwent ^{18}FDG-PET staging; 85% of pts were medically inoperable and 15% refused surgery. Pathological confirmation of malignancy was obtained in 35% of pts. All others had new and/or growing FDG-PET-positive lesions and CT-characteristics of malignancy. The following risk-adapted SRT schemes were used: 3x20 Gy (n=186;41%) for T1 tumors, 5x12 Gy (n=195;43%) for T1 tumors adjacent to the thoracic wall/mediastinum or T2 tumors, and 8x7.5 Gy (n=76;17%) for lesions adjacent to the pericardium or hilus.
Results: Median survival was 36 months (95% CI 30-42). Local failure was seen in 13 pts (2.8%), resulting in an actuarial local failure-free survival rate of 91.6% at 3 yrs. Regional recurrences occurred in 31 pts (6.8%). Actuarial regional-free survival at 3 yrs was 87.4%. Fifty-eight pts (12.7%) developed distant metastases. Actuarial distant failure free survival was 75.6% at 3 yrs. Survival and failure rates were not different in pts with or without histological confirmation of malignancy (p=0.37). On multivariate analysis, survival was correlated with pre-SRT performance score (p=0.01), lung function (p=0.03) and Charlson comorbidity score (p=0.02). Treatment was well tolerated, with fatigue (27%) being the most frequent early side effect, followed by dyspnea, cough, nausea and chest wall pain (each 5%). Late toxicity included chronic chest wall pain in 12 pts (3%), G≥3 radiation pneumonitis in 10 pts (2%), and rib fractures in 4 pts (1%).
Conclusions: SRT results in high control rates with acceptable toxicity. It has become the new standard of care for inoperable Stage I NSCLC pts. SRT should be discussed as an alternative to surgery, particularly as pts with an increased risk of surgical mortality can now be identified.
Disclosure: B.J. Slotman: Research funding from Varian medical systems; All other authors have declared no conflicts of interest.

39IN
HOW CLOSE ARE WE TO CUSTOMIZING CHEMOTHERAPY IN EARLY NSCLC?

J. Souglakos *Department of Medical Onoclogy, University General Hospital of Heraklion, Heraklion/GREECE*

Surgery alone is considered as the standard of care for patients with operable non–small-cell lung cancer (NSCLC). However, despite complete resection, 5-year survival rates have been disappointing, since one half of the patients will develop relapse and die from the disease. Cisplatin-based adjuvant chemotherapy offers a relatively small but statistical significant reduction in risk of death (approximately 4%) at 5 years. The disappointing results of long-term survival among patients with non-small cell lung cancer (NSCLC) may reflect the lack of knowledge of the ways in which molecular abnormalities of neoplastic cells affect responsiveness to anticancer therapy. For example, resistance to platinum compounds occurs partially because of detoxification or efficient repair of damaged DNA by the numerous members of the nucleotide excision repair (NER) system, including the endonuclease excision repair cross-complementing 1 (ERCC1). Clinical studies have demonstrated that response and survival of patients with advanced NSCLC improved in the presence of low ERCC1 expression. Moreover, data suggest that polymorphisms of ERCC1 Asn118Asn (C_T), ERCC2 Lys751Gln (A_C), and Asp 312Asn (G_A) may be associated with clinical outcome. Other trials suggest that specific genetic signatures are associated with prognosis in early-stage NSCLC. For example, three-gene signature (CSF1, EGFR, and CA IX) was associated with prognosis in early-stage squamous cell carcinoma, while a four-gene model based on expression of WNT3a, ERBB3, LCK, andRND3 could discriminate patients with poor prognosis lung adenocarcinomas.

Moreover, the identification of specific pathways which provide survival advantage or increased metastatic potential could help in the customization of treatment for patients with early stages NSCLC. For example, LKB1 inactivation in tumors with KRAS mutations leads to increase metastatic potential, in vitro studies. LKB1 inactivation is one of the most common genetic events in NSCLC and its significance in correlation with the KRAS mutations have never been studies in clinical samples. Overall, the remarkable advances in the understanding of NSCLC biology have not yet been translated into real benefit for patients with operable NSCLC.

Disclosure: The author has declared no conflicts of interest.

WORKSHOP: PATHOLOGY, BIOLOGY AND TRANSLATIONAL RESEARCH

40IN
EGFR MUTATIONS: CURRENT STATUS

R. Rosell[1], M. Taron[1], T. Morán[2], M.A. Molina[3], C. Costa[3], S. Benlloch[3], B. Massuti[4] *[1]Medical Oncology Service, Catalan Institute of Oncology, Badalona/SPAIN, [2]Oncology Service, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Barcelona/SPAIN, [3]Medical Oncology Service, USP Dexeus University Institute, Barcelona/SPAIN, [4]Oncology Service, Hospital General de Alicante, Alicante/SPAIN*

Non-small-cell lung cancer (NSCLC) driven by EGFR mutations occurs predominantly in never-smokers, women and non-squamous cell histologies. In the European population, the overall frequency of EGFR mutations is 15-17%; however, this can reach 40% in never-smokers, compared to 10% in former smokers and 5% in current smokers. In females, the probability of finding mutations is 30%, compared to 10% in males. The predominant histological subtype of adenocarcinoma could have some influence on the frequency of EGFR mutations although more clinical data is needed. A large prospective study in patients with EGFR mutations showed that response to erlotinib was 70%, progression free survival was 14 months, and median survival was 27 months. Acquired resistance has been related to the presence of the EGFR T790M mutation, and specific inhibitors of the T790M mutation are promising. Additionally, the overexpression of MET has been reported to be relevant. The detection of T790M is a technical issue that can be solved with an adequate laboratory assay. We have detected EGFR double mutations (T790M plus deletions or L858R) in 35% of pretreatment biopsies from 129 NSCLC patients and observed a negative correlation with progression free survival to erlotinib. The baseline gene expression of other receptor tyrosine kinases, such as MET, AXL, IGF-1R and IL-6 did not influence erlotinib outcomes. Erlotinib can cause double-strand breaks that are repaired mainly by homologous recombination. In experimental models, erlotinib sensitivity is highly influenced by BRCA1 status. In our experience, low levels of BRCA1 mRNA can prolong progression free survival to 27 months. In the multivariate analysis of progression free survival, only T790M, BRCA1 and PP2A/C were independent prognostic markers. In the multivariate analysis of survival, only T790M and BRCA1 were identified as independent markers. Based on our findings, we do not believe that T790M is the main cause of acquired resistance. Rather, we speculate that the amplification of the pathway of H2AX/RNF8/RNF168/RAP80/BRCA1 could be a main cause of resistance to protracted treatment with erlotinib. At present, we are investigating the role of BRCA1 SUMOylation and sensitivity to erlotinib.

Disclosure: All authors have declared no conflicts of interest.

41IN
EGFR FISH: CURRENT STATUS

I.I. Wistuba *Departments of Pathology and Thoracic/Head and Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston/USA*

Molecular classification directing personalized treatment of NSCLC will be essential to achieve meaningful improvements in patient outcomes. Strategies for patient selection using molecular diagnostic tests have the potential to increase the efficacy of molecular targeted therapy by optimizing and monitoring response to treatment. EGFR tyrosine kinase inhibitors (TKIs) have been demonstrated to significantly improve survival of NSCLC patients compared to best supportive care. Mutations and increased gene copy number of the EGFR gene have been associated with favorable response to EGFR-TKIs in NSCLC. While testing for EGFR mutations is being widely used as predictor of response and progression-free survival in NSCLC patients treated with EGFR TKI therapy, the molecular analysis of EGFR copy number using fluorescent in situ hybridization (FISH) methodology is still restricted to clinical trials. EGFR increased copy number by FISH (high polysomy and gene amplification) using the criteria developed by the University of Colorado Cancer Center, US, has demonstrated favorable survival outcomes after EGFR-TKI therapy in some clinical trials (i.e., BR.21 and ISEL), while it has demonstrated no improved benefit in survival with similar treatment in others (i.e., INVITE, INTEREST and TRIBUTE). This variability could be the result of multiple factors, including cross-study difference (i.e., patient population and trial design) as well as differences in the methodology used by the various laboratories for performing and interpreting the EGFR FISH assay. This assay has multiple technical challenges at pre-analytical (sample collection and processing) and analytical (hybridization technique and scoring of probe signals) levels which may lead to different interpretations of the results. Therefore, in order to prospectively validate the clinical usefulness of EGFR FISH assay as a predictor of outcome in EGFR-TKI treated NSCLC patients, studies will need very highly standardized FISH testing procedures. Finally, the complex biology of NSCLC, especially in the advanced stage, poses additional difficulties for an in situ genomic test, including among others, tumor heterogeneity, differences between primary tumors and metastases, and potential differences between chemotherapy naïve and treated tumors.

Disclosure: The author has declared no conflicts of interest.

42IN
KRAS AND OTHER MUTATIONS: CURRENT STATUS

W. Pao *Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Nashville/USA*

Treatment decisions for patients with lung cancer have historically been based upon tumor histology. However, with the emergence of new targeted agents, information about the molecular composition of tumors has become increasingly important. Here, we will review current knowledge about molecular subsets of non-small cell lung cancer that could have direct clinical relevance vis-à-vis targeted therapies. Subsets are defined by 'driver mutations' in EGFR, ALK, HER2, BRAF, KRAS, PIK3CA, AKT1, and MEK1. Treatment tailored according to the genetic makeup of individual tumors involves a paradigm shift but hopefully will lead to substantial therapeutic improvements.

Disclosure: W. Pao: Consultancy: MolecularMD, AstraZeneca, Bristol-Myers Squibb, Symphony Evolution Research funding: Exelixis, SGX Pharmaceuticals Patent: EGFR T790M testing

43IN
MOLECULAR AND PROTEOMIC ANALYSES OF SERUM

P.C. Mack *Department of Internal Medicine Hematology/Oncology, University of California, Davis Campus, Sacramento/USA*

In advanced NSCLC, routine detection of biomarkers predictive of response to therapy has proven highly challenging. Impediments to accurate detection include: limited availability of tumor specimens for correlative analysis; tumor heterogeneity and formalin-induced DNA artifacts. Fresh tissue is rarely acquired from patients presenting with metastatic NSCLC. Archival specimens, while sufficient for pathological diagnosis, are often too minimal for additional correlative studies. These limitations are not applicable to analysis of patient plasma or sera. Baseline blood specimens are available from essentially all consenting patients, and on-treatment or post-treatment draws are often obtainable. Collection of patient plasma is easily standardized, limiting variability from handling, and can be stored frozen in aliquots. Investigations into the clinical utility of blood-based tumor markers are ongoing on a number of fronts. Proteomic analysis of serum, such as those presented by Taguschi et al (JNCI, 2007), suggest that MALDI-TOF mass spectrometry can be used to generate profiles for selection of patients likely to benefit from EGFR tyrosine kinase inhibitors. This algorithm is currently being evaluated in the Southwest Oncology Group (SWOG) trial S0709: "A Phase II Selection Design of Carboplatin/Paclitaxel/Erlotinib or Erlotinib Alone in Advanced Non-Small Cell Lung Cancer (NSCLC) Patients with Performance Status 2 (PS 2) Selected by Serum Proteomics" to enrich for patients with serum profiles associated with clinical benefit. Shed tumor DNA in peripheral circulation is another potential source of predictive information. Studies using highly sensitive mutation detection techniques have identified the presence of KRAS and EGFR mutations in shed tumor DNA from NSCLC patients. We have recently demonstrated that the presence of EGFR mutations in plasma can predict significantly improved tumor response rates and progression-free survival (Mack et al JTO 2009). Multiplex profiling of plasma or serum cytokines, ligands, growth factors, soluble receptors and angiogenic factors may also yield prognostic, predictive or pharmacodynamic information with clinical utility.

Disclosure: P.C. Mack: Speaker honorarium DxS LTD

EARLY NSCLC CONTROVERSIAL ISSUES

44IN
NEW TRIALS IN EARLY DISEASE COMPARING SURGERY AND RADIATION

F.J. Lagerwaard *Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS*

Surgery has long been the undisputed treatment of choice in patients presenting with Stage I non-small cell lung cancer (NSCLC), while radiotherapy has been reserved for medically inoperable patients or those refusing surgery. Stereotactic radiotherapy (SRT), which is characterized by the use of ablative doses of radiation typically delivered in 3-5 fractions, achieves local control rates in excess of 90% for patients with stage IA peripheral tumors. Despite the very high radiation doses used, major toxicity is limited to approximately 5% of patients who were treated for peripheral tumors. Despite the lack of randomized data comparing conventionally fractionated radiotherapy with SRT, a majority of members of the European Society for Therapeutic Radiology and Oncology now consider SRT to be their treatment of choice for patients with inoperable stage I NSCLC [Widder J, pESTRO 2008]. The growing interest in evaluating SRT in patients fit to undergo surgery has generated controversy in some quarters. An excellent outcome was reported after SRT in a cohort of operable patients [Onishi 2007], and has prompted the initiation of phase II trials in this subset of operable patients. The results of the Japanese Clinical Oncology group 0403 trial, where accrual has already been completed, and the RTOG study 0618 in operable patients are awaited. However, an open discussion on choice of treatment can only take place after a randomized comparison. Two such prospective phase III trials comparing SRT with surgery for Stage IA NSCLC cancer are currently ongoing: the randomized Dutch ROSEL trial and the international STARS (Stereotactic Radiosurgery vs. Surgery) trial. Although both trials are broadly supported by the thoracic oncology community, patient accrual has thus far been slow. Some of the challenges facing these prospective trials will be discussed during the meeting.

Disclosure: F.J. Lagerwaard: The VU University medical center has a research agreement with Varian medical systems

45IN
SOLITARY PULMONARY NODULES: DIAGNOSIS AND MANAGEMENT

F.J.F. Herth *Department of Internal Medicine, Pneumology and Critical Care Medicine, University of Heidelberg, Heidelberg/GERMANY*

Lung cancer is diagnosed in approximately 220 000 people each year in the United States and is the leading cause of cancer death (incidence rate 72/100000). The need to work up and manage pulmonary nodules is encountered with increasing frequency in chest medicine.. Imaging with CT is very useful in the evaluation of lung cancer, but it lacks the sensitivity and specificity to firmly establish a diagnosis on its own. For taking treatment decisions regarding chemotherapy or surgical resection, tissue diagnosis is essential in most patients'. Similarly, while PET scanning is more sensitive than CT scanning in finding lung lesions, there are too many false positives to allow treatment decisions to be consistently based on PET imaging alone. As a result, while imaging plays a key role in the algorithms used to manage lung cancer, often a tissue diagnosis will be required. Bronchoscopy has been used in evaluating solitary pulmonary nodules (SPNs) and masses for more than 30 years. In patients with such nodules, the diagnostic procedure is usually performed as a transbronchial biopsy (TBBX) under fluoroscopic guidance. The yield depends greatly on the size and location of the abnormality and generally on the ability to visualize the lesion fluoroscopically.

Nodules that are too small to be visualized by conventional fluoroscopy during the procedure pose a particular problem. What are needed, therefore, are new methods for navigation and localization, independent of visualization by fluoroscopy, but still dependent on the technical skills of the bronchoscopist. The first promising new technologi therefore are the available navigation systems. On the other hand, thin bronchoscopes have been used in clinical practice and can be advanced to more peripheral bronchi than the conventional bronchoscope. However, it is difficult to identify the route to a pulmonary peripheral lesion under direct vision within the limited bronchoscopic examination time. Therefore, before performing bronchoscopy confirmation of the route to be used for the advance of the bronchoscope by CT is very important. Also here new approaches like virtual bronchoscopy based guidance system will increase the yield of the diagnostic workup of solitary pulmonary nodules

Disclosure: The author has declared no conflicts of interest.

46IN
PROGNOSTIC AND PREDICTIVE MARKERS FOR SELECTING PATIENTS

M. Taron *Medical Oncology Service, Institut Catala d'Oncologia, Badalona, Barcelona/SPAIN*

As we have previously shown (Rosell et al, PlosOne 2007), BRCA1 RNA expression levels in surgically resected NSCLC patients is an independent prognostic marker of survival. In addition, BRCA1 expression has also shown to be predictive: patients with high BRCA1 expressing tumors are sensitive to antimicrotubule drugs and resistant to cisplatin, and vice versa. Based on these findings, the Spanish Lung Cancer Group (SLCG) conducted a pilot study (SCAT; Spanish Customized Adjuvant Therapy in completely resected pN1/pN2 NSCLC) where patients (n=83) were prospectively treated with adjuvant chemotherapy according to BRCA1 RNA levels in the tumor specimens (assessed by real time quantitative PCR). Patients with low levels (lowest tercile) were treated with gemcitabine/cisplatin; patients with intermediate levels (middle tercile) were treated with docetaxel/cisplatin; and patients with high levels (highest tercile) were treated with docetaxel alone. As an exploratory analysis, Rap80 and Abraxas mRNA expression levels were also analyzed. For the entire population, median disease-free and overall survival were 22 and 43 months, respectively. In this study, no significant differences were observed in DFS and OS according to the three different groups of adjuvant treatment, showing the positive impact of selection by BRCA1 expression, even in patients treated with docetaxel alone. As a result of this pilot study, the SLCG opened a phase III randomized trial in completely resected pN1/pN2 NSCLC with a control arm, where patients are treated with adjuvant docetaxel/cisplatin chemotherapy, and an experimental arm, where patients are treated according to BRCA1 levels of expression, as previously described. At present, a total of 179 patients have been included from a planned total of 432 patients. PORT has been considered for N2 patients. Additional markers will be analyzed: EGFR and k-ras gene mutation status, as well as the expression of several DNA-repair genes.

Disclosure: The author has declared no conflicts of interest.

47IN
DO WE NEED CHEMOTHERAPY IN STAGE 1 NON-SMALL CELL LUNG CANCER?

N. Thatcher *Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester/UNITED KINGDOM*

Introduction The new TNM(7) staging system upstages large T2(b) N0M0 tumours from IB to IIA , T2(a) NIM0 are downstaged from IIB to IIA and T4N0,NI are downstaged from IIIB to IIIA ,with increased survival for the new clinical IB , IIa disease(Detterbeck et al., Chest 2009). Adjuvant therapy based on TNM6 The main controversy is the benefit or otherwise of treating 1B disease. In general adjuvant treatment for 1A is not recommended but is recommended for suitable patients with stage II and IIIA. The recommendation is based on the Western adjuvant trials of cisplatin (LACE metaanalysis) which revealed a worse survival in stage IA, HR 1.4 and only 0.93 in IB, but in stages II, HR was 0.83 and IIIA also 0.83 (Pignon et al., J Clin Oncol 2008).In Japan adjuvant tegafur-uracil is used, a meta-analysis mostly of stage 1 ,adenocarcinoma patients was associated with improved 5 and 7 year survivals p=0.001, but the patients are not widely representative of a Western population(Hamada et al., J Clin Oncol 2005). Two trials raised the issue of platinum based CT in stage IB. The CALGB trial with carboplatin paclitaxel showed no overall survival benefit p=0.12. In an unplanned subgroup analysis there was no improvement with primary tumours ≥ 4cms HR was 0.69 p =0.04(Strauss et al J Clin Oncol 2008). The JBR10 trial has recently been updated and continues to show a benefit for cisplatin vinorelbine, HR=0.78, p =0.04, unlike the IALT update (Butts et al J Clin Oncol 2010; Arriagada et al J Clin Oncol 2010). In stage 1B patients HR was 1.03, p = 0.87, when tumours = 0.02. For the larger ≥ 4cms tumours the HR was 0.66 versus 1.73 for smaller tumours, but p values for both were non significant. Conclusion Adjuvant treatment for stage 1A is not recommended, for 1B disease a positive routine practice recommendation is problematic. There are trials recruiting stage 1 patients and will allow the benefit or otherwise of adjuvant treatment to be prospectively analysed.

Disclosure: N. Thatcher: adjuvant- BMS, Roche GSK honoraria

SUPPORTIVE AND PALLIATIVE CARE

48IN
PREDICTION AND PREVENTION OF BONE METASTASES

No abstract received at time of going to press.

49IN
SUPPORTIVE TREATMENT: ANTIEMETICS AND NEUTROPENIA

M.S. Aapro *Oncology, Institut Multidisciplinaire d'Oncologie, Genolier/SWITZERLAND*

Supportive care needs of lung cancer patients are several, related to the underlying disease and its complications, including treatment induced neutropenia and vomiting. Chemotherapy regimens used for non-small cell lung cancer are rarely a cause for febrile neutropenia in more than 10% of the patients, while this is more frequent in small-cell lung cancer regimens. However, many of the studies excluded the not so rare patient with on-going infection or a high-risk, like past infection and on-going obstructive lung disease. The use of antibiotic prophylaxis to prevent infection and infection-related complications in cancer patients at risk of neutropenia remains a matter of debate. Current guidelines consistently advocate a risk threshold of 20% for routine G-CSF support in patients. We hope that the updated European guidelines for the use of G-CSF will be ready in April at this meeting. Despite the relevant progress achieved in the last 20 years, vomiting and, especially, nausea, continue to be two of the most distressing side effects of cancer chemotherapy. On June 2009 the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) organized a new Consensus Conference on Antiemetics in Perugia. This is a particularly relevant field for those treating lung cancer, where a highly emetogenic drug like cisplatin continues to play a major role. Aprepitant, a potent and selective antagonist of the neurokinin $(NK)_1$ neurotransmitter receptor is recommended to be part of a 3-drug preventative antiemetic regimen

including single doses of a 5-HT_3 receptor antagonist and dexamethasone given before highly emetogenic chemotherapy (MASCC level of consensus: High; MASCC level of confidence: High; ESMO level of evidence: I; ESMO grade of recommendation: A). No studies address the issue of whether palonosetron is superior to other 5-HT_3 receptor antagonists when an NK_1 receptor antagonist is used as recommended by guidelines. The Perugia committee was split on the topic if palonosetron should be recommended as the 5-HT_3 receptor antagonist of choice in prevention of cisplatin-induced acute nausea and vomiting, while this was accepted for anthracycline or other moderately emetogenic chemotherapy when an NK_1 receptor antagonist is not used.

Disclosure: M.S. Aapro is a consultant or speaker for Amgen, GSK, Helsinn, JnJ, Merck, Roche, Sandoz, sanofi aventis, Vifor

50IN
HOW TO MANAGE THE SIDE-EFFECTS OF CHEMOTHERAPY

T. Morán[1], V. Quiroga[2], S. Cros[1], L. Capdevila[1], A. Martinez[1], C. Bugés[1], R. Rosell[3] *[1]Oncology Service, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Barcelona/SPAIN, [2]Oncology Service, Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Barcelona/SPAIN, [3]Medical Oncology Service, Catalan Institute of Oncology, Badalona/SPAIN*

Anaemia in patients with cancer may be attributed to multiple factors. This anaemia is related to chemotherapy in approximately 60% of patients, while other causes have to be evaluated in 40% of the patients. Alternative mechanisms to chemotherapy may contribute to anaemia development, such as anaemia of chronic disease, blood loss, bone marrow infiltration, nutritional deficiency and haemolysis. Different modulators can mediate in the physiopathology of the anaemia: the production of IL-1 α/ β, TNF and α1-antitrypsin may reduce EPO production, suppress BFU-E and CFU-E and also impair iron utilization. The prevalence of anaemia in cancer patients varies depending on the type of cancer. The European Cancer Anaemia Survey evaluated 15,367 patients for up to 6 months. The prevalence of anaemia during follow up was 68% (Hb $<$12 g/dL) and 39% (Hb $<$ 10 g/dL). The prevalence of anaemia by treatment status was 40% in patients not receiving treatment, and 75% in patients under chemotherapy.

Fatigue is a common symptom in patients receiving chemotherapy: almost 100% of patients experience fatigue at some point in the disease. Decreased levels of Hb and increase in fatigue have a direct impact on quality of life. Mild and moderate anaemia has been related to greater symptom burden, lower functioning and decline in quality of life.

The goals of recombinant EPO for the treatment of cancer-induced anaemia are the improvement of Hb levels, the reduction of blood transfusions and the improvement of quality of life. Different reviews of the literature have demonstrated a benefit in the improvement of fatigue related to increased Hb levels and decreased need for blood transfusions.

Controversy in EPO administration arises from different studies that demonstrate an increased risk of thromboembolic disease, cardiovascular events and tumor progression. These events do not appear to affect survival using labelled dosage and clinical indications. Nevertheless, the clinician may have to balance the risks and benefits of using EPO therapy.

Disclosure: All authors have declared no conflicts of interest.

51IN
HOW TO MANAGE THE SIDE-EFFECTS OF RADIATION

M. Werner-Wasik *Radiation Oncology, Jefferson Medical College/Kimmel Cancer Center, Philadelphia/USA*

Acute esophagitis, AE, is a common side effect for patients receiving radiation therapy (RT) for thoracic tumors. Concurrent chemo-RT or hyperfractionation result in a 15-25% rate of severe (RTOG Grade $>$3) AE. Severe AE typically peaks 4-8 weeks from beginning of RT. Rare late esophageal damage, typically stricture, develop 3-8 months post-RT. There seems to be no threshold for RT dose association. Some risk of acute esophagitis occurs in the intermediate dose range(30-50 Gy) and an increasing effect is observed for higher doses. Doses of 74 Gy standard fractionated RT have been delivered in clinical trials with concurrent carboplatin and paclitaxel. Constant burning, unrelated to the act of swallowing and localized in the lower part of esophagus is more likely related to the reflux than to the AE.Incidental irradiation of the stomach, and associated gastritis symptoms, may occur when a lower-lobe lung mass is treated. Single institution studies suggested a benefit to amifostine in decreasing esophagitis, but a large cooperative group phase III randomized study of 243 patients by the RTOG did not confirm this. No amelioration of esophagitis was demonstrated with glutamine or sucralfate. Therefore treatment remains supportive, with diet modification, analgesia and fluid replacement if necessary. Neutropenia worsens AE symptoms. Conformal avoidance of esophagus or part of its circumference in radiation planning is beneficial. No single dosimetric or biologic parameter has been identified as a reliable predictor of radiation pneumonitis (RP). Limiting V20 (volume of both lungs receiving a dose of at least 20 Gy) to the max. of 37% remains a useful guideline for patients receiving standard RT. IMRT and/or proton RT may lower RP risk, but more investigation is necessary. Preliminary data indicate that increased FDG uptake in normal lung during RT may predict subsequent RP. Management of RP is entirely supportive. Infectious pneumonia, tumor recurrence, interstitial pneumonitis have to be excluded. Prednisone 60 mg for 1-2 weeks, followed by a slow taper of 10 mg per week and maintenance on 20 mg for a prolonged time is necessary. Esophageal infection such as candidiasis or herpes simplex may mimic AE. Preexisting gastroesophageal reflux may worsen symptoms of AE.

Disclosure: The author has declared no conflicts of interest.

WORKSHOP: MOLECULAR BIOLOGY

52IN
DISCOVERING NEW MUTATIONS IN LUNG CANCER AND NEW TARGETED THERAPIES

F. Ciardiello[1], F. Morgillo[2] *[1]Dipartimento di Internistica Clinica e Sperimentale "F. Magrassi A. Lanzara", Second University of Naples, Naples/ITALY, [2]Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale "F. Magrassi E A. Lanzara", Seconda Università degli Studi di Napoli, Naples/ITALY*

The last changes in cancer management have been obtained thanks to the data from tumor biology. Recently, a chromosome translocation has been recognized in approximately 5% of non-small cell lung cancer (NSCLC) patients, which generates fused mRNA encoding the amino-terminal half of tyrosine kinase echinoderm microtubule-associated protein like-4 (EML4) ligated to the intracellular region of the receptor-type anaplastic lymphoma kinase (ALK). EML4-ALK oligomerizes constitutively in cells and becomes activated to exert a marked oncogenicity. Suppression of ALK enzymatic activity could be an effective treatment strategy against this tumor. On the other side, the introduction of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) into the management of NSCLC patients has been associated with an objective response in 10-20% of patients. Subsequent studies have shown that patients responsive to such drugs have tumors containing somatic activating mutations in the EGFR gene, which have already been established in the clinic as valid predictors of increased sensitivity to EGFR TKIs. Although impressive clinical and radiological responses have been observed in these patients, tumor progression occurs. The two most commonly mutated oncogenes identified as predicting mechanisms of resistance encode for EGFR itself and KRAS. A secondary mutation in the EGFR gene indeed, named T790M, is thought to cause steric hindrance and impair the binding of TKIs; therefore a novel class of irreversible TKIs are currently under development to overcome this problem. By

contrast, even though KRAS mutations were identified in NSCLC tumors more than 20 years ago, only recently the clinical value of KRAS tumor status has been appreciated and somatic mutations of the gene have been assessed as a mechanism of de-novo resistance to EGFR tyrosine-kinase inhibition in patients with NSCLC. Basal and post-treatment tumor specimens will be needed to establish molecular profiles for each patient with NSCLC. In addition, novel, highly sensitive technology will be required to detect these mutations. In this way, treatment strategies in NSCLC are becoming increasingly tailored to the individual, and may set an example for other areas of oncology.

Disclosure: All authors have declared no conflicts of interest.

53IN

THE BIOLOGICAL SIGNIFICANCE OF TARGETED THERAPIES: THE DEVELOPMENT OF MTOR INHIBITORS

F.R. Khuri, S.S. Ramalingam, T.K. Owonikoko, S-Y. Sun, H. Fu *Thoracic Oncology, Winship Cancer Institute, Atlanta, GA/US*

Clinical trials conducted in selected patient populations have led to the approval of nine novel agents, three of them targeted, for non-small cell lung cancer (NSCLC) in the last twenty years. A recent evaluation of patients with stage IIIB/IV NSCLC diagnosed between 1988 and 2005 through the linked SEER-Medicare data base indicated that the utility of these agents has penetrated the US population as a whole. The development of targeted therapies has varied significantly from the development of classical and even novel therapeutic agents. Strategic approaches that have been highly successful in the development of agents for specific malignancies based on the principles of oncogene addiction have resulted in imatinib for CML and GIST tumors and gefitinib and erlotinib for EGFR-mutant lung cancer. Nonetheless, recent studies have shown that the number of molecular genetic changes in primary lung cancers can total fifty or greater, and while a series of new mutations have been identified in a small but meaningful subpopulation of lung cancer patients, such as those targeting EML4-ALK translocation, other approaches have proceeded along the lines of targeting selected convergence pathways for the treatment of advanced, refractory lung cancer. In many of these cases, initial approaches have shown that agents such as mammalian target of rapamycin (mTOR) or PI3 kinase inhibitors, which may have limited activities as single agents, could perhaps be better developed in combination with cytotoxic therapies in selected patient populations. While these agents, such as the mTOR inhibitors are active in down-regulating metabolic activities of certain tumors, as was recently shown in a phase IB pre-operative trial of everolimus in resectable NSCLC, only modest progress has been made to date in selecting those patient populations likely to respond to combinations of PI3K/mTOR axis inhibitors and cytotoxic agents. Explorations of combinations in the front line with platinums and taxanes and in the second line with either pemetrexed, docetaxel or erlotinib are ongoing.

Disclosure: The author has declared no conflicts of interest.

54IN

RANDOMIZED TRIALS IN PATIENTS WITH EGFR MUTATIONS

T. Mok *Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong/CHINA*

Iressa Pan-Asia Study (IPASS) is the first randomized study that showed EGFR-TKI to be equally effective as chemotherapy in a clinically selected population with a high incidence of EGFR mutation. We enrolled 1217 patients from 9 countries in Asia to receive gefitinib (n=609) carboplatin/paclitaxel (n=608). Gefitinib demonstrated superior PFS compared with chemotherapy (HR 0.74; 95% CI 0.65-0.85; p<0.0001). Tumor samples from 437 patients were evaluated for EGFR mutation and 59.7% was positive. PFS in EGFR mutation positive patients was longer for gefitinib than for chemotherapy (HR 0.48 95% CI 0.36-0.64; p<0.0001); in EGFR mutation negative patients PFS was longer with chemotherapy (HR 2.85 95% CI 2.05-3.98; p<0.0001). A Korean study (First-SIGNAL) with similar design randomized 313 non-/light smokers with adenocarcinoma to either gefitinib or gemcitabine/carboplatin. The study support the IPASS finding that EGFR mutation-positive patients having a higher tumor response rate and longer PFS. Two randomized studies from Japan have compared EGFR TKI with chemotherapy in patients with EGFR mutationã€, Mitsudomi et al randomized 177 chemotherapy-naïve patients with EGFR mutation positive adenocarcinoma to either gefitinib or docetaxel/cisplatin. Tumor response rate was 62.1% and 32.2% for EGFR TKI and chemotherapy, respectively, while the PFS was significantly in favor of the EGFR TKI (HR.49 95% CI 0.34 to 0.70 p<0.001). Kobayashi et al (2009) conducted a similar study and reported tumor response rate of 74.5% and 29.0% respectively. Consistent with other studies, HR for PFS was 0.357 (95% CI 0.252-0.507 p<0.001). Results from other similar studies comparing erlotinib with chemotherapy EURTAC study from Spain and OPTIMAL from China will available in the near future. Including IPASS there are four randomized studies that confirm the efficacy of first line EGFR TKI in patients with EGFR mutation. It has become clear that EGFR TKI is one of the standard first line therapy.

Disclosure: T. Mok: Advisory Board: Astrazeneca, Roche, Eli Lilly, Merck, Pfizer, Eisai Honorarium: Astrazeneca, Roche, Eli Lilly, Pfizer

55IN

MICRORNAS IN LUNG CANCER

M. Skrzypski *Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND*

MicroRNAs (miRs) are a new class of molecules involved in gene expression regulation. These short RNA chains (19-25bp) exert their effect through binding to target sequences on mRNA. Depending on the degree of complementarity microRNA may silence a target gene altogether or result in expression fine tuning of whole gene groups. This permissiveness of interaction places miRs in the centre of gene expression regulation.

MiRs expression assessment have been thus proposed as a basis for molecular diagnostic tests in the following applications: (1) lung cancer screening - miR detection in blood or serum; (2) prognostic tests for selection of high risk patients for adjuvant treatment after surgery; (3) predictive tests for choosing chemotherapy for patients with advanced disease. Additionally, miRs are potential targets for therapeutics. Feasibility of miR detection in blood have been demonstrated in a few cancer types. Such diagnostic test might greatly enhance the radiological screening or even provide an alternative screening method. Cancer specific expression of certain miRs make them particularly useful for these purposes. Several studies suggested prognostic relevance of miRs in lung cancer, e.g. miR146b, miR-155, miR-21, miR-191 and miR-15a in squamous cell lung cancer (Beer at al, 2009), or a 5-miR expression profile reported by Yu et al, 2008 in NSCLC. Interestingly there are differences in miR expression between histological types of NSCLC, which may preclude joint data analysis from different histologies. This and other methodological aspects of miR studies will be discussed in detail. Finally, new data indicate the feasibility and robustness of miR expression analysis in formalin fixed paraffin embedded samples (FFPE). If confirmed, such tests might become wildly applicable in routine oncology practice.

In terms of predictive value of miRs for chemotherapy response, preliminary data suggest that certain miR expression profiles may predict chemosensitivity in cancer cell lines.

Finally, anti-miR agents, e.g. locked nucleic acids (LNAs) will soon be investigated within clinical trials. Given the promising results in animals and safety data in humans, efficacy results are eagerly awaited.

Disclosure: The author has declared no conflicts of interest.

WORKSHOP: RADIATION

56IN
THE QUESTION OF VOLUME

L. Gaspar *Department of Radiation Oncology, University of Colorado Cancer Center, Aurora/USA*

The incidence and severity of treatment related pulmonary toxicity is associated with the dose and volume of normal lung irradiated. It is common for lung cancer patients to present with large bulky tumors. Current North American cooperative group studies are comparing various radiation dose intensity regimens for both small and nonsmall cell lung cancer. With the increase in tumor dose there is invariably an increase in the dose to surrounding normal lung. Retrospective studies indicate that the actuarial incidence of symptomatic pneumonitis is more than 30% with combined modality therapy. There are radiation dosimetry variables that are associated with the later development of pulmonary toxicity. For example, the relationship between V20 (the percent of normal lung receiving 20 Gy or more), and mean lung dose with pulmonary toxicity have been well documented. There is also a correlation with cytokines such as TGFβ1, normal lung irradiated and subsequent pulmonary toxicity. Efforts have been undertaken to minimize this toxicity by intensity modulated radiation treatment and pharmacological manipulation. Other possibilities include preradiation chemotherapy or adaptive radiation treatment, i.e. replanning patients during radiation treatment if their tumor has decreased in size. Prospective studies are in development to test these options.

Disclosure: The author has declared no conflicts of interest.

57IN
THE QUESTION OF DOSE

No abstract received at timerof going to press.

58IN
THE QUESTION OF FRACTIONATION

D. Ball *Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne/AUSTRALIA*

Empirically it has been found that the delivery of a radical course of radiotherapy as multiple small doses (fractionation) over a period of 6 to 7 weeks maximizes the therapeutic ratio by allowing the administration of total doses high enough to have some chance of sterilizing the cancer, and at the same time minimizing the risk of serious morbidity in incidentally irradiated late reacting tissues, which are particularly sensitive to changes in dose per fraction. Other theoretical benefits include reoxygenation of hypoxic tumours as regression occurs, and synchronization of clonogens in radiosensitive phases of the cell cycle. In patients with non-small cell lung cancer (NSCLC), attempts to increase the total dose further by reducing the dose per fraction without significantly altering overall treatment time (hyperfractionation) have demonstrated that it is feasible, but without improving survival. But if hyperfractionation is combined with a reduction in overall treatment time, as in the CHART study, there is an improvement in local control and survival, even though the total dose (54 Gy) was lower than in the control arm (60 Gy). This is an important observation, as it is consistent with accelerated repopulation being a cause of treatment failure in NSCLC. We do not know however if CHART is more or less effective than concomitant chemoradiation. Further, if the benefits of CHART are reliant on the epidermal growth factor receptor (EGFR), could they be duplicated using conventional 2 Gy fractions and EGFR blockade? Fractionation is less important if the total dose of radiotherapy falls short of the maximally tolerated dose, as in palliative treatments; or if late reacting critical tissues are excluded from the high dose region, as in the treatment of peripherally situated stage I NSCLC using image guidance and multiple beam arrangements or arcs. However, the use of large doses per fraction has been associated with serious toxicity in the treatment of tumours located close to the mediastinum or brachial plexus. In these settings, can we justify hypofractionation when the safer and well established alternative of conventional fractionation is available?

Disclosure: D. Ball: I am a member of advisory boards for Lilly Oncology and Astra Zeneca.

59IN
THE QUESTION OF INDUCTION OR CONSOLIDATION?

F. Mornex[1], N. Girard[2] *[1]Département de Radiotherapie Oncologie, Centre Hospitalier Lyon Sud, Pierre Benite/FRANCE, [2]Respiratory Medicine, Reference Center for Orphan Pulmonary Diseases, Louis Pradel Hospital, Lyon/FRANCE*

Radiotherapy is one of the major therapeutic options in thoracic oncology. Chemoradiotherapy is the standard treatment for unresectable locally-advanced non-small cell lung cancer. Concurrent chemoradiation leads to a significant survival benefit when compared to exclusive radiotherapy or sequential chemoradiation, owing to a better local, rather than systemic, tumor control. Current modalities of radiation in this setting include three-dimensional conformal treatment planning, allowing dose escalation and combination with most recent chemotherapy agents to occur. Most of the time, during concomitant chemoradiation, chemotherapy reduction dosages must be achieved to preserve a good patient tolerance. In order to deliver higher doses of chemotherapy and to increase systemic control rates, several investigators developed mixed therapeutic sequences, associating induction and/or consolidation chemotherapy, before and/or after concurrent chemoradiation. Overall, results from phase II-III studies indicate that both induction and consolidation strategies are feasible and may increase local and systemic tumor control. Even if some recent data suggested a potential benefit on progression-free survival with consolidation, available meta-analyses concluded that no significant differences exist between induction and consolidation regarding overall survival. In a routine practice setting, we strongly favor induction chemotherapy, which (1) allows the initiation of the treatment sequence while preparing the patient for radiotherapy with shorter delays, (2) may facilitate radiotherapy through tumor control and GTV decrease, (3) leads to select most appropriate patients that do not present with early progression and (4) allows to test the tumor chemosensitivity. Future developments of induction and consolidation treatment in locally-advanced non-small cell lung cancer consists of evaluating new systemic agents, including targeted therapies. Even if maintenance with EGFR tyrosine kinase inhibitors has been disappointing in this setting, a better selection of patients and the use of monoclonal antibodies may provide more promising results.

Disclosure: All authors have declared no conflicts of interest.

60IN
CLINICAL OUTCOMES AND TREATMENT PLANNING STRATEGIES FOR ADVANCED-STAGE NON-SMALL CELL LUNG CANCER (NSCLC) TREATED BY INTENSITY MODULATED RADIATION THERAPY (IMRT) OR 3DIMENTIONAL CONFORMAL RADIATION THERAPY (3DCRT) WITH CONCURRENT CHEMOTHERAPY (CCT)

R. Komaki *Radiation Oncology, UT MD Anderson Cancer Center, Houston/USA*

Background: IMRT has been used in our institution to treat locally advanced NSCLC for which the dose-volume constraints for 3D conformal therapy (3DCRT) could not be met. The purposes of this study are 1) to

review the clinical outcomes and 2) to establish corresponding clinical guidelines for IMRT treatment planning.

Materials and methods: Clinical data were reviewed for lung cancer patients treated with IMRT at our institution from 2002-2005. The patient cohort included those who had stage III-IV NSCLC, and who had definitive concurrent chemoradiation. Patients were excluded if they had a history of major lung surgery, prior chest radiotherapy, or mixed 3DCRT and IMRT plans. Clinical outcomes and major toxicities including pneumonitis and esophagitis were analyzed based on medical records and clinical follow-up. IMRT treatment plans and dosimetric parameters were reviewed. Guidelines for IMRT treatment planning were developed based on the existing clinical outcome and dosimetry data.

Results: In total, 87 patients were included in this study. The median follow-up time was 10 months (range, 1.1-43.8 months). 61% of patients were treated to a dose range of 63-66 Gy (see Table 1). The 2-year locoregional control, disease free survival, and overall survival were 41%, 23%, and 57%, respectively. The rate of grade 3 and higher treatment-related pneumonitis at 12 months was 11%. The rate of grade > acute esophagitis was 34%. In achieving effective IMRT treatment plans, mean lung dose and the volume of normal lung receiving low-dose radiation were used as important constraints to minimize pulmonary toxicity. The number of IMRT beams should be limited within the range of 5-7 beams, with the beam angles being carefully selected to spare healthy lung. The other physical parameters that affected low-dose radiation and were thus considered during IMRT treatment planning included the number of MLC segments and monitor units used.

Conclusions: IMRT with CCT may be an effective and safe modality in treating advanced-stage NSCLC with concurrent chemotherapy. Dose distributions for IMRT treatments should be carefully planned considering normal tissue toxicity and minimization of exposure to healthy lung.

Disclosure: The author has declared no conflicts of interest.

THE NEW ERS/IASLC/ATS CLASSIFICATION OF LUNG ADENOCARCINOMA

61IN
INTRODUCTION AND PATHOLOGY

E. Brambilla[1], W. Travis[2] *[1]Département D'Anatomie et Cytologie Pathologiques, University Hospital Grenoble, Grenoble/FRANCE, [2]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York/USA*

Despite advances in molecular understanding of carcinogenesis steps of this tumor in the past decade, there remains a need for a universally accepted criteria for adenocarcinoma subtypes in particular bronchioloalveolar carcinoma (BAC). The specific aim and project objectives were to develop a multidisciplinary subclassification of lung adenocarcinoma defining clinical / histologic, radiologic, molecular subtypes of lung adenocarcinoma and to propose an international standard for histologic subclassification of lung adenocarcinoma, the backbone of the multidisciplinary classification. The major changes in this classification include : 1) Cessation of the use of the term BAC. This old concept of BAC now appears in 5 different places in the classification 2) Addition of a category of minimally invasive adenocarcinoma (MIA). Patients with small solitary (usually less than 2 cm) adenocarcinoma with an invasive area of less than 5 mm can have 100% 5-year survival. 3) The category of mixed subtype adenocarcinoma is dropped because it was comprizing 90% of our diagnosis, invasive subtypes are now declined in predominant patterns with other patterns defined with a percentage in tumor. 4) The former mucinous BAC now called mucinous adenocarcinoma with lepidic pattern represents the first most important variant of adenocarcinoma. 5) This classification will make recommendations regarding the diagnosis of adenocarcinoma versus other non small cell lung carcinoma in small biopsies and cytology. The distinction between squamous cell from large cell and adenocarcinoma rests on a panel of special stains including mucin and immunohistochemical markers including TTF1, CK5-6 and P63 in small biopsies with an appearance of non small cell lung carcinoma (NOS). A number of gene mutations, gene copy number increase and molecular pathways have been associated strongly with each of the histological adenocarcinoma patterns, containing potential therapeutic targets.

Disclosure: All authors have declared no conflicts of interest.

62IN
THE NEW ERS/IASLC/ATS CLASSIFICATION OF LUNG ADENOCARCINOMA: RADIOLOGICAL ASPECTS

K. Garg *Diagnostic Radiology, University of Colorado at Denver and Health Sciences Center, Denver/USA*

There is a widely divergent clinical, radiologic, molecular and pathologic spectrum within lung adenocarcinoma. Despite remarkable advances in understanding of this tumor in the past decade; there remains a need for a universally accepted criteria for adenocarcinoma subtypes, in particular bronchioloalveolar carcinoma (BAC). The use of the term BAC encompasses a broad spectrum of tumors ranging from solitary small peripheral lung tumors with a 100% 5-year survival to widespread advanced disease with a 10% 3-5 year survivals, with widely varying use of terminology. The widespread availability of MDCT and abundance of new information obtained especially from low-dose CT lung cancer screening programs, have increased our understanding of the management and types of small peripheral lung nodules, in particular, the subsolid pulmonary nodules. Subsolid nodules are now known to frequently represent the histologic spectrum of peripheral adenocarcinomas. Pending revisions in multidisciplinary classification of these lesions, this includes premalignant atypical adenomatous hyperplasia (AAH), carcinoma in-situ or bronchiolalveolar carcinoma (AIS/BAC), minimally invasive (MIA) and invasive adenocarcinoma. Thin section CT has emerged as a new biomarker for lung adenocarcinoma subtypes. GGO nodule correlates with lepidic growth and better clinical outcome than part-solid or solid nodules. Pure GGO lesions are typically FDG-PET negative whereas more aggressive and invasive tumors manifesting as solid or part-solid lesions are metabolically active. Key messages from radiology lecture are: 1) The term BAC is confusing and it should no longer be used in reference to adenocarcinoma manifesting as GGO. The new terms proposed for the adenocarcinoma subtypes that cause this pattern are AIS/MIA and lepidic predominant adenocarcinoma 2) Mucinous adenocarcinoma (previously called BAC) is usually a solid tumor or as consolidation (not GGO). 3) Multiple lesions – careful description of each lesions is desirable because multiple synchronous/metachronous primaries are not uncommon (which may show different sizes and attenuation patterns).

Disclosure: The author has declared no conflicts of interest.

63IN
SURGERY

P.E. Van Schil[1], H. Asamura[2], T. Mitsudomi[3], V. Rusch[4], M. Tsuboi[5] *[1]Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem/BELGIUM, [2]Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo/JAPAN, [3]Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya/JAPAN, [4]Department of Thoracic Surgery, Memorial Sloan-Kettering Cancer Center, New York/USA, [5]Thoracic Surgery & Oncology, Tokyo Medical University & Hospital, Tokyo/JAPAN*

Although no prospective, randomized trials exist comparing surgery and radiotherapy in early stage lung cancer, surgical treatment has traditionally been

considered the treatment of choice. After a prospective randomized trial of the Lung Cancer Study Group published in 1995, comparing lobectomy to lesser resections for peripheral T1N0 lesions, lobectomy became the procedure of choice and the minimal resection to be performed. Stimulated by large screening programmes for lung cancer, the role of sublobar resection is currently being reconsidered for very early lung cancer. This particularly applies to non-solid or part solid ground glass opacities on chest computed tomography which mostly correspond to adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) in the new ERS/IASLC/ATS classification. Most experience has been gained in Japan where thoracic surgeons deal with small lung lesions for a prolonged period of time. Specific interest centers on lung nodules ≤ 2 cm. Already in 1995, Noguchi presented a novel classification for small adenocarcinomas subdividing them in an alveolar replacement and non-replacement type. In non-randomized studies sublobar resections, wide wedge resection or anatomical segmentectomy, were found to be valid oncological procedures in specific subgroups. Recently, treatment algorithms were proposed for lung nodules ≤ 2cm which are classified in the 7th TNM edition as T1a tumors. In some specific subgroups lymph node sampling rather than systematic nodal dissection may be appropriate. For AIS or MIA having an excellent prognosis, lymph node sampling or dissection may not be required. Specific guidelines for frozen section examination of these lesions have to be developed. Multiple lung adenocarcinomas are not a contra-indication for surgical exploration when they are considered to be multiple, early stage primary tumors without evidence of mediastinal lymph node invasion. However, before sublobar resection can readily be recommended as standard treatment for early stage lung cancer ≤ 2cm, the results of ongoing randomized trials in Japan and the USA are awaited for. These studies will also provide a deeper insight in the behavior and clinical characteristics of these tumors.

Disclosure: All authors have declared no conflicts of interest.

IMAGING: STATE-OF-THE-ART

64IN

HOW TO MEASURE T STATUS, DIFFERENT IMAGING TECHNIQUES, DIFFERENT IMAGING METHODS

W. De Wever *Department of Radiology, University Hospitals Leuven, Leuven/BELGIUM*

Measurement of lung tumor is important for staging and follow-up. Especially in the new lung cancer system, tumor size has become a major descriptor in T staging. (Multi-detector) Computer Tomography is a widely used imaging technique to determine the size of tumor. Tumor measurement can easily performed using electronic rulers on diagnostic monitors. Window settings (lung versus mediastinal window) can influence measurement of tumor size. The same windows should be used on subsequent examinations to measure any lesions. Measurements obtained using lung settings are more accurate irrespective of collimation than measurements obtained using soft tissue settings. Slice thickness, reconstruction algorithm and tube current can also affect size measurement of solid nodules. Slice thickness of 1.25 mm and high-spatial-resolution algorithms are recommended when measuring tumor size. Tumor can be measured in an uni- (minimal versus maximal) or bidimensional way. This can be done on transverse or on reformatted images. Measurements of tumor size on CT are often inconsistent, especially in small tumors (< 3 cm). This can also lead to an incorrect interpretation of tumor response. Measurement differences are greatest when the edge of the lesion is irregular, speculated or when the tumor consists of ground-glass attenuation components. The interobserver variability is larger than the intraobserver variability. Consistency can be improved if the same reader performs serial measurements for any one patient. Computer aided diagnosis is a very promising tool in the measurement of tumor size. Measurement of unidimensional lesion size with the computer method is more accurate than reader measurement and can be considered significant when estimating the outcome of therapy in a patient. Semiautomatic volumetry of lung tumor is sufficiently accurate and repeatable.

Disclosure: The author has declared no conflicts of interest.

65IN

NEW NON-INVASIVE IMAGING TECHNIQUES IN LUNG CANCER (EXCLUDING PET)

O. Lucidarme *Service de Radiologie Centrale, Groupe Hospitalier Pitié Salpêtrière, Paris/FRANCE*

Many clinical trials of modern therapies have shown that targeted therapy may not lead to substantial tumor volume reduction, especially soon after therapy. Hence conventional measurements of the tumor size change may be insensitive or markedly delayed even when there may be substantial therapeutic effect. Thus, the clinical use of targeted therapies leads to develop new imaging methods that are able to assess the microcirculation or the cellularity of the tumor. This is the role of the different functional imaging techniques that use indirect method to provide surrogate markers of the microcirculation or of the microscopic cellular organization of the tumor. Dynamic imaging of the microcirculation using either DCE MRI, or functional CT are all based on the same principle which consists of injecting a known amount of contrast agent and obtaining the curve of signal intensity change over the time. The enhancing curve provides information on blood flow, on capillary surface, on endothelial permeability and on the volume of the extracellular, extravascular space. Diffusion weighted MRI provides information on tissue cellularity, and the integrity of cellular membranes by measuring the random motion of the water molecules (apparent diffusion coefficient: ADC) in tissue which is modified by interactions with hydrophobic cellular membranes. Then vascular changes and necrosis or cellular lysis induce by treatment will lead to decrease dynamic parameters and/or to increase water diffusion and corresponding ADC values respectively. There are now convincing data to support their usages for monitoring response to a variety of treatments mainly for brain tumors, but also for liver, kidney, rectal or breast cancers. However these techniques remain considerably more complex than conventional anatomical imaging. Their limitations must be known and they still require validation, ideally against clinical outcome before allowing their adoption as established surrogate end points of drug effects.

The principles of functional MRI and CT in oncology, results expected, their limitations and studies testing these techniques will be presented and discussed.

Disclosure: The author has declared no conflicts of interest.

66IN

HOW SHOULD PET–CT INFLUENCE OUR DECISION MAKING?

J. Vansteenkiste *Respiratory Oncology Unit, University Hospital Gasthuisberg, Leuven/BELGIUM*

The 1st clinical report on FDG-PET in thoracic oncology came out in 1990 (Kubota, JNM 1990). Over the last 20 years, the technique has revolutionised the imaging of lung cancer. We will discuss three of the settings where the findings have impacted on clinical decision making. In the assessment of solitary pulmonary nodules, PET-CT is proven to be superior to CT alone in several studies and meta-analyses (Fischer, Lancet Oncol 2001). For lesions <1 cm, however, current PET scanners are at their limitation of sensitivity, and other algorithms with CT follow-up are proposed (MacMahon, Radiology 2005). In lesions >1 cm, the added value of PET is highest for lesions with an intermediate probability of cancer (i.e. between 5 and 60%) (Gould, Chest 2007). Several studies and meta-analyses also convincingly demonstrated that NSCLC staging is improved use of PET-CT (Fischer NEJM 2009). This is due to more accurate non-invasive locoregional lymph node

(LN) staging than with CT alone, because PET-CT orients LN tissue sampling techniques, and due to improved extrathoracic staging. Some – but not all – randomised studies have shown a reduction of invasive procedures and of futile surgery (Van Tinteren, Lancet 2002; Viney JCO 2004; Maziak Ann Int Med 2009).Whether improved treatment outcomes are due to stage migration (Morgensztern, JTO 2008) or better choice of therapeutic modalities (Wauters, 2010) remains unsolved. A 3rd setting is the assessment of induction therapy in combined modality treatment for stage III (Vansteenkiste, Lancet Oncol 2004). This is more difficult, as quantification of FDG-uptake is needed here, in contrast with previous indications. The performance of PET-CT in assessment of LNs is not as good as at initial LN staging. Therefore, tissue sampling tests (echo-endoscopy, mediastinoscopy) play an important role. Apart from LN downstaging, the other important element in prediction of outcome after combined modality treatment (CMT) is pathologic response in the primary tumour. The latter is far better predicted by PET than by CT, and consequently PET-response was related to outcome in several prospective studies. A combination of LN downstaging by tissue tests and tumour response by PET may be one of the most powerful predictors of outcome after CMT (Dooms, JCO 2008).

Disclosure: The author has declared no conflicts of interest.

MESOTHELIOMA

67IN

SURGERY FOR MPM; EXTRAPLEURAL PNEUMONECTOMY (EPP) VS PLEURECTOMY/DECORTICATION (P/D)

M. Tsuboi *Thoracic Surgery & Oncology, Tokyo Medical University & Hospital, Tokyo/JAPAN*

Standard treatment for all but localized malignant pleural mesothelioma (MPM) is generally not curative. Although some patients will experience long-term survival with aggressive treatment approaches, it remains unclear if overall survival (OS) has been significantly altered by the different treatment modalities or by combinations of modalities. The goal of surgery in the multimodality treatment approach is to achieve a macroscopic complete resection, with adjuvant therapies directed at residual microscopic disease. For patients who are eligible candidates, surgical resection plays an important role. Both extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D) have evolved for the surgical treatment of MPM. However, the optimal procedure for resection of malignant pleural mesothelioma is controversial. Knowledge of the similarities and differences between the two operations that have evolved-EPP and P/D-is prerequisite to understanding the complex issues associated with patient selection, diagnosis, pathologic staging, preoperative assessment, perioperative management, and adjuvant treatment. Both operations are technically complex. Overall survival reported in a recent multicenter analysis of these two operations supports the use of P/D for early stage MPM provided that a complete resection is feasible; otherwise EPP will confer a survival advantage. For stage II disease, however, EPP demonstrates a possible advantage. The focus in stage III disease should remain on the ability to achieve macroscopic complete resection, rather than N2 disease. P/D can provide palliative relief from symptomatic effusions, discomfort caused by tumor burden, and pain caused by invasive tumor. Operative mortality from P/D is less than 2%, while mortality from EPP has ranged from 6% to 30%. For patients who undergo P/D, local recurrence (within the surgically operated hemithorax) is the most common form of recurrence. For patients who have undergone EPP, the pattern of recurrence is predominantly a combination of local and distant failure. The local recurrence rates, however, seem to be lower than rates seen after P/D. At present, the choice of operative mode should be tailored to the extent of primary disease, patient co-morbidities, and type of multimodality therapy planned.

Disclosure: The author has declared no conflicts of interest.

68IN

THE ROLE OF RADIOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA TREATMENT

C. Le Pechoux[1], A. Paumier[1], D. Planchard[2], J. Margery[2], P. Ruffie[2] *[1]Department of Radiotherapy, Institut Gustave Roussy, Villejuif/FRANCE, [2]Department of Medicine, Institut Gustave Roussy, Villejuif/FRANCE*

Malignant pleural mesothelioma (MPM) is a rare tumour of great concern to chest physicians and oncologists because of its difficult pathological diagnosis and poor prognosis with median survival time ranging from 9 to 17 months. Radiation oncologists may take care of such patients in 3 situations:

- as prophylaxis to reduce the risk of parietal seeding along the drainage sites after drainage or thoracoscopy
- as adjuvant post-operative treatment in an attempt to improve locoregional control after resection in a subgroup of selected patients with early-stage disease
- and for palliation of symptoms for patients with painful chest wall infiltration or nodules.

The role of radiotherapy in the prevention of parietal seeding was at first explored in a small randomized trial which concluded that prophylactic drain site radiotherapy, could prevent the development of subcutaneous metastasis. Other small randomized trials have not confirmed these results. Concerning post-operative radiotherapy after extra-pleural pleuro-pneumonectomy (EPP), data from the literature are limited, and come mostly from retrospective studies or phase II prospective studies. Post-operative irradiation should only be proposed in clinical trials, as a part of multimodal treatment. Conformal radiotherapy has been used in recent phase II prospective studies. According to the dose and technique used, the local recurrence rate may vary between 13% and 50%. The ability to cover fully all the areas at risk of recurrence, is limited by dose constraints to the surrounding normal structures (heart, liver, contralateral lung and spinal cord). Preliminary results of intensity-modulated radiotherapy in the adjuvant setting seemed particularly promising as they could provide good local control and protect organs at risk. However, severe pulmonary toxicity has also been reported so that it should not be recommended outside of clinical trials.

Further studies are needed to establish better the role of radiotherapy. Recent studies have underlined the importance of radiotherapy technique both in terms of local control and toxicity. A randomized multicenter European study is ongoing to answer the question of adjuvant post-operative radiotherapy after EPP (SAKK study).

Disclosure: All authors have declared no conflicts of interest.

69IN

SYSTEMIC TREATMENT AND MOLECULAR PATHWAYS

R.A. Stahel *Klinik und Poliklinik für Onkologie, Universitätsspital, Zürich/SWITZERLAND*

The treatment of malignant pleural mesothelioma continues to be a challenge. The palliative effect of combination chemotherapy and potential benefit of early versus late chemotherapy has been documented from studies using mitomycin C, vinblastine and cisplatin. The MS01 trial comparing the outcome of patients treated with active symptom control alone or symptom control with either MVP or vinorelbine was unable to demonstrate a significant difference in quality of life or survival, however an exploratory analysis suggested a survival advantage for the vinorelbine group. Based on the results of a phase III trial and the registration of pemetrexed, its use in combination with cisplatin has become the

preferred choice of chemotherapy. Phase II studies and the results of the pemetrexed international expanded access program suggest similar activity when pemetrexed is combined with carboplatin. Vinca alkaloids also have activity in malignant pleural mesothelioma. Studies include the use of vinorelbine alone or in combination with cisplatin and vinflunine. The role of second line chemotherapy and optimal choice of agent needs to be defined. Gefitinib and erlotinib were found to have no clinical activity. In contrast, clinical signals were reported with the multitargeted tyrosine kinase inhibitors vatalanib, sorafenib and sutinib prompting further clinical studies with this group of agents. While an earlier randomized phase II study of bevacizumab in combination with cisplatin and gemcitabine was negative, the agent is currently investigated in combination with platin and pemetrexed. Other agents under investigation are bortezomib and vorinostat. Molecular studies identified inactivation of the neurofibromatosis-2 (NF2/merlin) signaling and of INK4a/ARF gene to be key events in tumorigenesis. Inactivation of NF2 signaling is due to gene mutation or functional inactivation of the protein which may depend, e.g., on PTEN deletion or overexpression of CPI-17 oncogene. NF2 signaling involves the mammalian Hippo cascade which inhibits YAP activity by phosphorylation. YAP is a transcription factor promoting tumorigenesis when active. Amplification of chromosomal 11q22 region including YAP was identified in a subset of mesothelioma, indicating an additional way of NF2 signaling inactivation.

Disclosure: The author has declared no conflicts of interest.

SCREENING

70IN
SPIRAL CT

R.J. van Klaveren *Pulmonology, Erasmus MC, Rotterdam/NETHERLANDS*

When lung cancer is intercepted in its early stages, lung cancer can be treated with a surgical resection. However, most patients present when they are symptomatic and in an advanced disease stage. The hypothesis is that if a larger proportion of the lung cancer cases could be detected in an early stage, this might translate into an improved outcome. Randomized controlled trials in the 1970s and 1980s did not validate this principle. With the advent of new technology and the introduction of low-dose multidetector computer tomography, new hopes have been raised. In order to address the effectiveness and cost-effectiveness of LDCT screening for lung cancer, several observational cohort studies and randomised clinical trials have been launched. A major drawback of current screen regimens is, however, that they lead to a high rate of false positive test results and to low positive predictive values. This translates into high rates of subsequent work-ups, costs, loss of quality of life, potential morbidity and low acceptance of these screening programs among the public. Although lung cancer screening and surgical resection for early stage lung cancer may offer a potential curative treatment, it is not free of complications. Therefore, the number of participants with a false positive test result in a screening program should be as low as possible. In the Dutch-Belgian low-dose multi-detector CT lung cancer screening trial (NELSON) a novel screening strategy has been used based on the size of new nodules and the volume doubling times of existing nodules with growth by semi-automated software only, without use of PET, FNA or evaluations after antibiotics. This reduced the proportion of test positives to only 2%. In conventional regimens the proportion of test positives ranges from 15-50%. The NELSON nodule management strategy will increase the acceptance of possible future screening programs. However, CT screening for lung cancer should still be regarded as investigate and needs to be confirmed in well-designed randomized controlled trials before implementation on a large scale.

Disclosure: The author has declared no conflicts of interest.

71IN
DO WE NEED TO SCREEN PERSONS EXPOSED TO ASBESTOS?

N. van Zandwijk *ADRI/Bernie Banton Centre/, University of Sydney, Sydney/AUSTRALIA*

Asbestos, a group of naturally occurring mineral silicates, was introduced into our environment approximately a century ago. Specific properties such as resistance to corrosive and thermal effects and increased tensile strength have resulted in its introduction into over 3000 products. Asbestos readily breaks into small, easily inhaled fibers that may elicit lung fibrosis, (asbestosis), lung cancer and malignant mesothelioma. In most industrialized countries asbestos has been banned from work and home environments but current widespread use of asbestos in developing countries indicates that the epidemic of asbestos-related disease will continue to grow in the decades to come. Asbestos-exposed individuals have justifiable anxiety about their future. In some countries monitoring of individuals with occupations involving asbestos exposure has been effectuated. Unfortunately surveillance with radiographic examinations and pulmonary function tests has been shown of little value. At the same time studies attempting to define biomarkers for early detection have shown that Soluble Mesothelin-related Protein, Osteopontin and Megakaryocyte-Potentiating Factor aren't sensitive enough to be introduced in the clinic (1). It has become clear that even in high-risk populations significant variations in cancer risk exist. More accurate risk prediction is expected to assist in balancing potential risks and benefits of screening. Risk models for lung cancer prediction have been developed and easily obtained clinical information can be used to identify individuals, who may benefit from increased surveillance (2). Thus, future screening studies in asbestos-exposed individuals are expected to concentrate on subgroups with very high risk. A better definition of high risk in combination of sophisticated radiographic and biomarker techniques are new tools to be tested and will hopefully assist in preventing the lethal consequences of asbestos exposure. 1. Pass HI. Semin Thorac Cardiovasc Surg, 2009; 2. Spitz MR et al. J Natl Cancer Inst, 2007.

Disclosure: N. van Zandwijk: Advisory Boards: Eli Lilly & Company, MerckSerono and AstraZeneca

72IN
MOLECULAR SCREENING

C. Mascaux[1], G. Anthoine[2], N. Peled[1], V. Ninane[3], A. Burny[4], J. Sculier[5], F.R. Hirsch[6] *[1]Department of Medical Oncology, University of Colorado Cancer Center, Anschutz Medical Campus, Aurora/USA, [2]Intensive Care and Thoracic Oncology, Institut Jules Bordet, Brussels/BELGIUM, [3]Pneumology, CHU Saint-Pierre, Brussels/BELGIUM, [4]Laboratory of Molecular and Cellular Biology, Faculté Universitaire des Sciences Agronomiques de Gembloux (FUSAGx), Gembloux/BELGIUM, [5]Department of Intensive Care and Thoracic Oncology, Jules Bordet Institute, Brussels/BELGIUM, [6]Medicine-Oncology, University of Colorado Cancer Center, Aurora/USA*

Recent technological advances have made it possible to study molecular events preceding the development of invasive cancer. It is expected that molecular studies will identify biomarkers for early detection of lung cancer, by using more readily obtainable biologic samples (blood, sputum, exhaled breath) being applicable to large-scale cost effective screening in high-risk groups. Recently, our group defined transcriptomic profiles by miRNA and mRNA for detecting pre-cancerous stages and invasive lung cancer. We performed gene expression profiling in 122 biopsies at all successive stages from normal bronchial epithelium of smokers, through all intermediate stages, to lung invasive squamous cell carcinoma. We obtained a signature of 382 genes, which allows for the discrimination of malignant and premalignant bronchial tissue (invasive and pre-invasive lesions at high-risk to progress) from benign one (normal tissue and

low-grade lesions which very rarely evolving toward cancer), with a sensitivity and specificity of 93% and 88%. In parallel, our group studied miRNA a subset of 60 samples from the transcriptomic study. MiRNA patterns of expression were able to segregate high-grade preneoplastic lesions (severe dysplasia and CIS) and SCC from the low-grade lesions (metaplasia, mild and moderate dysplasia) with sensitivity and specificity up to 83% and 100%, respectively. The mRNAs and miRNAs profiles differentially expressed between these stages are thus potential tools for early detection of lung cancer at pre-invasive stages. An ongoing study aims to validate our findings in a prospectively collected independent set of fresh frozen bronchial biopsies. Afterwards, we will select candidate mRNAs and miRNAs from bronchial biopsies studies and assess them in prospectively collected plasma from the same cohort. Detecting these biomarkers in plasma would be a potential approach for non-invasive screening of lung cancer. As also studying volatile organic compounds in exhaled breath from the same patients, we propose a clinical strategy for early detection of lung cancer by combining a plasma test based on detection of selected RNAs by RT-PCR together with exhaled breath test, expecting that these two non-invasive tests detect early lung cancer with a very high sensitivity and specificity.

Disclosure: F.R. Hirsch: Advisory Boards: AstraZeneca, Merck Serono, BMS/Imclone, Syndax, Pfizer, Boehringer-Ingelheim, Lilly Oncology, GSK, OSI/Genenetech/Roche Research Funding: AstraZeneca, OSI, Genentech, Syndax, Biogen-Idec, Ventana-Roche, Merck, Genmab. All other authors have declared no conflicts of interest.

STAGE III NSCLC: STATE-OF-THE-ART

73IN
PROGNOSTIC FACTORS IN STAGE III NSCLC

T. Berghmans *Medicine, Institut Jules Bordet, Brussels/BELGIUM*

The overall prognosis of lung cancer is poor. During the last decade, there were an increasing number of articles related to the study of survival prognostic factors (PF) in NSCLC. For this presentation, we selected only those dealing specifically with stage III NSCLC. Among the published potential PF, some variables are more consistently associated with survival. The prognostic role of disease stage was recently confirmed within stage III NSCLC patients in the very large international study performed by the IASLC, proposing a new TNM classification. Respective 5-year survival rates for clinical stage IIIA and IIIB were 19% and 7% ($p < 0.0001$). Other PF in stage III NSCLC have been proposed in a heterogeneous literature e.a. due to variations in the populations, to the type of treatment or to the variables taken into consideration for the PF analyses. The most frequently reported PF were performance status, age, some characteristics of the primary tumour (size, local extension) or of the mediastinal lymph node involvement (N stage, number of metastatic nodal stations) and the objective response to treatment. Unfortunately, none of these clinical PF are accurate enough to perform meaningful individual prognosis. Their utility stays principally in the comparison of different groups of patients or in the choice of stratification criteria for clinical studies. The prognostic role of new biological markers has been assessed in a few heterogeneous studies of limited sample size, not all comparing biological to clinical factors in multivariate survival analyses. Although not uniformly reported, some PF were suggested: apoptotic index, bcl-2, p53, hMSH2 (a mismatch repair gene), Fas or the rhTRAIL DR5 receptor. The prognostic role of the metabolic tumoural activity measured by the SUV on ^{18}F-FDG-PET was suggested in a literature meta-analysis of small retrospective studies, needing confirmation in prospective studies taking into account classical PF. Conclusion: Disease stage and performance status are the most prominent PF in stage III NSCLC, while other clinical and therapeutic variables have some prognostic value. Biological factors and SUV are new promising PF, their definitive role being to be confirmed in stage III NSCLC.

Disclosure: The author has declared no conflicts of interest.

74IN
OPTIMISING THE SYSTEMIC THERAPIES IN A MULTIMODAL APPROACH

K. O'Byrne *Oncology, St James Hospital, Dublin/IRELAND*

Despite significant advances in the optimisation of care for resected and advanced non-small cell lung cancer, the most controversial area of management centres around locally advanced disease. Recent randomsied controlled trials have failed to show an improvement in survival for patients undergoing surgical resection following either chemoradiotherapy or versus radiotherapy following induction chemotherapy for stage IIIA, N2 positive disease. As a result of these trials chemoradiotherapy has been adopted as the treatment of choice for proven N2 disease. There are, however other considerations. In the aforementioned randomised trials patients that underwent a lobectomy appeared to have an improved outcome. A recent meta-analysis of 5 studies presented at the British Thoracic Oncology Group demonstrated that radiotherapy provided no advantage over surgery with a trend to better outcomes for surgery. There is also mounting evidence that the zonal distribution of N2 disease may have a role in determining who should undergo surgery based on survival outcomes. Therefore in certain N2 patient populations surgery followed by adjuvant chemotherapy +/- post-operative radiotherapy may result in the optimal long term survival. For the patient with unresectable N2 or N3 disease the optimal treatment based on current evidence is concurrent chemoradiotherapy. Tumour volume, however, has a direct effect on outcome with long term survival being unlikely with a tumour diameter >4 cms. The role of induction chemotherapy in reducing tumour burden prior to radical radiotherapy or the use of shrinking field radiotherapy as the tumour responds to chemoradiotherapy in improving patient outcomes has not been tested in randomsied controlled trials. Finally there may be a role for surgery in T4 tumours involving a mediastinal structure such as the aorta or vena cava as part of a multi-modal approach. Looking to the future chemoradiotherapy incorporating agents such as pemetrexed and cetuximab requires optimisation. Also meta-analysis confirms that three drug regimens have higher response rates than two drug regimens. Their use in the neoadjuvant and adjuvant settings may improve outcomes for resected and unresectable locally advanced non-small cell lung cancer.

Disclosure: K. O'Byrne: I have received honoraria for lectures and advisory board work and have participated in clinical trials with Merck Serono and Lilly Oncology

75IN
IMPROVING THE THERAPEUTIC RATIO OF CHEMORADIATION: BIOLOGY MEETS TECHNOLOGY

D. Zips[1], S. Appold[1], M. Baumann[2] [1]*Radiation Oncology/ Oncoray, Technische Universität Dresden / University Hospital and Medical Faculty, Dresden/GERMANY,* [2]*Department of Radiation Oncology, University Hospital and Medical Faculty, Dresden/GERMANY*

Better understanding of the biological determinants and advanced radiation technology led to improved outcome after chemoradiation in patients with lung cancer. Milestones were the optimization of time-dose-fractionation and schedules of combined therapies, introduction of functional imaging for treatment planning and monitoring of response, novel radiation techniques as well as implementation of image-guidance allowing high-precision delivery and control for respiratory motion. Advances in imaging and radiation technology have been shown to be not only useful to increase the radiation dose to the tumour but also to spare normal tissues. Equally important for the progress in radiotherapy were fundamental insights into the cellular and molecular mechanisms of radiation response of tumours and normal tissues.

Together, biology-driven optimization embedded into high-tech radiotherapy represents a promising environment for further developments.

Disclosure: D. Zips: Research grants by Siemens, Bayer Schering, Boehringer Ingelheim Austria. Honoraria by Merck, Astra Zeneca. Member of the Lilly advisory board radiotherapy; S. Appold: Clinical reviewer for ESTRO-Equal. Honoraria from Merck; M. Baumann: Research grants by Siemens, Bayer Schering, Boehringer Ingelheim Austria. Honoraria by Merck, Astra Zeneca.

76IN
WHICH PATIENTS ARE CANDIDATES FOR SURGERY?

W. Weder *Division of Thoracic Surgery, University Hospital Zurich, Zurich/SWITZERLAND*

Stage III disease is characterised by its heterogeneity. It includes patients with locally advanced tumor with infiltration of the chest wall or the mediastinum in combination with lobar lymph node metastasis (T3, N1) or tumors infiltrating organs or central structures such as trachea, aorta, vertebra (T4) and on the other hand tumors of any size located within the lung parenchyma with metastasis to the mediastinal lymph nodes either ipsilateral (N2) or contra lateral (N3).

Furthermore N2 or N3 disease is not a uniform entity and encompasses a broad spectrum of metastatic lymph node involvement from microscopic disease found unexpectedly at surgery to multilevel bulky lymph node involvement. Treatment recommendations in some subgroups are relatively clear in others discussed controversially and differ between institutions. Treatment recommendations especially for surgery have to be balanced with risk of morbidity and mortality and this again differs quite largely between institutions. The heterogeneity of Stage III disease and the difference in treatment related mortality and morbidity of surgically treated patients is a dilemma for giving a brief recommendation who the surgical candidates are.

There are a few basic rules for surgical treatment of lung cancer. In general, patients profit from surgery only, when resection is complete with free resection margins. Complete resection of metastatic lymph nodes is more problematic to define but is defined to be in those cases in which the highest mediastinal lymph nodes are free. Several studies confirm this definition by showing a superior long term survival in those patients who fulfil these criteria.

When the question has to be answered, who is a candidate for surgery in Stage III disease and then it is advisable to differentiate between T3/T4 tumors from N2 disease.

Tumors with infiltration into the chest wall or the mediastinum are recommended to be radically resected by a lobectomy including chest wall resection and mediastinal lymph adenectomy. Adjuvant chemotherapy is recommended in physically fit patients. Adjuvant radiotherapy is indicated when the resection margin is not clear. Theses patients may achieve a five year survival within a range of up to 40 – 50%.

Patients with infiltration of the carina, aorta or spine are potential candidates as well but should be treated by surgeons with a high experience with these procedures to avoid a high treatment related morbidity or even mortality. More and more of these resections are done after induction chemo or chemo-radiotherapy and it has been shown that surgical morbidity is not increased.

None of the other stages of NSCLC led to a more controversial discussion regarding the overall management than N2 disease. Depending on the experience of the team responsible for treatment decisions, different algorithms are applied. Due to the lack of fully convincing randomized trials the diversity of phase II studies and especially the heterogeneity of the study population, it is not surprising that the available evidence is interpreted differently and discussed controversially. Survival data may differ widely between studies and an explanation is often elusive. Patient selection is among other factors the key for differences in outcome. Unfortunately N2 disease is often imprecisely described. Several authors have proposed that N2 disease should be divided into subgroups. For example Robinson proposed 4 subgroups (1. Incidental nodal metastasis found on final pathology, 2. Nodal metastasis recognized intraoperatively, 3. Nodal metastasis recognized by prethoracotomy staging, 4. Bulky or fixed multistation N2 disease). The question, whether N2 disease can be considered resectable, cannot be answered easily since several co-founding factors play a role. The question includes at least for different aspects. The first aspect is regarding the technical resectability. The surgeon has to answer if the affected lymph nodes are completely removable from a macroscopic standpoint. This question is a prerequisite and is typically answered by analysing images especially the CT or PET/CT by an experienced surgeon. Further tests such as mediastinoscopy may be needed for final evaluation. The second and even more critical aspect relates to the question if local resection is useful for the patient since N2 disease may be the tip of an iceberg and indicate more than just locally advanced disease, a disease with systemic spread of tumor cells to other organs. The third aspect regarding the usefulness of resection is the response rate of the tumor and mediastinal lymph nodes to neoadjuvant chemo- or chemoradiotherapy. Finally the fourth aspect has to take into account the risk benefit ratio for the patient regarding the treatment. It is relevant for the decision making to evaluate to what risk the patient is exposed when a lobectomy or pneumonectomy is performed after neoadjuvant therapy.

When the question has to be answered if N2 disease is resectable or in other words when surgery is indicated or not, subgroups can be defined which allow a clear answer and most oncologists, surgeons and radiotherapists might agree. One subgroup is N2 metastasis found unexpectedly during surgery. If a radical resection of the tumor as well of the lymph nodes is possible and tolerated by the patient, surgery should be completed and adjuvant therapy is recommended. On the other hand in cases of bulky multistation N2 at initial diagnosis and especially after neoadjuvant therapy, surgery is not indicated since the patient will not experience a profit. The main controversy occurs in cases with initially diagnosed N2 disease at either a single or in some adjacent stations but surgically resectable. These patients are recommended either to undergo neoadjuvant chemo- or chemo-radiotherapy followed by surgery. Definitive chemo-radiotherapy is reserved for those who are not completely resectable or high perioperative mortality. However the term resectable is not clearly definable on preoperative imaging and depends from the expertise and subjective judgement of the surgeon.

Despite the fact that two randomized trials did not show a survival benefit in the arm which included surgery after chemo-radiotherapy in comparison to chemo-radiotherapy alone there remain some open questions. The North American intergroup 0196 trial reported a treatment related mortality of 7.9% in the surgical arm in comparison to 2.1% in the medical arm. The mortality was especially high in pneumonectomies with 26%. Despite this unusually high mortality the 5 year survival in the surgical arm in those patients with complete clearance of the mediastinal lymph nodes was 41% and significantly higher. Furthermore patients who underwent a lobectomy experienced a significantly better survival than non-surgical patients. Taken into account that other centres report much lower perioperative mortality even in pneumonectomies after neoadjuvant therapy the role of surgery has to be considered at least in centres with a high expertise. We reported recently a 3% mortality rate in 172 pneumonectomies after chemoradiotherapy for stage III disease treated in two different centers.

In the EORTC trial reported by van Meerbeck there was also no survival benefit in the surgical arm in comparison to the chemoradiotherapy alone arm and the overall 5-year survival was 16.4months. However 50% of the patients had an incomplete resection and the patients which were included had irresectable N2 at study entry. In the multicenter phase II SAKK study reported by Betticher patients with N2 disease and treated by neoadjuvant chemotherapy and surgery the 5-year overall survival was superior with 27.6 months. This outcome was even better in those patients who experienced a complete remission of the mediastinal nodes and underwent surgery.

It is of importance that patients who present with N2 disease should be evaluated by a multidisciplinary team including an experienced surgeon in thoracic oncology in order to select patients for the appropriate treatment either in a study protocol or an individualised regimen which respects the local expertise. Further aspects and other data will be discussed in detail during the conference.

Disclosure: The author has declared no conflicts of interest.

STAGE III NSCLC INVITED PAPERS

77IN

INDUCTION TREATMENT – CHEMOTHERAPY OR CHEMORADIATION?

J.P. van Meerbeeck *Department of Respiratory Medicine, University Hospital, Ghent/BELGIUM*

Concomitant chemoradiotherapy at systemic doses results in superior outcome compared to sequential chemoradiotherapy, at the cost of a moderately increased toxic morbidity and is considered the present standard. Three randomised trials have compared chemotherapy and chemoradiotherapy as induction regimen in stage III NSCLC proceeding to surgery; 1 more is ongoing and 1 has been prematurely closed due to a lack of accrual (table). Ongoing Korean and Swiss trials compare the optimal intensity of induction treatment. Taken together, these trials suggest that induction chemoradiotherapy results in better rates of resectability, pathological downstaging and pathological complete remissions than chemotherapy alone, without significantly affecting overall or progression-free survival survival. Our present systemic induction treatment is still poor. It is unclear whether new cytotoxic drugs will result in an improved outcome, as most third generation drug containing induction combinations seem to have a similar activity in locally advanced disease. Many's expectations are turned towards an incremental effect of adding a targeted biological agent to the standard induction treatment, either during or following radiotherapy. The latter approach was not successfull in a trial conducted by SWOG, wherein patients with stage III were treated with consolidation docetaxel after chemoradiotherapy and then randomised between gefitinib, a small molecule oral inhibitor of the Epidermal Growth Factor Receptor (EGFR) and placebo. A detrimental effect of gefitinib was observed. Early data on the concomitant use of chemoradiotherapy and cetuximab and bevacizumab are promising and need randomised confirmation. Several retrospective and single institutional prospective series show an improved rate of pathological complete remission with higher total doses of radiotherapy, administered concomitantly with standard cisplatin-based combination chemotherapy, suggesting that an improvement in local control is likely to be mostly obtained by improvements in the radiotherapy delivery Current practice guidelines allocate a category 1 evidence to definite concomitant cisplatin-based chemoradiation in selected patients with stage III NSCLC.

Disclosure: The author has declared no conflicts of interest.

78IN

HOW TO RESTAGE A PATIENT AFTER A PREOPERATIVE TREATMENT

G. Stamatis *Thoracic Surgery and Endoscopy, Ruhrlandklinik, Essen/GERMANY*

Multimodal treatment concepts have become a therapeutic option for patients with stage IIIA and in selected cases stage IIIB NSCLC. An important question remains whether a better local control and survival are obtain by induction treatment and surgery compared to standard chemoradiotherapy. Complete resection is an essential factor in the potential of cure, therefore, an important aim of restaging procedures in these patients will be to guide the multidisciplinary decision on whether the patients is a candidate for surgery. For T4 tumors the re-evaluation of tumor viability and metastatic spread in the surrounding structures remains a challenge for anatomic imaging because the reduction of tumor size, which does not occur immediately after cell death, is used as a diagnostic criterion. Morphologic and functional changes in PET/CT scans before and after induction treatment can provide the clinician with information about the prediction of response of the primary tumor. The percentage of remaining FDG signal normalized to the initial SUV has turned out as a better variable for prediction of response. In some cases a VATS procedure before surgery is helpfull to define tumor ivasion and local operability. A major concentration on these restaging issues is warranted since is now agreed that sterilisation of the mediastinal lymph-nodes after induction therapy has an impact on the prognosis of patients with stage IIIA-N2 disease, and accurate staging after therapy may rationally guide diverse therapeutic interventions in these patients. At the present time, neither CT, PET nor PET/CT scans are accurate enough to make final further therapeutic decisions for mediastinal nodal involvement. An invasive technique providing cytohistological information is still recommended at the present time by the European Society of Thoracic Surgeons (ESTS). Endoscopic (EBUS-FNA or/and EUS-FNA) or surgical (mediastinoscopy, remediastinoscopy, VATS) invasive procedures may be utilized the precise choice depending on the availability of the technique and expertise of the centre.

Disclosure: The author has declared no conflicts of interest.

79IN

THE MORBIDITY OF SURGERY AFTER INDUCTION TREATMENT

A.J. Torres, J.R. Jarabo, J. Calatayud, A.M. Gómez, E. Fernández, R.M. Sánchez, F. Hernando *Department of Surgery, Thoracic Surgery Unit, Hospital Clinico San Carlos, Complutense University of Madrid, Madrid/SPAIN*

Surgical treatment offers the best chance for patients with early stages of non-small cell lung cancer (NSCLC). In IIIA-B staged patients multimodality treatment including surgery may be feasible in selected cases. Induction chemo- (CT) or chemoradiotherapy (CRT) has gained acceptance even in early staged cases. The effect of induction therapy on postoperative outcomes remains unclear. Some authors (Roberts 2001) shown that neoadjuvant CT increased life-threatening surgical complications, whereas other reports do not find an increasing in postoperative complications after CT (Perrot 2005). Furthermore, the widespread agreement among thoracic surgeons trying to avoid pneumonectomies due to their association with complications after induction treatment (Martin 2001) remains debatable according with recent reports (Takedo 2006, Mansour 2007). . Factors as pulmonary function tests (PFTs), cardiac function, performance status, age and comorbidity probably determine the deleterious effect of neoadjuvance on surgical outcomes. It has been reported a decrease in the percent diffusion capacity of the lung for diffusion of carbon monoxide (LDCO) after CT or CRT.

Recent reports suggest that preoperative doses of 60 Gy are safe (Sonett 2004, Cerfolio 2009, Milman 2009), obtaining important therapeutic benefits without higher rates of postoperatory complications as bronchopleural fistula.

In conclusion, several items must be kept in mind when designing a multimodality approach to NSCLC:

- A selection process by a multidisciplinary team, with a great role of a specialized oncological thoracic surgeon.
- Identification of underlying comorbidities with a special attention to PFTs (including LDCO).
- A correct restaging after induction treatment to identify persisting N2 disease.

- Special surgical care (reinforcement of bronchial stump, avoidance of pneumonectomy (especially right), use of steroids postoperatively, and optimal medical management).

Disclosure: All authors have declared no conflicts of interest.

80IN
OPTIMAL TREATMENT FOR PS2 PATIENTS

No abstract received at time of going to press.

METASTATIC NSCLC: STATE-OF-THE-ART

81IN
OLIGOMETASTASES: THE POINT OF VIEW OF THE SURGEON

B. Passlick *Department of Thoracic Surgery, University Medical Center Freiburg, Freiburg/GERMANY*

Considering oligometastatic NSCLC two different situations should be considered. First patients with intrathoracic metastasis either to the same lobe (2010 classified as T3) or to a different ipsilateral lobe (2010 classified as T4). In surgical series patients with ipsilateral additional nodules can be encountered in about 4 - 5% of the cases. Patients with additional nodes in the same lobe have a relatively good 5-year survival rate up to 28%. Similarly, patients with T4-tumors due ipsilateral metastases have a 5-year survival rate of 22%. Depending on the co-morbidity and the functional reserve an anatomic resection (lobectomy) in combination with a segmentectomy or wedge-resection is regarded as the treatment of choice.

The second group of patients with oligometastatic lung cancer are patients with extrathoracic metastatic disease. They represent almost 10% of all M1 patients. Among those 5% will have metastases to the brain, 4% to the adrenal glands, 2% to the bones and up to 1% will have single liver metastasis.

Looking at the patients with brain metastasis several prognostic factors have been identified: nodal status positive versus negative), performance status, and primary tumor symptoms (yes or no). In patients with metachronous single brain metastasis a long-term survival can be reached in 16 - 20% of the cases. In our own institution a long-term survival of more than 40% has been reached in patients with complete resection and negative mediastinal nodes. The same long-term survival rates can be reached in patients with single adrenal metastasis. In patients with single ipsilateral adrenal metastasis this can be done in combination with the lobectomy, in all other patients laparoscopic adrenalectomy is the treatment of choice.

In summary, patients with oligometastatic non-small cell lung cancer are rare. If probably staged (PET-CT) a complete resection of the primary tumor and all metastatic disease is recommended. An important prerequisite for a long-term outcome is a negative mediastinum. An adjuvant systemic chemotherapy is mandatory.

Disclosure: The author has declared no conflicts of interest.

82IN
OLIGOMETASTASES: THE POINT OF VIEW OF THE RADIOLOGIST

H. Choy, S.K. Jain *Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas/USA*

Since Halsted's initial description of the contiguous spread of cancer, data illustrating long term, disease free survival in patients with metastases led to Hellman's proposed theory of oligometastases. His theory described a disease state with a limited number of metastases that had not evolved to widespread disease. If this is the case, one could implement aggressive local therapy as curative-intent treatment for oligometastases. Surgical resection data for pulmonary metastases has illustrated improvements in survival, with a 5 year and 10 year overall survival (OS) of 36% and 25% respectively. Based on this improvement in survival with aggressive local control (LC), radiotherapy has also been explored for select patients. Newer techniques, such as stereotactic body radiation therapy (SBRT) that involves precise delivery of an "ablative" tumorcidal dose is now being investigated. This advanced form of radiotherapy involves meticulous treatment planning with accurate patient positioning and immobilization, daily imaging, and sophisticated tumor motion control. Because of success with SBRT in the treatment of primary lung tumors, this technique is now being applied in the oligometastatic setting. Phase II data from Rochester illustrated that 49 patients with 121 metastatic lung lesions had a 3 year actuarial LC rate of 91%. Mean OS time was 23.4 months and treatment was tolerated well with 2% grade 3 toxicity. Data from Germany showed that 61 patients with lung metastasis treated for 71 lesions with SBRT had a 2 year actuarial LC rate and OS rate of 73.7% and 65.1% respectively. Hoyer et al. published phase II data assessing SBRT in colorectal metastasis with 12 patients with pulmonary mets treated to 45 Gy in 3 fractions. Two year actuarial LC rate was 86%. Recently, a multi-institutional, prospective phase I/II trial evaluating SBRT in patients with 1-3 lung metastases treated to 60 Gy illustrated an actuarial 2 year LC rate of 96%, median survival of 19 months, and grade 3 toxicity rate of 8%. In the oligometastatic setting, these studies suggest that SBRT is both well tolerated and effective, with results comparable to metastectomy, and could be a valuable non-invasive treatment option for patients.

Disclosure: All authors have declared no conflicts of interest.

83IN
THE ROLE OF FIRST-LINE TARGETED THERAPIES

C. Gridelli *Division of Medical Oncology, "S.G. Moscati Hospital", Avellino/ITALY*

Molecularly targeted therapies have recently extended the therapeutic options available for the treatment of patients with advanced non-small-cell-lung cancer (NSCLC). Currently two types of therapeutic targets are developed: vascular endothelial growth factor (VEGF) and its receptors and epidermal growth factor receptor (EGFR). Bevacizumab is the first monoclonal antibody (mAb) against VEGF which in combination with chemotherapy compared to chemotherapy alone, as first line treatment, has shown to increase by two months the median survival of advanced non squamous histology NSCLC patients. Other antiangiogenic agents, including sorafenib, VEGF-trap and ASA404 are being tested in ongoing clinical trials which could to clarify their role in the management of NSCLC. Targeting the EGFR has played a central role in advancing NSCLC research, treatment, and patient outcome over the last several years. EGFR inhibition in NSCLC cancer is achieved via small molecular tyrosine kinase inhibitors (TKIs), such as erlotinib or gefitinib; or mAbs such as cetuximab. Cetuximab has show that when added to first line chemotherapy significantly prolongs survival compared to chemotherapy alone (FLEX trial). Trials incorporating TKIs with chemotherapy in first line treatment, failed to produce a survival benefit. The identification of patients that are likely to benefit from EGFR TKI therapy is a priority for patients with advanced NSCLC. Previous, uncontrolled clinical trial have suggested that first-line treatment with gefitinib would be efficacious in selected patients with NSCLC. At the molecular level, most patients with partial or complete responses to TKIs harbored specific mutations in the gene that encodes EGFR. Recently in a large phase III trial (IPASS) in chemotherapy-naive Asian patients with adenocarcinoma who were never smokers or former light smokers, gefitinib was more effective than carboplatin plus paclitaxel in prolonging progression-free survival. In a prespecified subgroup analysis, EGFR-mutation-positive status

is a strong predictor of a better outcome with gefitinib. The EURTAC trial assessing the role of erlotinib in EGFR mutated tumors is ongoing. Despite the recent therapeutic improvements, the overall survival for most patients with advanced-stage disease remains modest, and clinical trials that investigate the activity of novel agents, and incorporate patient selection based on clinical and molecular factors, are required.

Disclosure: C. Gridelli: Honoraria as speaker bureau and advisory board member for Roche, Merck-Serono

84IN

CUSTOMIZING SYSTEMIC THERAPY IN PATIENTS WITH ADVANCED LUNG CANCER

P. Germonpré *Pneumology Service, Antwerp University Hospital, Edegem/BELGIUM*

Until recently non-small cell lung cancer (NSCLC) was considered as a single disease entity, whereby the treatment decissions were mainly based on the stage of the tumor, and the performance status and comorbities of the patient. Currently we are at the dawn of customized treatment for advanced NSCLC based prognostic and predictive charateristics of both the patient or the tumor. A growing body of evidence shows that tumor-specific biomarkers can predict response to therapy in NSCLC. However most of these predicitve biomarkers still require validation in phase III trials of customized treatment. Histology has recently emerged as a potential predictive factor for treatment with EGFR-TKIs or pemetrexed. In patients with an adenocarcinoma the response rates for EGFR TKIs are higher (without necessarily translating into superior survival), while three large phase III trials demonstrated that the pemetrexed efficacy differs significantly according to NSCLC histology. However we should move beyond histology as a predictive marker, as it is clear that underlying molecular factors are responsible for these findings. The IPASS trial proved that a molecular selection based on EGFR mutation status is superior in terms of predicting benefit from treatment with EGFR TKI. The sensitivity to pemetrexed on the other hand seems to correlate to the thymidylate synthase expression (high expression in squamous cell carcinoma, low expression in adenocarcinoma and variable expression in large cell carcinoma). Although the relationship between DNA repair systems and survival in NSCLC patients treated with cisplatin-based chemotherapy has been extensively studied, prospective validation of molecular selection based on these molecular markers is lacking. Currently such a trial using BRCA1 and RAP80 as genetic markers is ongoing. Bevacizumab-containing regimens are contraindicated in patients with squamous cell NSCLC because of an increased risk of inducing life-threatening hemoptysis. Patient rather than tumor-related factors are also correlated with treatment-related toxicities. For example, a deficiency of serum cytidine deaminase activity is associated with the occurence of early severe toxicities with gemcitabine.

Disclosure: The author has declared no conflicts of interest.

85IN

MAINTENANCE THERAPY

S. Novello[1], M. Giaj Levra[1], E. Capelletto[2], S.G. Rapetti[2] *[1]Thoracic Oncology Unit, University of Turin, Ospedale San Luigi, Orbassano/ITALY, [2]Thoracic Oncology Unit, University of Turin, Orbassano/ITALY*

Maintenance Therapy for patients (pts) with metastatic non–small cell lung cancer (NSCLC) the 5-year survival rate is equal to 2.8%, leaving an unmet medical need for this population. According to the recently released ASCO Clinical Practice Guideline Update cytotoxic chemotherapy should be stopped at disease progression or after 4 cycles in pts whose disease is not responding to treatment and, also in case of response, doublet cisplatin-based chemotherapy should not be administered for no more than 6 cycles. Maintenance therapy (first-line treatment is continued or switched to another agent beyond 4-6 cycles) is gaining recognition as a possible approach, as clinical trials have demonstrated a survival benefit. Early (maintenance therapy) versus delayed (at the time of progression) administration of docetaxel was tested in a randomised study: median progression-free survival (PFS) significantly favored early docetaxel with a trend of a better overall survival (OS). Pemetrexed (pem) was tested in a phase III study as a maintenance therapy (vs placebo) in pts with advanced NSCLC who did not progress after 4 cycles of platinum-based doublet chemotherapy. PFS was significantly longer with pem (4.3 vs 2.6 mo; hazard ratio [HR] = 0.50). OS was also significantly improved (13.4 vs 10.6 mo; HR = 0.79) and pem was generally well tolerated during long-term exposure. A pre-planned subset analysis showed in non-squamous histology a survival benefit of 5 months (HR 0.70) for pts treated with pem. Erlotinib (erl) in the maintenance setting was explored in two phase III studies. In one of these 889 pts who had not progressed on 4 cycles of platinum-based chemotherapy were randomized to maintenance with erl or placebo. Maintenance therapy with erl resulted in a better disease control rate at 12 weeks (40.8% vs 27.4%), with a statistically significant improvement in PFS (12.3 weeks vs 11.1 weeks) compared with placebo (HR = 0.71; p = .000003) and in OS (12 vs 11 mo, HR 0.81). The available evidence support the maintenance approach for pts (with response or stable disease) without relevant clinical toxicities and asking to continue therapy. For those pts with clinical relevant toxicity with first line therapy or preferring a treatment holiday and monitoring, starting timely second line remains an appropriate alternative.

Disclosure: All authors have declared no conflicts of interest.

METASTATIC NSCLC: BIOLOGY FROM THE BENCHMARK TO BEDSIDE INVITED PAPERS

86IN

THE IDENTIFICATION OF NOVEL TARGETS FOR DEVELOPING NEW CLINICAL TRIALS

J. Mazières *Department of Pneumology, Larrey Hospital, CHU Toulouse, Toulouse/FRANCE*

Continuing progress in basic cancer research and drug development has led to discoveries of new agents or strategies for molecular targeting in novel cancer therapies. These new agents suppress tumour growth through multiple mechanisms such as cell cycle control, activation of tumour suppressor genes, essential signal pathway blockage, tumour vaccines, tumour microenvironment modification, etc. Rapid translation of these exciting discoveries into clinical practice requires timely support to accommodate the special needs of novel cancer therapy development. In the field of lung cancer, molecular targets or processes such as EGFR, IGFR, ALK, angiogenesis have been well identified and studied from bench to bedside with an impact on patient survival. Nevertheless, some of the new drugs have been disappointing essentially due to the absence of biomarker-based patients selection. Patient selection should be considered as early as possible in the drug development process. This may be followed by a recruitment expansion only in selected patients at higher doses to interrogate biological hypotheses. Moreover, the dose-limiting toxicities of targeted therapies are frequently markedly different from those of cytotoxic anticancer drugs. Target modulation can be assessed by phase 0 clinical trial that are designed to evaluate the pharmacodynamic effect of a new drug that is expected to be correlated with its clinical activity. In addition to the shift in the initial phase of drug development, the design of phase II and III studies may also need to change to adapt clinical development to the needs of modern drug development without compromising assessment of relevant end points, especially in confirmatory pivotal trials. Randomized phase II studies in selected patient

populations employing various dose levels, guided by biomarkers of activity and randomized assignment of potential responders to either the study drug or placebo and withdrawal of subjects who do not benefit because of disease progression, may help to optimize classical phase II studies. Enrichment of patients in phase III studies may be an essential tool to prevent negative trials. Demonstration of benefit based on hard clinical end points is also considered to be pivotal for modern innovative drugs. The paradigm shift in the development of novel anticancer drugs is the change from widely used chemotherapy to drugs for selected patient populations or even for niche indications. A very tight collaboration among clinicians, basic researchers and pharmaceutical companies is mandatory in order to investigate new potential target and to design new relevant clinical trials. Some examples of new targets, new clinical trial and optimization of translational research will be discussed.

Disclosure: The author has declared no conflicts of interest.

87IN

THE ROLE OF ANTI-ANGIOGENIC AGENTS (TKIS)

M. Reck *Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf/ GERMANY*

Dysregulation of angiogenesis in solid tumors enables tumor growth and metastasis. Receptors that mediate angiogenesis, and their ligands, have been identified; among these, vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase play a central role. First-Line Treatment: In a randomized phase III trial (ESCAPE trial) the addition of sorafenib to standard chemotherapy didn′t improve overall survival (OS) or progression-free survival (PFS) but was associated with a higher mortality rate in patients with squamous cell lung cancer histology (Scagliotti 2008). Results of a second randomized trial (NEXUS trial) are awaited. Cediranib at a dose of 30 mg combined with chemotherapy did improve response rate (RR) and PFS but was associated with unacceptable toxicity (Goss 2009). Second-Line Treatment: Combination of vandetanib and docetaxel showed a statistical significant improvement in PFS, RR and a trend in OS compared to docetaxel (Herbst 2009). However two additional trials which compared the combination of vandetanib and pemetrexed with pemetrexed and vandetanib with erlotinib didn′t meet the primary endpoint of statistically significant PFS prolongation (de Broer 2009, Natale 2009). In two similar randomized phase III trials the VEGFR-TKI BIBF1120 is evaluated either in comb. with docetaxel or with pemetrexed compared to docetaxel or pemetrexed. The primary endpoint of both trials is significant prolongation of PFS. Sunitinib which has shown a median PFS of 12.0 weeks and a median OS of 23.4 weeks (Socinski 2008) has been investigated in a randomized trial in comb. with erlotinib compared to erlotinib. Results are awaited for 2010. In heavily pretreated patients sorafenib has shown improvement in PFS in a randomized phase II trial compared to placebo (Schiller 2008). Currently a randomized phase III trial compares the efficacy of sorafenib with placebo in patients failing at least two lines of previous chemotherapy. Conclusion: The role of antiangiogenic TKI in treatment of NSCLC hasn′t been defined yet and is currently investigated in a large number of randomized trials. One of the most important challenges for the future is the identification of predictive markers which might help to select patients who benefit from treatment with these new drugs.

Disclosure: M. Reck: I have received honoraria for lectures from Hoffmann-La Roche, Lilly, Merck and AstraZeneca. I served on the Advisory Board of Hoffmann-La Roche, Lilly, Merck and AstraZeneca.

88IN

PREDICTIVE MARKERS OF TUMOR RESPONSE

B. Besse *Department of Medicine, Institut Gustave Roussy, Villejuif/ FRANCE*

In the last decade, treatment of non-small-cell lung cancer (NSCLC) was steadily improved by optimizing cytotoxic chemotherapy and integration of targeted therapies. Further improvements could be expected by individualizing therapy based on predictive biomarkers. To date, the "quest" for the perfect predictive molecular marker has been mainly based on retrospective database with 2 types of technology. (1) High throughput technology; Despite huge efforts and millions of Euros spent worldwide each year to identify predictive biological signatures, there has been limited progress and only one signature (Metagene) is being evaluated prospectively; (2) single biomarker approach; we may distinguish such a biomarker in 3 categories of therapeutic agents: cytotoxic agents, tyrosine kinase inhibitors and antiangiogenic agents. In the 'cytotoxic setting', DNA repair pathways have provided the most promising biomarkers for cisplatin resistance, as the expression of ERCC1 & MSH2 or the level of BRCA1 mRNA. Others candidate biomarkers such as the cell cycle regulator p27, class III β-tubulin or thymidylate synthase had been linked to a benefit of chemotherapy. With regard to targeted therapies, specific activating mutations located in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are associated with an improved response to EGFR-directed tyrosine kinase inhibitors (TKIs) in NSCLC patients. In contrast, mutations in KRAS or c-Met amplification are associated with resistance to EGFR-directed TKI therapy. EML4-ALK variant seems to be a good candidate for ALK inhibitors. Although antiangiogenic therapies are actively studied in NSCLC, no predictive biomarker has been identified so far and the patients' selection still rely on clinical and pathological profile. Because many biomarkers have only been characterized in retrospective studies, prospective validation in well designed clinical trials is mandatory. Important issues are availability of sufficient tumor material, validation of detection methods, and confirmation of the survival benefit in properly designed clinical trials. According to the present promising data, individualized therapy based on tumor features is feasible and may improve outcome of patients with NSCLC in the future.

Disclosure: The author has declared no conflicts of interest.

89IN

MOVING FORWARD IN THE FIELD OF NEW ORAL INHIBITORS

F. Cappuzzo *Department of Medical Oncology, Istituto Clinico Humanitas IRCCS, Rozzano, Milan/ITALY*

Non-small cell lung cancer (NSCLC) remains the main cause of cancer death in the world. Unfortunately, at the time of diagnosis, the vast majority of patients have a metastatic disease and a definitive cure is not achievable. Currently, the standard treatment consists in platinum-based chemotherapy, with the addition of the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab in certain patients. Recent advances in the knowledge of cancer biology led to the identification of several potential molecular targets that play a key role in cancer development and progression. Selective targeting of cancer cells based on their molecular phenotype can provide effective anti-cancer activity avoiding the commonly experienced side effects induced by chemotherapy. Moreover, many of the agents under investigation have the advantage of oral administration. Among these agents, the reversible Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) gefitinib and erlotinib demonstrated to produce dramatic and durable response in some patients with NSCLC, particularly in those harbouring an activating mutation of the EGFR

gene. Four large phase III randomized trials comparing standard chemotherapy versus gefitinib in chemonaive NSCLC demonstrated the superiority of gefitinib at least in terms of progression free survival, in EGFR mutant patients.. These data strongly support EGFR testing in NSCLC together with an early usage of EGFR-TKIs in individuals with an EGFR mutation. Specific molecular events, including the presence of EML4-ALK fusion gene, could be responsible for the lack of sensitivity to anti-EGFR strategies observed in some patients and even in EGFR mutants, after an initial response, all patients inevitably acquire resistance. Therefore, new oral agents are under investigation, including ALK inhibitors, cMET inhibitors and the new class of irreversible EGFR-TKIs. Preclinical and clinical data suggested that such agents are effective in patients with specific biological characteristics highlighting the importance of incorporating prospective molecular genotyping into clinical trials of novel targeted agents.

Disclosure: The author has declared no conflicts of interest.

TUMOR BIOLOGY AND PATHOLOGY

90O

CXCR4 OVER-EXPRESSION BY IMMUNOHISTOCHEMISTRY (IHC) HERALDS POOR OUTCOME IN METASTATIC NSCLC

S. Otsuka, A. Klimowicz, K. Kopciuk, S. Petrillo, E. Stolte, M. Konno, W. Boland, D. Morris, T. Magliocco, G. Bebb *Tom Baker Cancer Centre and University of Calgary, Calgary/CANADA*

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. In vitro, CXCR4 expression has been shown to correlate with migration, invasion and adhesion. High CXCR4 expression in resected tumors is associated with poorer clinical outcome, but its effect on outcome in advanced non-small cell lung cancer (NSCLC) has not been explored. We investigated the effect of CXCR4 expression on outcome in stage IV NSCLC.

Methodology: 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 NSCLC and tissue arrays (TAs) generated. Specimens were randomly assigned into tester and validator cohorts. CXCR4 expression within NSCLC cells was analyzed by IHC (Epitomics) using the HistoRx PM-2000 platform then correlated with clinical outcome. CXCR4 high expression cutoff was determined as mean expression plus 1 SD. Statistical analysis was performed using the Kaplan-Meier method, multivariate analysis and Spearman's rank correlation.

Results: Between 2003-2006, 832 patients were diagnosed with stage IV NSCLC with 303 tissue samples available, 200 suitable for TA generation. The overall survival of patients whose tumors were suitable for TA generation was similar to the general cohort. Automated IHC for CXCR4 was successfully completed on the tester cohort of 103 patients. High expressers (10.7% of the tested stage IV patients) had a significantly poorer clinical outcome with a median overall survival (MOS) of 2.7 months vs 6.1 months for the low expressers (P=0.0001). CXCR4 over-expression was associated with squamous histology, smoking history and a higher rate of brain metastases.

Conclusions: CXCR4 is expressed in most NSCLC tumors. CXCR4 over expression is associated with significantly poorer survival in stage IV NSCLC patients. Our results suggest that novel therapeutic strategies, possibly involving anti-CXCR4 drugs, should be tested in CXCR4 over-expressers. Staining on a validation cohort is underway and full data will be presented.

Disclosure: All authors have declared no conflicts of interest.

91O

NESTIN EXPRESSION IN NON-SMALL CELL LUNG CANCER AND ITS RELEVANCE WITH PROGNOSTIC SIGNIFICANCE

C. Zhenguang[1], W. Tao[2], L. Honghe[1], Y. Xuhui[3], X. Peng[3] *[1]Thoracic Department, 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou/CHINA, [2]Center for Stem Cell Biology and Tissue Engineering, Sun Yat-sen University, Key Laboratory for Stem Cells and Tissue Engineering, Ministry of Education, 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou/CHINA, [3]Center for Stem Cell Biology and Tissue Engineering, Sun Yat-sen University, Key Laboratory for Stem Cells and Tissue Engineering, Ministry of Education, 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou/CHINA*

Background: As an intermediate filament protein and important neural stem cell marker, nestin has been detected in several progenitor cells during development. Recent reports indicated nestin may be re-expressed under neoplastic transformation and exerted its activity by linking to malignant characteristics so that nestin could be a new and simple diagnostic tool for evaluation of tumor prognosis. Investigation to the association of nestin expression with prognosis in non-small cell lung cancer (NSCLC) would enable the use of nestin as a biomarker of the disease.

Methods: Using immunohistochemistry method, we investigated the expression of nestin in 52 cases of NSCLC specimens and also successfully detected nestin expression in three NSCLC cell lines by immunocytochemistry staining, RT-PCR and western blot. Next, we analyzed association of nestin expression with clinical and pathological characteristics of NSCLC and assessed its influence on patients' prognosis. Moreover, we revealed nestin expression in A549 and H460 cell lines, blockaded nestin expression by shRNA-mediated knockdown, and demonstrated the variety of tumor cells proliferation, apoptosis and subcutaneous growth in vivo.

Results: Nestin expressed in tumor cells of 86.5% samples and three NSCLC cell lines. When the median histoscore of nestin was used as cutoff value (8.4), significant differences of nestin expression could be observed between poor and well differentiation ($p = 0.007$) or between adenocarcinoma and squamous cell carcinoma ($p = 0.000$). The median survival time of the patients with a low nestin expression was more than 60 months as compared with 23 months among those with high nestin expression ($p = 0.003$). This difference corresponded to a 3.42-fold increased risk of dying for patients with high nestin expression ($p = 0.009$) and remained significant in multivariate analysis (hazard ratio, 3.366; $p = 0.034$) independent of other clinicopathological features. Stable siRNA-mediated knockdown nestin expression decreased proliferation and increased apoptosis of A549 and H460 tumor cells prominently. In vivo, knockdown of nestin expression inhibited growth of A549 and H460 cells when implanted as tumor xenografts.

Conclusions: Our results identified nestin expression in NSCLC tissues and cell lines. Knockdown of nestin expression revealed down-regulation of proliferation and up-regulation of apoptosis in NSCLC cell lines. Nestin might be a strong and independent favorable prognostic marker for NSCLC.

Disclosure: All authors have declared no conflicts of interest.

92O

OVEREXPRESSION OF THE SIGNAL TRANSDUCER VAV1 IS A PROGNOSTIC FACTOR IN RESECTABLE NON SMALL CELL LUNG CANCER PATIENTS

E. Sapir[1], G. Laizer[2], S. Katzav[2], U. Izhar[3], E. Pikarsky[4], G. Amir[5], N. Peylan Ramu[1] *[1]Oncology and Radiation Therapy, Hebrew University, Hadassah Medical Center, Jerusalem/ISRAEL, [2]Department of Experimental Medicine and Cancer Research, Hebrew University, Hadassah Medical*

Center, Jerusalem/ISRAEL, [3]Thoracic Surgery, Hebrew University, Hadassah Medical Center, Jerusalem/ISRAEL, [4]Pathology, Hebrew University, Hadassah Medical Center, Jerusalem/ISRAEL, [5]Patology, Hebrew University, Hadassah Medical Center, Jerusalem/ISRAEL

Background: Better knowledge of the molecular abnormalities and their effects on responsiveness to therapy may improve our ability to predict and eventually improve long term survival of resectable non small cell lung cancer (NSCLC). Remarkable advances in the understanding of NSCLC biology have been made, including alterations in gene products directly related to drug activity. Physiological expression of Vav1 is restricted to the hematopoietic system, where its best-known function is as a GDP/GTP nucleotide exchange factor, an activity strictly controlled by tyrosine phosphorylation downstream of cell surface receptors. We previously found that Vav1 is widely expressed in lung cancer and plays a critical role in its pathogenesis. Thus, Vav1 expression could define a subset of tumors that is signified by specific clinical characteristics.

Methods: We retrospectively collected clinical and pathological information of 140 patients with resectable NSCLC treated at the Hadassah Medical Center. We prepared a tissue microarray containing 3 tumor and 3 normal lung cores from each case. Immunohistochemical staining for Vav1 protein expression was performed and analyzed by automated image analysis by the Ariol SL50 robotic image analysis system.

Results: From 8/1994 until 12/2001, 140 patients (pts) with NSCLC underwent wedge resection (7), lobectomy (105) or Pneumonectomy (28). Pts' age range: 40 - 84 years. M/F ratio: 2/1 and 81% had non squamous disease. Stage I - 46%, II - 34% and III −20%. Additional therapy included adjuvant radiotherapy in 17 pts and neoadjuvant chemotherapy in 3 pts. Presently 39 pts (28%) are well and alive. We divided the pts into 3 groups according to VAV1 protein expression: To examine the effect of gene expression on survival of patients we used the Cox model. The median survival for each group was: Low-39.5, Medium-36, High-64 months. HR (High vs. Low and Medium groups) was 0.63 with p - 0.04. These results were also demonstrated by the Kaplan-Mayer curves.

Conclusions: 1. Overexpression of Vav1 indicates higher overall survival in resectable NSCLC. 2. VAV1 may be identified as a potential therapeutic target and an instrument for decision making for therapy

Disclosure: All authors have declared no conflicts of interest.

93O

METHYLATED SHOX2 DNA IN BRONCHIAL LAVAGE – A HIGHLY SPECIFIC MOLECULAR TUMOR MARKER FOR LUNG CARCINOMA

B. Schmidt[1], V. Liebenberg[2], D. Dietrich[2], M.J. Walshaw[3], T. Schlegel[2], C. Kneip[2], T. Liloglou[4], M. Fleischhacker[5], C. Witt[1], J.K. Field[4] *[1]Medizinische Klinik m.S. Pneumologie, Charité-Universitätsmedizin, Berlin, Berlin/GERMANY, [2]Product Development, Epigenomics AG, Berlin/GERMANY, [3]Respiratory Medicine, Liverpool Heart and Chest Hospital Trust, Liverpool/UNITED KINGDOM, [4]Roy Castle Lung Cancer Research Programme, University of Liverpool Cancer Research Centre, Liverpool/UNITED KINGDOM, [5]Medizinische Klinik m.S. Onkologie Und Hämatologie, Charité-Universitätsmedizin, Berlin, Berlin/GERMANY*

In patients with suspected lung cancer the objective of the diagnostic workup is to establish a definitive diagnosis using the least invasive diagnostic procedures. Especially when conventional methods like histology and cytology cannot establish the diagnosis, molecular tests may provide additional information to clinicians and pathologists. A lung specific tumor marker with a low rate of false positive results could be of clinical value by speeding up the existing workup and avoiding laborious and eventually risky procedures. Objective: The goal of this retrospective study was to evaluate DNA methylation of the SHOX2 gene as a tumor marker to detect malignant lung disease in patients with suspected lung cancer using a bronchial lavage material obtained for cytology and confirm results from an earlier study in a larger and independent study population. Methods: Bronchial lavage specimen from 475 subjects undergoing workup for suspected lung cancer, 257 patients with lung carcinoma and 218 control samples from patients with non-malignant lung disease were included in the study. The samples were obtained at two European centers (Charité Berlin and University of Liverpool). SHOX2 methylation was measured by quantitative real-time PCR. Results: DNA methylation of SHOX2 was shown useful for distinguishing lavage specimen of patients with lung carcinoma from samples of patients without malignant disease with high specificity. A ROC analysis of the test performance exhibited an AUC of 0.86 [95% confidence interval, 0.83-0.89]. At a specificity of 99% [3/218 without disease] the tumor marker showed a sensitivity of 55% [141/257 with malignant lung disease] in this population comprised of the major histological lung cancer subtypes. Squamous cell carcinoma alone was detected at an even better sensitivity of 71% 66⁄93 at the same high specificity. Conclusion: These results show that detection of SHOX2 gene methylation in bronchial lavage specimens taken from patients with suspected lung cancer is a promising tumor marker to identify patients with lung carcinoma. The development of a diagnostic test based on this marker and a clinical study for its prospective performance evaluation are currently ongoing.

Disclosure: V. Liebenberg: I am an employee of Epigenomics AG, Berlin, Germany; D. Dietrich: I am an employee of Epigenomics AG, Berlin, Germany; T. Schlegel: I am an employee of Epigenomics AG, Berlin, Germany; C. Kneip: I am an employee of Epigenomics AG, Berlin, Germany; J.K. Field: The work presented was performed without financial interest requiring disclosure. Nevertheless, currently negotiations regarding an Advisory board membership are ongoing and might lead to such a relationship in future. All other authors have declared no conflicts of interest.

94O

GENE EXPRESSION PROFILES IN NON-SMALL CELL LUNG CANCER (NSCLC) AND IN CORRESPONDING HEALTHY LUNG TISSUES IN SMOKERS VS. NON-SMOKERS

A. Szymanowska-Narloch[1], M. Skrzypski[2], M. Taron[3], H. Dienemann[4], W. Rzyman[5], M. Jarzab[6], T. Muley[7], E. Jassem[1], R. Rosell[8], J. Jassem[2] *[1]Department of Allergology, Medical University of Gdansk, Gdansk/POLAND, [2]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND, [3]Medical Oncology Service, Catalan Institute of Oncology, Badalona, Barcelona/SPAIN, [4]Department of Thoracic Surgery, University of Heidelberg, Heidelberg/GERMANY, [5]Department of Thoracic Surgery, Medical University of Gdansk, Gdansk/POLAND, [6]Department of Tumor Biology, Center of Oncology Maria Sklodowska-Curie Memorial Institute Branch Gliwice, Gliwice/POLAND, [7]Translational Research Unit, University of Heidelberg, Heidelberg/GERMANY, [8]Medical Oncology Service, Catalan Institute of Oncology, Badalona/SPAIN*

Background: About 5-15% of all lung cancer patients are non-smokers. Defining biological factors of NSCLC development in patients not subjected to cigarette smoke carcinogens is of particular importance. The aim of this study was to compare expression of key genes related to etiology of NSCLC in smoking vs. non smoking patients in tumor samples and in corresponding healthy lung tissue.

Methods: We analyzed snap frozen tumor samples from 85 surgically treated NSCLC pts (39 non-smokers and former smokers and 46 smokers), with corresponding 70 normal lung tissue samples (from 32 and 38 pts, respectively). Expression of 21 genes (including genes associated with smoking, kinases, hormonal receptors, growth factor receptors, transcription factors, genes indirectly involved in HPV infection pathways and other) was assessed by RT-PCR with the use of microfluid cards (MFC). Analysis of

RT-PCR was performed with relative quantification $2^{-\Delta\Delta C}{}_T$. Subunit 18S, POLR2A and ESD were used as normalization genes.
Results: Expression of 11 genes was higher in healthy lung tissues compared to tumors: PgR (p=0.0000), TGFBR2 (p=0.00000), TGFBR3 (p=0.0000), AR (p<0.0001), EPHB6 (p<0.0001), RRAD (p<0.0001), AHR (p=0.0003), ESR1 (p=0.0006), IGF2 (p=0.0014), DLG1 (p=0.0016) and CSF1R (p=0.0048), whereas 6 genes showed higher expression in tumors: BIRC5 (p=0.0000), AKR1B10 (p<0.0001), CHRNA6 (p<0.0001), CDKN2A (p<0.0001), SOX9 (p<0.0001) and ESR2 (p=0.002). Five genes were significantly overexpressed in tumors of non-smokers vs. smokers: PgR (p<0.0001), RRAD (p<0.0001), AR (p=0.0006), CSF1R (p=0.0009) and TGFBR2 (p=0.002), whereas one (BIRC5) was downexpressed (p=0.0007).
Conclusions: Gene expression in NSCLC is strongly related to smoking history. Overexpression of PgR and AR in tumors suggests possible hormonal dependence. Some other molecular distinct features may prompt new treatment strategies.
Disclosure: All authors have declared no conflicts of interest.

95O
RELIABLE CLASSIFICATION OF NON-SMALL CELL LUNG CARCINOMA USING A NOVEL MICRORNA-BASED APPROACH

W.H. Westra[1], J.A. Bishop[1], H. Benjamin[2], H. Cholakh[3] *[1]Pathology, The Johns Hopkins University School of Medicine, Baltimore/USA, [2]Pathology, Rosetta Genomics Ltd, Rehovot/ISRAEL, [3]Pathology, Rosetta Genomics Inc., Philadelphia/USA*

Background: Advances in targeted lung cancer therapy now demand accurate classification of non-small cell lung cancer (NSCLC). MicroRNAs (miRNAs) are recently-discovered short, non-coding genes that play essential roles in tissue differentiation during normal development and tumorigenesis. For example, hsa-miR-205 is a miRNA that is highly expressed in lung squamous cell carcinomas (SqCCs) but not in non-squamous lung carcinomas. The differential expression of miRNAs could be exploited to distinguish squamous from non-squamous tumor types.
Methods: 102 resected NSCLCs were classified as SqCC or adenocarcinoma (AC) based on their histologic features and immunohistochemical profiles (p63, TTF-1 and Napsin). Corresponding pre-operative biopsies/aspirates that had been originally diagnosed as poorly differentiated NSCLCs were available for 21 cases. A qRT-PCR diagnostic assay which measures the expression level of hsa-miR-205 was used to classify the carcinomas as SqCC or AC based solely on expression levels. The two sets of diagnoses were compared.
Results: Using conventional methods of lung cancer classification (i.e. microscopy and immunohistochemistry), 52 resected lung carcinomas were classified as SqCCs and 50 as ACs. There was 100% concordance between the histologic diagnoses and miRNA-based diagnosis. MiRNA profiling also correctly classified 20 of the 21 preoperative biopsy specimens.
Conclusions: MiRNA profiling is a highly reliable strategy for accurately classifying NSCLCs. Indeed, classification is consistently reliable even in small aspirates and biopsies of poorly differentiated tumors. Confirmation of its reliability across all tumor grades and specimen types (aspirates, biopsies and resections) represents an important step towards broad application. Quantitative separation of squamous and non-squamous NSCLCs may not only directly benefit patients by individualizing oncologic therapy, but will enhance objectivity among those trials correlating clinical endpoints with defined pathologic variables.
Disclosure: W.H. Westra is a consultant for Prometheus Laboratories Inc. This lab markets miRNA technology for the classification of lung cancer. Funding for travel has been provided by Rossetta Genomics. H. Benjamin: Authors affiliated with Rosetta Genomics are full-time employees and/or hold equity in the company, which develops microRNA based diagnostic products and may stand to gain by publications of these findings; H. Cholakh: Authors affiliated with Rosetta Genomics are full-time employees and/or hold equity in the company, which develops microRNA based diagnostic products and may stand to gain by publications of these findings. All other authors have declared no conflicts of interest.

96O
COMBINED TARGETING OF AROMATASE AND EPIDERMAL GROWTH FACTOR RECEPTOR IN NON-SMALL CELL LUNG CANCER

I. Kritikou[1], E. Giannopoulou[2], A.K. Koutras[2], H. Kalofonos[2] *[1]Clinical Oncology Laboratory, Department of Medicine, University of Patras, Patras/GREECE, [2]Department of Medicine, Division of Oncology, Clinical Oncology Laboratory, University of Patras, Patras/GREECE*

Background: Targeted therapy provides an exciting project for treatment of non small cell lung cancer (NSCLC). Aromatase catalyses the final step of estrogen synthesis in several tissues including lung. EGFR signaling is implicated in cell proliferation and metastasis. Cross-talking between these pathways has been reported. The aim of this study is to evaluate the antitumor effect of the combined inhibition of aromatase and EGFR.
Material and methods: In vitro experiments were performed on H23, H358 and A549 NSCLC cell lines. Exemestane and erlotinib were applied. Cell proliferation was measured by MTT assay and cell death by annexin V/propidium iodide assay. Cell migration was determined by boyden chamber assay. pEGFR status was estimated using an appropriate ELISA kit and EGFR location was detected by immunofluorescence.
Results: Exemestane and erlotinib, either alone or in combination, inhibited cell proliferation, through an increase in cell apoptosis. However, the combination of the agents had a synergistic effect only on H23 cells. The tested agents and their combination inhibited migration of H23 cells. Exemestane inhibited H358 cell migration whereas erlotinib reversed this effect. No change was found on cell migration of A549. Further, pEGFR levels were increased by exemestane in H23 cells and decreased in A549 cells. These experiments are in progress for H358 cells. Moreover, it was found that EGFR translocated in mitochondria after exemestane application in H23 cells while erlotinib reversed this effect. These experiments are ongoing for H358 and A549 cells.
Conclusions: Although each agent alone exerted an antitumor effect on the proliferation of all cell lines, their combination had a synergistic effect on H23 cells. Exemestane activated EGFR pathway in H23 cell line suggesting the treatment of these cells should include an anti-EGFR agent.
Disclosure: All authors have declared no conflicts of interest.

97PD
IMMUNOHISTOCHEMISTRY WITH MUTATION SPECIFIC ANTIBODIES DETECTING THE STATUS OF EGFR MUTATIONS IN NON-SMALL-CELL LUNG CANCER

J. Yu[1], D. Li[2] *[1]Cell Biology, Cell Signaling Technology, Danvers/USA, [2]Pathology, Second Xiangya Hospital, Changsha/CHINA*

Background: Activating mutations within the tyrosine kinase of epidermal growth factor receptor (EGFR) are found in approximately 10-30% of non-small-cell lung cancer (NSCLC) patients and the association between EGFR mutations and response to EGFR tyrosine kinase inhibitors (TKIs) in NSCLC has been consistently confirmed in a number of studies. Deletions in exon 19 and the L858R substitution in exon 21, accounting for approxi-

mately 90% of all EGFR mutation, are the best characterized sensitizing mutations in adenocarcinoma (AC). This study was designed to evaluate immunohistochemistry (IHC) with mutation specific antibodies to detect mutant EGFR proteins in NSCLC for patient selection to TKI therapy.
Design: We have screened 410 cases of paraffin embedded NSCLC patient tumor samples, which included 330 cases of AC and 80 cases of other types of NSCLC, by IHC using total EGFR antibody and exon 19 delE746_A750 and L858R mutation specific antibodies. The result was confirmed by DNA sequencing. In addition, we compared patient response to TKIs with the IHC staining result in 32 patients who were treated by TKI prior the screening.
Result: Screening a panel of the tumor samples with the mutation specific antibodies showed the sensitivity of the IHC assay is 86% and the specificity is 99% as compared with direct and mass spectrometry based DNA sequencing. Among these, there were 32 advanced disease cases treated by Iressa until disease progression. In three month following up: 1 case complete response (CR), 8 cases partial response (PR), 2 cases stable disease (SD), 21 cases progression of disease (PD). The total effective rate (CR+PR) was 28.1% and disease control rate (CR+PR+SD) was 34.4%. 9 of the 32 cases (28.1%) were IHC positive: 1 CR, 7 PR, 1 SD. Total effective rate (CR+PR) of IHC positive cases was 88.9% and disease control rate (CR+PR+SD) was 100.0%.
Conclusion: IHC with mutation specific antibodies to detect mutant EGFR proteins is a rapid, specific and cost efficient methodology. The positive staining is not just highly correlative to the sequencing result, but also correlative to tumor response to TKIs.
Disclosure: All authors have declared no conflicts of interest.

98PD

QUANTITATIVE ANALYSIS OF PLASMA DNA IN RESECTABLE NSCLC, CHRONIC INFLAMMATORY RESPIRATORY DISEASES AND HEALTHY CONTROLS

A. Szpechcinski[1], K. Maszkowska-Kopij[2], W. Kupis[3], E. Puscinska[4], P. Bielen[5], T. Orlowski[3], P. Sliwinski[5], J. Chorostowska-Wynimko[1] *[1]Laboratory of Molecular Diagnostics and Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw/POLAND, [2]Outpatient Department, National Institute of Tuberculosis and Lung Diseases, Warsaw/POLAND, [3]Department of Thoracic Surgery, National Institute of Tuberculosis and Lung Diseases, Warsaw/POLAND, [4]Department of Lung Diseases, National Institute of Tuberculosis and Lung Diseases, Warsaw/POLAND, [5]Department of Diagnosis and Treatment of Respiratory Failure, National Institute of Tuberculosis and Lung Diseases, Warsaw/POLAND*

Background: minute amounts of free-circulating DNA are present in plasma of healthy individuals, whereas increased levels are found in malignant pathologies including non-small cell lung cancer (NSCLC). Intensified cell death processes seem to play a crucial role in release of genomic DNA into a bloodstream. Thus, quantitative analysis of plasma DNA might be useful for monitoring of treatment effectiveness in NSCLC by indication patient's physiological response. However, it remains questionable whether the elevated release of free-circulating DNA into the bloodstream of NSCLC patients results from malignancy or chronic respiratory inflammation.
Methods: plasma samples were collected from 30 NSCLC patients (I-IIIA) before and after surgery, patients with chronic inflammatory respiratory diseases (30 COPD, 30 sarcoidosis, 20 asthma), and 25 healthy volunteers in order to free-circulating DNA extraction and real-time PCR quantification.
Results: NSCLC group showed significantly higher mean plasma DNA concentration with respect to patients with chronic respiratory inflammation and healthy controls (12.10 vs. 3.90 vs. 2.85 ng/ml, respectively; $p=0.001$). Furthermore, drastic increase in plasma DNA levels up to mean 68.74 ng/ml was observed a week after the primary tumor resection. Most NSCLC patients with no disease recurrence during 6-12 month follow-up demonstrated reduced plasma DNA levels with respect to presurgical plasma DNA concentration values.
Conclusions: NSCLC is associated with elevated concentration of free-circulating DNA in plasma, and chronic respiratory inflammation does not seem to contribute to this phenomenon. We speculate that postsurgical trauma causes drastic increase in plasma DNA levels, whereas a trend towards reduction of free-circulating DNA amount is observed in relapse-free patients. The study is to be continued and the groups extended.
Disclosure: All authors have declared no conflicts of interest.

99PD

IMPACT OF CENTRAL REVIEW WITH UNDERTAKING OF IMMUNOHISTOCHEMISTRY ON THE DIAGNOSIS OF LUNG CANCER

H. Charalambous[1], C. Charalambous[2] *[1]Medical Oncology, Bank of Cyprus Oncology Centre, Nicosia/CYPRUS, [2]Histopathology, Nicosia General Hospital, Nicosia/CYPRUS*

Introduction: Increasingly with more multidisciplinary team working 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 Immunohistochemistry (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 (sq) and non-squamous types (non-sq), which now has major therapeutic implications.
Methods: Between 2006 and 2009, following referral to one clinical oncologist (HC) with the diagnosis of Lung Cancer, all histopathology specimens coming from private histopathologists in Cyprus (without site specialization for Lung Cancer and without IHC being undertaken) were referred for central review to a specialized Lung pathologist (CC) in the Nicosia General Hospital. This was undertaken in 34 cases. Comparison was made between the initial histology diagnosis and the final diagnosis following central review and IHC.
Results: There was concordance for 20 out of 34 specimens (59%). There were 7 major changes in diagnosis (21%): 2 NSCLC changed into SCLC, 2 SCLC into lymphoma, 1 lymphoma into adenocarcinoma, 1 adenocarcinoma into mesothelioma and 1 carcinoid into metastasis from bladder cancer. There were also 7 cases (21%) where the subclassification of NSCLC changed, 4 from sq to non-sq, 1 from non sq to sq, whilst 2 changed but remained non squ. There were also 2 cases (6%) where only NSCLC classification was used in the original report. Hence in total for 14 patients (41%) there were potential treatment implications as a result of this review. See main results in table underneath.
Conclusion: This study shows the importance of undertaking central review including IHC for all patients referred with an initial diagnosis of lung cancer.

Private/Primary H&E Diagnosis	Final Histopathology Diagnosis
Adeno 10	Adeno 8
	Squ 1
	Mesothelioma 1
SCLC 9	SCLC 7
	Lymphoma 2
Squ 5	Squ 1
	Adeno 4
NSCLC 4	SCLC 2
	Adeno 2
Lymphoma 1	Adeno 1

Disclosure: All authors have declared no conflicts of interest.

100PD

EVALUATION OF ERCC1, BRCA1, THYMIDYLATE SYNTHASE (TS), CLASS III BETA TUBULIN(BTUBIII), P53R2, RRM2 IN STAGE I-III NON-SMALL CELL LUNG CANCER (NSCLC): A TISSUE MICROARRAY (TMA) STUDY

F. Grossi[1], C. Genova[1], E. Rijavec[1], D.F. Merlo[2], S. Salvi[3], M. Mannucci[2], M. Taviani[4], L. Morelli[5], G.B. Ratto[5], M. Truini[3] *[1]Medical Oncology, National Institute for Cancer Research, Genoa/ITALY, [2]Epidemiology and Biostatistics, National Institute for Cancer Research, Genoa/ITALY, [3]Pathology, National Institute for Cancer Research, Genoa/ITALY, [4]Thoracic Surgery, University of Genoa, Genoa/ITALY, [5]Thoracic Surgery, National Institute for Cancer Research, Genoa/ITALY*

Previous studies have shown that high levels of BRCA1, TS and bTubIII and low levels of ERCC1 and RRM1 expression are associated with poor prognosis in NSCLC patients (pts) treated with surgery alone. Also, clinical studies suggest that ERCC1, RRM1, BRCA1 and bTubIII expression is associated with resistance to several agents. Tumor tissue samples from 82 pts with stage I-III NSCLC who underwent surgery between 7/2005 - 3/2007 were analyzed. Viable tumor was sampled in triplicate for TMA analysis, and slides were stained by immunohistochemistry (IHC) with antibodies against ERCC1, BRCA1, TS, bTubIII and P53R2, RRM2 (subunits of RRM). All tissue arrays were examined and independently scored by two observers (M.T. and S.S.), blinded to the patients. The score was calculated using the following formula: (1 + I) x PC, where I represents the staining intensity and PC represents the percentage of tumor cells that stained at each intensity, respectively. A categorical value (positive vs negative) was used for statistical analyses of marker expression. In addition, IHC expression profiles were correlated with clinicopathological features. During a median follow-up time of 41 months (range 28-54), a total of 13 deaths was observed. In univariate analysis, P53R2 expression was significantly higher in adenocarcinoma compared to squamous samples (mean score 59.3 vs 4, $p=0.01$), whereas TS expression was significantly higher in squamous tumors (mean score 39.2 vs 3.1, $p=0.03$). bTubIII expression was significantly higher in stage I vs stage II pts (mean score 200.2 vs 49.2, $p=0.023$). No significant association was seen between ERCC1, BRCA1, RRM2 expression and any clinicopathological features. The small number of deaths is insufficient for meaningful prognostic evaluation. In conclusion, this study confirms the different expression of TS in adenocarcinoma compared to squamous pts and suggests a possible role of p53R2 as a marker for histological differentiation. The significantly higher expression of bTubIII in stage I compared to stage II pts may explain a stage-specific different efficacy of adjuvant chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

101PD

THE DETECTION OF CIRCULATING TUMOR CELLS IN LUNG CANCER PATIENTS

J. Klein[1], J. Srovnal[2], Z. Kolar[3], J. Skarda[3], P. Skalicky[1], T. Janaskova[4], M. Hajduch[2] *[1]The 1st Department of Surgery, University Hospital Olomouc, Czech Republic, Olomouc/CZECH REPUBLIC, [2]1Laboratory of Experimental Medicine, University Hospital Olomouc, Czech Republic, Olomouc/CZECH REPUBLIC, [3]Department of Pathology, University Hospital Olomouc, Czech Republic, Olomouc/CZECH REPUBLIC, [4]Department of Pneumology, Hospital Ostrava-Vítkovice, Ostrava/CZECH REPUBLIC*

Objectives: The role of circulating tumor cells (CTC) and nucleic acids in prognostication in non-small cell lung cancer patients is controversial, but may be better defined with advancing technologies of detection of such cells or free tumor DNA with higher precision, and improved clinical-pathological correlations. Biomarker measurements of the minimal tumor cell dissemination disease have the potential to monitor the molecular status of tumors without invasive tumor biopsy, at the time of treatment selection.

Patients: This is a pilot study to test for the presence of circulating tumor cells (CTC) samples of the peripheral blood, blood from vv. pulmonales and bone marrow in 21 lung cancer patients undergoing curative surgery.

Methods: We used real-time RT-PCR method for absolute gene expression quantification of carcinoembryonic antigen (CEA), epidermal growth factor receptor 1 (EGFR1), human telomerase reverse transcriptase (hTERT), palate, lung and nasal epithelium associated (PLUNC) and hepatocyte growth factor receptor (c-met).

Results: All tested markers are characterized by high specificity and sensitivity for CTC detection in lung cancer patients. CTC positivity using CEA was found in 40% (8/20) of vv.pulmonales blood samples, in 43% (9/21) samples of peripheral blood and 52% (11/21) samples of bone marrow. Using EGFR we detected CTC positivity in 25% (5/20) of vv.pulmonales blood samples, in 10% (2/21) samples of peripheral blood and 43% (9/21) samples of bone marrow.

Conclusions: This pilot study shows that the CTC detection in lung cancer is technically possible and high specific and sensitive markers for the monitoring of CTC are available. The clinical relevance of this minimal tumor cell dissemination is under permanent debate. It is our hope that validation of postoperative persistence or re-appearance of tumor cells may help to identify patients in need of an adjuvant systemic therapy. Optimalization of the panel of specific tumour markers and evaluation of their validity in monitoring of the minimal residual disease in lung cancer patients need to be investigated in larger studies.

Disclosure: This study was supported by grant IGA MZCR NS 10285-3 2009. All authors have declared no conflicts of interest.

102PD

INHIBITION OF CARMA3 IMPAIRS LYSOPHOSPHATIDIC ACID-INDUCED LUNG CANCER CELL MIGRATION AND INVASION THROUGH NF-KAPPAB

J. Sun[1], J. Cai[2], Y. Feng[3] *[1]Department of Molecular Cellular Oncology, The University of Texas M.D. Anderson Cancer Center, Houston/USA, [2]Surgery, Wenzhou Medical University Affiliated No.2 Hospital, Wenzhou/CHINA, [3]Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin/CHINA*

Lung cancer is the leading cause of cancer deaths in both women and men in the United States and throughout the world. Lung cancer can be triggerd by lysophosphatidic acid (LPA). LPA is a type of G protein-coupled receptor ligand, and a bioactive mediator that induce cell proliferation, migration, invasion, and production of angiogenic factors in lung cancer cell lines. LPA activates NF-kappaB, which is an important transcription factor and plays critical roles in tumorigenesis, such as migration and invasion. We have previously reported that CARMA3 (CARD and MAGUK domain-containing protein 3) is indispensable in LPA-induced nuclear factor kappa B (NF-kappaB) activation in mouse embryonic fibroblast cells. However, it remains unknown whether the CARMA3 plays an important role in LPA-induced lung cancer cell migration and invasion. In the present study, using CARMA3 shRNA, we knockdowned its protein expression level in lung cancer cell lines. Consistent with previous reports, we found that down-regulation of CARMA3 strikingly impaired LPA-induced IKK activity and NF-kappaB activation in lung cancer cells. In addition, in vitro transwell migration and matrigel invasion assays demonstrated that CARMA3 shRNA

significantly attenuated LPA-induced lung cancer cell motility and invasiveness. Together, our results provide the evidence that CARMA3 serve as a critical regulator in LPA-induced, NF-kappaB-mediated lung cancer cell migration and invasion. Therefore, we speculate that CARMA3 may represent an attractive therapeutic target for lung cancer cell and many other alignancies.

Disclosure: All authors have declared no conflicts of interest.

103P

CLINICAL AND BIOLOGICAL FEATURES ASSOCIATED WITH EML4-ALK FUSION GENE IN NON SMALL CELL LUNG CANCER

C. Choi[1], S.H. Jang[2], Y.I. Hwang[2], J.H. Jung[3], Y.Y. Lee[4], J.C. Lee[4] *[1]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, Seoul/KOREA, [2]Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Anyang/KOREA, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam/KOREA, [4]Department of Internal Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological & Medical Science, Seoul/KOREA*

Purpose: The EML4-ALK fusion gene has been detected in 5-7% of lung adenocarcinomas. We evaluated the incidence, prognosis and the characteristics of ALK-rearranged non-small cell lung cancers and the optimal diagnostic modality to detect ALK rearrangements in routine clinical practice.

Experimental design: Seven hundred and nine surgical specimens of non-small cell lung cancer from two institutions were analyzed. To identify ALK rearrangements immunohistochemistry were performed. We also examined ALK rearrangements by fluorescent in situ hybridization (FISH). The clinicopathologic characteristics of tumors with and without ALK reaarangemets were compared. EGFR and KRAS mutations were determined by DNA sequencing.

Results: We identified 49 (6.9%) non-small cell lung cancer with ALK rearrangements within our cohort by immunohistochemistry. Forty-three (87.8%) of the 49 EML4-ALK tumors were adenocarcinomas. ALK reaaranement was associated with never smoking ($p < 0.001$) and female ($p < 0001$). Among 372 cases ALK rearrangement was identified by FISH in 9 (2.4%) cases. Eight (88.9%) was negative in immunohistochemistry. Patients in the EML4-ALK fusion gene in adenocarcinoma had no effect on progression free survival and overall survival.

Conclusions: The patients most likely to harbor EML4-ALK are never smokers with adenocarcinoma. But EML4-ALK was not prognostic factor.

Disclosure: All authors have declared no conflicts of interest.

104P

VALUE OF EGFR GENE MUTATION ANALYSIS IN CHINESE NON SMALL CELL LUNG CANCER PATIENTS

M. Sun[1], L. Shen[2], X. Cai[2], H. Chen[3], X. Du[2], X. Zhou[1] *[1]Tissue Bank, Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai/CHINA, [2]Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai/CHINA, [3]Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai/CHINA*

EGFR inhibitors Erlotinib and Gefitinib are of very important in treating late stage adenocarcinoma of lung due to a longer survival related to EGFR mutation, more frequently in Asian, female and non smoker patients, although EGFR inhibitor has not been used as first choice treatment for advanced Asian patients. We included 92 Chinese cancer patients into the study of EGFR mutation. Among them 60 were lung cancer and the others were either the patients without clear diagnosis or necessary for differentiation diagnosis including 11 supraclavicular lymph node biopsies, 7 Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) for mediastinal masses and 14 masses of different other sites. EGFR mutation was checked. Thirty nine out of 92 patients possessed mutation in EGFR gene (42.39%, 39/92). In lung cancer patients the mutation counted 46.67% (28/60) and it increased to 58.14% (25/43) in adenocarcinoma only. Squamous carcinoma, large cell carcinoma and poorly differentiated carcinoma did not show any mutation in our study. In EBUS-TBNA samples 42.86% mutation (3/7) was detected, close to our mutation rate in lung cancer. Around half mutation were located in exon 19 and around one third in exon 21. There was a tendency of a lower exon 19 mutation in older patient group (median age 58, >58 vs. ≤ 58,) (35.71%, 5/14 vs. 58.82%, 10/17, $P=0.0581$) and a higher exon 21 mutation in younger group (64.29%, 9/14 vs. 23.53%, 4/17, $P=0.0800$). The mutation in exon 19 was found more frequent in male patients (71.43%, 10/14), while the mutation rate of exon 19 and exon 21 in female patients was comparative (43.47%, 10/23 in exon 19 and 47.83%, 11/23 in exon 21). Mutation in exon 20 was rare (4 mutations found). A relatively high mutation rate of supraclavicular lymph node (36.37%, 4/11) was seen, in comparison to the one in other variant sites was low (20.00%, 4/20). One exon 19 mutation of a metastatic adenocarcinoma located in uterus muscle layer was detected. Our data suggest that EGFR mutation analysis show its value both in selection of EGFR TKI treatment and in differentiation diagnosis of some common metastasis lesions. In Asian patients group, mutation analysis in EBUS-TBNA samples demonstrates to be of important in providing treatment hint.

Disclosure: All authors have declared no conflicts of interest.

105P

DOMINANT-NEGATIVE AGGREGATION OF P53 AS A NOVEL MECHANISM OF TUMOUR SUPPRESSOR GENE INACTIVATION

J. Xu, J. Reumers, J. Couceiro, F. Rousseau, J. Schymkowitz *Switch Laboratory, Vrije Universiteit Brussel, Brussels/BELGIUM*

It remains largely unexplained why the most aggressive p53 missense mutations possess dominant-negative activity, why they often display gain of oncogenic activity and why the presence of these mutants leads to lifetime extension and accumulation of p53 in tumours. Here we show, both in cultured cells and in murine and human tumours, that the dominant-negative activity of p53 mutants is tetramer-independent and instead results directly from the increased aggregation propensity of these mutants. Upon aggregation, mutant p53 is able to induce the co-aggregation of the wild type p53 and its family members p63 and p73 into cellular inclusions. Aggregation explains equally well the lifetime extension and accumulation of both mutant and wild type p53 in tumours, as suppression of the aggregation propensity in these mutants fully restores wild type p53, p63 and p73 activity. Finally, we classify patient data from the literature according to aggregating versus non-aggregating mutants and find a significant difference in the second hit (loss of heterozygosity) and clinical outcome both with respect to therapeutic response and long-time survival. The poorer clinical outcome of patients with aggregating mutants suggests that gain-of-function is also a consequence of aggregation and that inhibition of p53 aggregation might be a valuable therapeutic strategy.

Disclosure: All authors have declared no conflicts of interest.

106P

PROGNOSTIC IMPORTANCE OF P27KIP1 EXPRESSION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

S. Ariad[1], J. Freedman[1], I. Lazarov[1], A. Bolotin[2], N. Sion-Vardy[3] [1]*Department of Oncology, Soroka University Medical Center, Beer Sheva/ISRAEL,* [2]*Department of Epidemiology, Ben Gurion Unversity of the Negev, Beer Sheva/ISRAEL,* [3]*Department of Pathology, Soroka University Medical Center, Beer Sheva/ISRAEL*

Introduction: Tumor node metastasis (TNM) staging and histological grading are acceptable classification systems for lung cancer (LC), but not satisfactory to predict prognosis. p27Kip1 (p27) plays an important role in cancer cell cycle regulation by inhibiting cyclin–CDK complex activity in the nucleus. Recent evidence however, suggests that under certain conditions, p27 may function as an oncogene rather than a tumor suppressor gene. Although most studies in LC patients indicated that loss of p27 protein expression diminishes chance of survival, some investigators reported opposite findings. We assumed that this discrepancy could be attributed to the inclusion of different groups of patients, lack of stratification by histological grade, or non-standardized methodology.

Patients and methods: Ninety-two patients of all stages with previously untreated non-small cell lung cancer (NSCLC) were included. Tumors diagnosed as adenocarcinoma were evaluated for grade. The IHC localization of p27 was scored through a semiquantitative method. IHC studies were also performed for p53, and Pirh2. The association between p27 H-Score values and time-to-progression (TTP) and overall survival (OS) was analyzed with population-averaged, panel-data models by using generalized estimation equations (GEE). TTP and OS time were analyzed with Cox proportional hazards regression models.

Results: The mead H-Score value for p27 was equal to 91.2 + 83.7. The relationship between p27 H-Score to TTP or OS time was polynomial for both. Short TTP in patients with metastasis or whose tumors progressed during the eight-month period after diagnosis was statistically associated with overexpression of Pirh2 ($P < 0.001$). In patients whose tumors progressed later, long TTP was associated with LC of the non-adenocarcinoma type ($P = 0.027$), p27 H-Score ($P = 0.032$), and well-differentiated adenocarcinoma ($P = 0.047$). None of the parameters was found to correlate with OS time.

Conclusions: The interpretation of p27 H-Score has to be collaborated with other clinico-pathological parameters which indicate metatasis or may predict TTP. The non-linear relationship may reflect different biological effects of p27 on cell proliferation.

Disclosure: All authors have declared no conflicts of interest.

107P

USING REAL TIME (RT)-PCR FOR GLUTATHIONE-S-TRANSEFRASE P1 (GSTP1) GENE TO MEASURE FREE CIRCULATING DNA IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

L.E. Raez[1], E.S. Santos[2], T. Talebi[1], C. Quintero[1], G. Walker[1], E. Lopez[1], M. Farias[1], R. Singal[1] [1]*Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami/USA,* [2]*Oncology, University of Miami, Miami/USA*

Purpose: Measurement of free circulating DNA (free DNA) as predictor for chemotherapy response (complete: CR, partial: PR, stable: SD or progression: PD) in newly diagnosed patients (pts) with advanced non-small cell lung cancer (NSCLC). There is evidence that tumors shed DNA into the blood stream and the plasma DNA concentrations increase in pathological situations associated with cell death.

Material and methods: Every two cycles of chemotherapy, free DNA was measured (ng/ml) in blood samples from NSCLC patients by real time (RT)-PCR for Glutathione-s-transefrase P1 (GSTP1) gene. Nonparametric tests were used to examine the relationship between baseline DNA level and patient characteristics (Wilcoxon rank sum test: WRST) and to test changes from baseline after two treatment cycles (Wilcoxon signed rank test: WSRT).

Results: We enrolled 32 pts, all treated with platinum-based chemotherapy. Baseline data were available for 26 pts: 19 males, 23 White, and 16 Hispanic. All pts had stage III/IV and 19 were adenocarcinomas. Responses were: PR: 27%, SD: 58% and PD: 12%. No association was found between baseline FCDNA and age (< 68 v ≥ 69, $p=0.200$), gender ($p=0.954$), ethnicity ($p=0.385$), PS (0 v ½, $p=0.732$), stage ($p=0.978$), histology (adenocarcinoma vs. other, $p=0.386$), or smoking history ($p=0.648$). Measurements after 2 treatment cycles were available for 13 pts. Nine patients had higher levels of free DNA after 2 cycles of chemotherapy compared with baseline, while 4 showed a decrease. The difference was marginally significant, $p=0.080$, (WSRT). No association was found between baseline free DNA level and response following 2 treatment cycles: $p=0.545$, Kruskal-Wallis test comparing 7 patients with PR against 15 with SD and 3 with PD. Change in free DNA was not associated with response: $p=0.316$ comparing 4 PR and 9 SD (8) or PD (1); $p=0.445$.

Conclusion: We have documented here important changes in the amount of free DNA in NSCLC patients on chemotherapy, however, these changes have not achieved statistical significance yet. Results increasing the number of pts and number of samples per pt as per protocol will be presented in the meeting.

Disclosure: All authors have declared no conflicts of interest.

108P

SNIP1 EXPRESSION CORRELATES WITH THAT OF RB AND HDAC1 IN PRIMARY LUNG CANCERS AND INTERFERES RECRUITMENT OF HDAC1 TO RB IN VITRO

H. Jeon[1], J.Y. Park[2], J. Fukuoka[3], J. Jen[4] [1]*Department of Biochemistry & Cell Biology, Kyungpook National University, School of Medicine, Deagu/KOREA,* [2]*Department of Internal Medicine, Kyungpook National University, School of Medicine, Deagu/KOREA,* [3]*Lab of Anatomic Pathology, Toyama University Hospital, Toyama/JAPAN,* [4]*Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester/USA*

Smad nuclear interacting protein 1 (SNIP1) regulates gene expression through interactions with multiple transcription regulators. The Rb tumor suppressor gene plays a critical role in controling cell proliferation and differentiation. It recruits HDAC1 protein into the E2F complexes to repress transcription. Phosphorylation of Rb by Cdk4/6 and Cdk2 displaces HDAC from the pocket domain and releases its transcriptional repression activity. In here, we show that SNIP1, Rb and HDAC1 were significantly coexpressed in lung cancer tissues in a tissue microarray containing 300 non-small cell lung cancers. There was a strong correlated expression between staining for SNIP1 and Rb, SNIP1 and HDAC1 ($P=0.00003$, $P=0.00006$, respectively). Functionally, SNIP1 competes with HDAC1for binding Rb and reducing HDAC1 activity. We found that phosphorylation of Rb was reduced by knockdown of SNIP1. Knockdown of SNIP1 caused reduction of tumorigenesis of lung cancer cells. These findings suggest that SNIP1 is involved in the Rb/HDAC1 chromatin remodeling pathway and may play a role in lung cancer progression.

Disclosure: All authors have declared no conflicts of interest.

109P

FTIR SPECTROSCOPY OF A549 CELLS TREATED WITH PMF: STRUCTURAL CHANGES IN DNA AND CELL MEMBRANE

G.A. Ahmed[1], F.A. Khorshid[2], T.A. Kumosani[2] *[1]Biochemistry, King Abdulaziz University-Faculty of Science, Jeddah/SAUDI ARABIA, [2]Biochemistry, King Fahd Medical Research Centre-King Abdulaziz University-Faculty of Science, Jeddah/SAUDI ARABIA*

Cancer becomes one of the leading causes of death in many countries all over the world. PMF (new natural product extracted from PM 701) has been proved recently as selective anticancer agent. FTIR spectra of human lung cancer cells (A549) treated with PMF for different time intervals ranging from 5min up to 24hr were examined. The results revealed that characteristic bands alterations were identified in the apoptotic cells arising from cellular protein, lipid and DNA, there were specific changes that affected the secondary structure of proteins in the apoptotic lung cells appeared in the FTIR spectra confirmed with the second derivative analysis. The dominant protein structure shifts from α-helix in the control cancer cells (untreated) to parallel β-sheet and random coil structure indicating modification protein secondary structure in the apoptotic cells treated up to 24 hr and these changes in the secondary structure of proteins are time dependant. In addition the total cellular lipid content increases starting from the first 5 to 15 min up to 24hr of treatment while the amount of DNA decreases dramatically during treatment with PMF as observed in difference spectrum. A characteristic internucleosomal ladder of DNA fragmentation was observed with A549 cells treated with PMF for 30 min. Moreover, the pH values were recorded for all samples during the time of treatment, at all times of treatment, the pH values increased significantly after adding PMF to A549 cells the maximum value was obtained at 2hr of treatment.

Disclosure: All authors have declared no conflicts of interest. pectroscopy

110P

TARGETING ER-GOLGI HOMEOSTASIS IS AN ADVANTAGEOUS THERAPEUTIC STRATEGY IN LUNG CANCER

V. Zismanov[1], L. Drucker[2], M. Gottfried[3] *[1]Lung Cancer Research Laboratory, Meir Medical Center, Kfar Saba/ISRAEL, [2]Oncogenetic Laboratory, Meir Medical Center, Kfar Saba/ISRAEL, [3]Lung Cancer Unite Oncology, Meir Medical Center, Kfar Saba/ISRAEL*

Heat shock protein 90 (Hsp90) is a molecular chaperon essential for folding and stability of multiple oncogenes and an established target in cancer therapeutics (lung included). Misfolded proteins accumulate in the ER, induce ER stress, and activate response pathways such as the ubiquitin proteasome system (UPS), which orchestrates turnover of cellular proteins and histone deacetylases (HDACs) that critically recruit misfolded protein aggregates (un-degradable by UPS), into dedicated organelles. Indeed, Hsp90 inhibition causes unfolded proteins accumulation and ER stress. The therapeutic efficacy of such inhibition may be augmented by co-administering it with other drugs that disrupt response signals that enable ER-Golgi homeostasis. We aimed to examine the effect of combined treatment of Hsp90 antagonist with proteasome or HDAC inhibitors on human lung cancer cell lines fate (viability, proliferation, cell cycle, death, death mode) and ER-Golgi homeostasis (protein synthesis, UPR, autophagy, other Hsps, FOXO). Hsp90 inhibitor (17-DMAG) co-administration with HDAC inhibitor (PTACH) or proteasome inhibitor (Velcade) yielded a synergistic increase in apoptosis of lung cancer cell lines. Reduced viability was demonstrated in all cell lines with all drug combinations except 17-DMAG and PTACH co-administered to H1299 cells. Interestingly, combined 17-DMAG and PTACH induced elevated H1299 viability despite the increased cell death. We hypothesized that this phenomenon may result from increased H1299 proliferation and in accordance determined higher levels of PCNA in treated cells. Analyses of ER stress markers (BiP, CHOP, and pJNK) in the treated cancer cells are underway. Our findings provide proof-of-concept that targeting ER-Golgi homeostasis is therapeutically beneficial in lung cancer cell lines.

Disclosure: All authors have declared no conflicts of interest.

111P

NR2E1 INHIBITS CELL PROLIFERATION IN LUNG SQUAMOUS CELL CARCINOMAS BY REGULATING ENTRY TO CELL CYCLE

D. Barh[1], P. Sindhurani[2], A. Bhattacharjee[3] *[1]Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri/INDIA, [2]Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri/INDIA, [3]Bioinformatics Laboratory, Department of Biotechnology and Bioinformatics, North Eastern Hill University, Shillong/INDIA*

Objective: Orphan nuclear receptor and transcription regulator NR2E1 (TLX) regulates neural stem cell proliferation and self-renewal through Wnt/beta-catenin pathway [PMID: 20010817] and mutations in the gene have been implemented for bipolar disorder [PMID: 18205168]. Recently, NR2E1 promoter has been found hyper-methylated and can be considered as methylation marker in lung squamous cell carcinomas (LSCCs) [PMID: 18162535]. NR2E1 upregulates SIRT1 expression [PMID: 19555662] and interacting with histone demethylase (LSD1) and HDACs (HDAC3, HDAC5), it regulates PTEN, P21, and CDK-inhibitor transcription [PMID: 18391013, PMID: 17873065] and thereby it may regulate cell cycle and cell proliferation. NR2E1 also interacts with GSPT1, HSP90AB1, and MED1. This study was aimed to explore the role NR2E1 plays in LSCC tumorigenesis.

Methods: In silico approaches were used in this analysis. Briefly, an experimentally validated NR2E1 promoter (600 bp) was retrieved using Genomatix "Gene2Promoter" module. Thereafter CpG and transcription factor (TF) binding sites within this sequence were predicted using respectively, Methylator and MATCH programs. Lung and cell cycle specific affected TFs due to hyper-methylation were identified by comparing Methylator and MATCH results. VisANT and Osprey tools were used for protein-protein interaction network based functionality analysis using NR2E1, its promoter binding TFs, and NR2E1 interacting proteins.

Results: Twenty one CpG sites are predicted to be hyper-methylated and there are at least 4 lung and 8 cell cycle specific TF binding sites (including E2F, MYB) found with in NR2E1 promoter sequence. Two cell cycle specific TFs (E2F and YY1) and one lung specific TF (NF1) are affected due to hyper-methylation. Key nodes and shortest pathway analysis from protein-protein and TFs-interaction network based functionality analysis shows that NR2E1 inhibits cell proliferation by regulating entry to cell cycle.

Conclusions: Our results suggest that NR2E1 is a negative regulator of cell growth and proliferation that exerts it function by regulation entry to cell cycle.

Disclosure: All authors have declared no conflicts of interest.

112P

CORRELATION OF FACTOR XIII ACTIVITY WITH CELL-TYPES AND STAGES OF NON-SMALL CELL LUNG CANCER

J.H. Kim[1], I.B. Suh[2], K.H. Jung[1], G.Y. Hur[3], S.Y. Lee[3], S.Y. Lee[4], J.J. Shim[3], K.H. In[4], K.H. Kang[3], S.H. Yoo[4] *[1]Department of Internal Medicine, Korea University Ansan Hospital, Ansan/KOREA, [2]Department of Clinical Pathology, Kangwon National University Hospital, Chuncheon/KOREA, [3]Department of Internal Medicine, Korea University Guro Hospital, Seoul/KOREA, [4]Department of Internal Medicine, Korea University Anam Hospital, Seoul/KOREA*

Background: Factor (F) XIII is a thrombin-activated plasma transglutaminase zymogen, which has been reported to support hematogenous tumor cell metastasis. The purpose of this study is to examine the correlation of FXIII activity with cell-types and stages of non-small cell lung cancer (NSCLC), comparing with healthy subjects.

Methods: Forty-seven NSCLC patients were enrolled; 22 adenocarcinoma, 17 squamous cell carcinoma, and 8 undifferentiated NSCLC; 5 stage I, 1 stage 2, 21 stage III, and 20 stage IV. Age-, gender-, and smoking status-matched healthy subjects were selected from participants of The Korean Health and Genome Study, an ongoing population-based prospective cohort study. FXIII activity was measured using fluorescence based protein arrays. Fabricated amine modified glass slides were incubated with fibrinogen, and diluted plasma was mixed with reaction buffer including CaCl2 and thrombin. Then reaction mixture was applied to the array wells and the FXIII catalyzed incorporation of pentylamine into fibrinogen was probed with Cy3-conjugated streptavidin and scanned with a fluorescence scanner. The FXIII activity was expressed as relative fluorescence units (RFU).

Results: The FXIII activity of the NCSLC group (78.7±3.8 RFU, mean±SEM) was significantly higher than that of the Healthy group (63.2±2.3 RFU) ($p=0.03$). In the subgroup analysis, FXIII activities were significantly different among adenocarcinoma (89.2±8.9 RFU), squamous cell carcinoma (70.3±5.2 RFU), undifferentiated NSCLC (52.4±3.7 RFU) and Healthy groups ($p=0.015$, by Kruskal-Wallis test). FXIII activity in the adenocarcinoma NSCLC group was significantly higher than those of other cell types and Healthy groups ($p<0.05$). The stage IV group (76.8±8.7 RFU) showed significantly higher FXIII activity than other stages and Healthy groups ($p<0.05$). The FXIII activity of stage IV adenocarcinoma group (95.7±10.7 RFU) was significantly high, comparing with other cell type-stage combinations and Healthy group ($p<0.05$).

Conclusions: FXIII activity showed correlation with cell types and stages of NSCLC, suggesting potential roles of FXIII in progression and metastasis of NSCLC.

Disclosure: All authors have declared no conflicts of interest.

113P

ACCURACY OF CYTOLOGY IN THE IDENTIFICATION OF HISTOLOGIC SUBTYPE IN NON-SMALL CELL LUNG CANCER (NSCLC)

M. Tiseo[1], R. Nizzoli[1], A. Guazzi[1], M. Bartolotti[1], F. Gelsomino[1], M. Majori[1], L. Ferrari[1], M. De Filippo[1], E.M. Silini[1], A. Ardizzoni[2] *[1]Medical Oncology, Parma Hospital, Parma/ITALY, [2]Medical Oncology, Parma University Hospital, Parma/ITALY*

Background: The importance of histological sub-typing for non small cell lung cancer (NSCLC) has recently increased due to the emerging differences in the medical treatment between squamous and non-squamous cancer. Many NSCLCs present at diagnosis in advanced stage and diagnosis is often obtained by fine needle aspirate (FNA) cytology. In this study we investigate how reliable is FNA cytology diagnosis in sub-typing NSCLCs as compared to histology.

Methods: From 2002 up to 31/03/2009, a total of 875 cytological exams for lung cancer suspicion have been performed. 369 patients had a cytological (MGG stain +/- PAS/PAP) diagnosis of primary NSCLCs on trans-bronchial needle aspirate (TBNA) or trans-thoracic needle aspirate (TTNA) samples by an experienced cytologist (RN, AG). Of these patients, 171 (46%) underwent a parallel or subsequent histological diagnosis (HE +/- HIC) on bronchial biopsy or major surgery as performed in blind and independently by dedicated pathologists (EMS).

Results: Of 171 cases investigated for comparison, at cytology 151 (88%) had a specific subtype diagnosis (90 adenocarcinoma, 56 squamous cell carcinoma, 5 large cell carcinoma), and 20 cases (12%) were defined as NSCLC not otherwise specified (NOS). At histology, 155 had a specific subtype diagnosis (87 adenocarcinoma, 60 squamous cell carcinoma, 4 adeno-squamous carcinoma, 2 large cell carcinoma, 1 small cell carcinoma, 1 mesothelioma) and 16 cases (9%) resulted NSCLC NOS. Concordance between cytology and histology was found in 118 (80%) cases. Predictive value of cytologic diagnosis was 84% for adenocarcinoma and 79% for squamous cell carcinoma.

Conclusions: On the basis of the high concordance between cytology and histology, our data indicate that cytology in expert hands is reliable for both identifying lung malignancy and NSCLC sub-typing. FNA cytology is acceptable for diagnosis and treatment planning in most cases and especially when other more invasive approaches are unfeasible.

Disclosure: All authors have declared no conflicts of interest.

114P

ROLE OF NUCLEAR MORPHOMETRY IN DIAGNOSIS OF SPUTUM CYTOLOGICAL ATYPIA IN SMOKERS

R. Kulshrestha[1], V. Vijayan[2] *[1]Pathology, Vallabhbhai Patel Chest Institute, Delhi/INDIA, [2]Respiratory Medicine, Vallabhbhai Patel Chest Institute, Delhi/INDIA*

Background: Cytological atypia of exfoliated cells in sputum has been shown to be associated with both prevalent and incident lung cancer. However the clinical utility of sputum cytological atypia remains uncertain to date. One reason for this is the subjective classification of sputum cytology by pathologists into normal with or without squamous metaplasia, mild atypia, moderate atypia, severe atypia and carcinoma with lack of clear criteria between the grades.

Methods: We reviewed the sputum samples submitted to Pathology department, Vallabhbhai Patel Chest Institute over a five year period from 2005 to date. Total of 1304 samples were received for sputum cytology evaluation in smokers. On the basis of cytology these cases had been classified into (i) Normal, (ii) Inadequate/unreadable, (iii) Inflammatory expectorate, (iv) Inflammatory expectorate with atypia, (v) Carcinoma. In cases with atypia nuclear morphometry was done using the Nikon 90i microscope and image analyzer. The nuclear area, nuclear perimeter and nuclear shape of the atypical cells was assessed and compared to mature squamous epithelial cells in the control group.

Results: Of the total 1304 specimen received, 189 cases, 14.49% were within normal limits, 296 cases 22.69% were inadequate/unreadable, inflammatory expectorate was seen in 674 cases, 51.69%, Inflammatory expectorate with atypical cells was present in 127 cases, 9.74% and diagnosis of carcinoma was made in 18 cases, 1.38%. Nuclear morphometry for grading of atypia revealed an increase in nuclear size in moderate atypia when compared to control. Further increase in atypia was associated with nuclear pyknosis, hyperchromasia and bizarre shape of cells with increase in nuclear cytoplasmic ratio.

Conclusion: Sputum cytology is a simple cost effective noninvasive method of assessment of the central airway lesions. In smokers it can detect

cytological atypia which when accurately graded using nuclear morphometry, may prove to be the much needed marker for lung cancer in this high risk population.

Disclosure: All authors have declared no conflicts of interest.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY AND TOBACCO CONTROL

115O

PROGNOSTIC FACTORS OF DISEASE RECURRENCE AND OVERALL SURVIVAL IN ELDERLY VERSUS YOUNG PATIENTS IN SURGICALLY RESECTED NON SMALL CELL LUNG CANCER

B. Al-Alao[1], E.N. Mc Govern[1], V.N. Young[1], K. O'Byrne[2] [1]*Cardiothoracic, St. James's Hospital, Dublin/IRELAND,* [2]*Oncology, St James Hospital, Dublin/IRELAND*

Introduction: Prognostic factors for overall survival and disease free survival in elderly patients after surgical resection are not well described. We report the outcomes in elderly (older than 70 years) and young (70 years or less) with stage I-III non small cell lung cancer (NSCLC) after surgical resection.

Methods: A retrospective study of patients diagnosed with NSCLC after surgical resection at major cancer centre from 1998 to 2008. Demographic, pathologic, treatment, and follow-up data were collected. Recurrence rates and overall survival were calculated by the Kaplan-Meier method. Potential prognostic factors were examined by Cox regression multivariate analysis.

Results: Of the 593 patients included in the study, 204 were older than 70 years at diagnosis. In this elderly cohort, the median age was 74 years (range, 70-104 years) and 74 of them were women (36.3%). Clinical and pathologic characteristics were not statistically different between the elderly and younger cohorts, with the exception that older patients were more likely to have Lobectomy and Sub-lobar resections (90.7% versus 75.1%, $p < 0.0001$) and less likely to have multiple lymph nodes involved (19.1% versus 26.2%, $p = 0.03$) compared with the younger cohort. In the elderly cohort, while male gender (HR 1.6;$p<0.05$) and intra-tumoural vascular invasion (ITVI) (HR 2.24;$p<0.003$) were both associated with overall mortality, only lympho-vascular space invasion was a predictor of disease recurrence (HR 2;$p<0.05$). In comparison, in the younger cohort; while several risk factors has been associated with increased overall mortality (male gender (HR 1.6;$p<0.008$)), smoking status (HR 2;$p<0.05$), ITVI (HR 1.9;$p<0.003$), larger tumour size (HR 3.7;<0.001), multiple lymph nodes involvement (HR 2.23;<0.002)), only smoking status (HR 2.24;$p<0.003$) and ITVI (HR 1.4;$p<0.05$) were correlated to disease recurrence.

Conclusions: Although overall survival was similar in both cohorts, disease recurrence was significantly different. Certain risk factors can play different prognostic role in different age groups for overall and disease free survival. Treatment options should be tailored according to age.

Disclosure: All authors have declared no conflicts of interest.

116PD

SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR: A NEW INDEPENDENT RISK MARKER OF RESPIRATORY CANCER

A. Langkilde[1], T.W. Hansen[2], S. Ladelund[1], A. Linneberg[3], O. Andersen[1], S.B. Haugaard[1], J. Jeppesen[4], J. Eugen-Olsen[1] [1]*Clinical Research Centre, Copenhagen University, Hvidovre Hospital, Hvidovre/DENMARK,* [2]*Clinical Physiology, Copenhagen University, Faculty of Health Sciences, Hvidovre Hospital, Hviodvre/DENMARK,* [3]*Research Centre for Prevention and Health, Copenhagen University Hospital, Glostrup, Glostrup/DENMARK,* [4]*Department of Medicine, Glostrup University Hospital, Glostrup/DENMARK*

Introduction: Biomarkers of low-grade inflammation may predict cancer development. Recently, we found elevated plasma levels of the inflammatory marker soluble urokinase plasminogen activator receptor (suPAR) to be associated with increased risk of cancer development in the general population. In this study we tested whether increased baseline plasma suPAR levels are related to development of more specific cancer types in the general population.

Participants and methods: 2528 individuals from the population based Danish MONICA10 study, aged 41, 51, 61, and 71 years were included and followed for a median of 12.6 years, during which 368 developed cancer. Cancer cases were diagnosed according to ICD10 codes. Subjects with incident cancer at baseline were excluded. suPAR levels were measured using a commercially available ELISA (suPARnostic, ViroGates, Denmark).

Results: During the follow-up, respiratory (n=57), gastrointestinal (n=100), and other cancer types (n=211) were registered. Baseline median suPAR level was 4.01 ng/ml (range 1.34 to 17.80). In Cox regression analyses using age as underlying time and adjusting for time since blood sampling, alcohol, sex, smoking, and BMI, an increase of 1 ng/ml suPAR was associated with hazard ratios (HR) of 1.60 (95% CI: 1.23-2.09, $P<0.001$) for respiratory, 0.92 (95% CI: 0.69-1.24, $P=0.59$) for gastrointestinal, and 1.32 (95% CI: 1.12-1.56, $P<0.001$) for other cancer types. Plasma suPAR levels remained associated with respiratory cancer (HR 1.49, 95% CI: 1.11-2.00, $P=0.009$) and other types of cancer (HR 1.40, 95% CI: 1.17-1.67, $P<0.001$), after additional adjustment for the inflammatory markers C-reactive protein (hsCRP) and leukocyte numbers.

Conclusion: Elevated plasma suPAR levels correlate with increased risk of developing respiratory cancer and other cancer types, but not with gastrointestinal cancer in the general population. Our findings imply that different disease mechanisms underlie respiratory and gastrointestinal cancer development. The finding that suPAR is associated with respiratory cancer independently of age and smoking suggests that inclusion of suPAR in screening programmes may identify individuals at high risk of developing lung cancer.

Disclosure: O. Andersen: Ove Andersen is mentioned as inventor on a patent on suPAR and prognosis owned by Copenhagen University Hospital Hvidovre, Denmark. S.B. Haugaard: Steen B Haugaard is mentioned as inventor on a patent on suPAR and prognosis owned by Copenhagen University Hospital Hvidovre, Denmark. J. Eugen-Olsen: Jesper Eugen-Olsen is co-founder, board member, and shareholder of ViroGates, Denmark, the company that produces the suPARnostic assay All other authors have declared no conflicts of interest.

117PD

ABSTINENCE AND EFFECTIVENESS OF SMOKING CESSATION PROJECT: EXPERIENCES OF INDIAN CANCER NGO ABOUT PREDICTABLE FACTORS

P.D. Shankpal, V. Sankpal *Community Care, HAOI, Dhule/INDIA*

Aims: Cigarette smoking is the single biggest avoidable cause of death and disability in developing countries. Smoking cessation programs are non-

existent in Indian healthcare system. Smoking behavior is multifactorial. Motivation is a fundamental aspect in smoking cessation.

Objectives: 1] To assess effectiveness and factors associated with outcome of the smoking-cessation program 2] Investigate timeframe of the quit-tobacco rate from the beginning of the project to one year after quitting. 3] Analyze predictable factors of smoking cessation.

Methods: 188 non-filtered tobacco-users from rural India were enrolled in the project. This retrospective study was based on motivation, dependence, conviviality with smokers and tobacco abstinence after one year. This QUIT-Smoking project was carried out by 3 counseling sessions per week. Subject-evaluation was done bi-monthly. Sex, age, smoking pattern, previous attempts to quit, education, marital status, psychological background, other addictions and nicotine dependence through the Fagerstrom Test for Nicotine Dependence (FTND) were evaluated as predictors of abstinence by univariate analysis. Individual counseling done for behavioral modification by psychologist were conducted.

Results: Total of 239 smokers were willing to quit, but 153 completed study. Mean age of participants was 4, previous attempts to quit was recorded in 78%, umber of cigarettes 31/day, FTND 5.99 2.11. 123 subjects reported abstinence at one year. Reduced abstinence was associated more in females [93%, $p=0.03$]. Mean age at beginning of smoking habits was 16 years. Co-morbidities in study group were as follows: respiratory disease >60%; cardiovascular disease >13%; depression >38%. Main reasons for cessation efforts: health: 62%, family/society pressure: 23%, children: 4% and economy: 11%. Dependence was high in 73%. QUIT-success rate in young smokers <35 yrs was 22%, whereas rate >65 years of age was 40%. In our project, 30% participants with tobacco-addicts stopped smoking. 68% Quit smoking by end of this project. Sustained quit rates after 12 months increased from 16% to approximately 41% during the first year of this program.

Conclusions: Our NGO project "STOP-QUIT & Live Long" successfully motivated 62% of subjects to stop smoking within one year. Unavailability of nicotine replacement therapies reduced our success rate. Abstinence was more difficult in young male smokers with depression. Counseling/motivation were highly effective in reducing incidence of thoracic cancers in the long-term. Our experience/data suggests the need for combined efforts by IASLC, ESMO & community NGO's working in the tobacco control field. The ELCC 2010 Conference must expedite such NGO initiatives in resource-poor nations.

Disclosure: All authors have declared no conflicts of interest.

118PD

ASSESSING THE KNOWLEDGE OF TWO LUNG CANCER RELATED FACTORS IN HOSPITAL STAFF SMOKERS WILLING TO QUIT

J.E. Alonso, A. Sanchez, B. Gallego, I. Herrero, E. Chacon, S. Bello *Respiratory Service, Hospital Miguel Servet, Zaragoza/SPAIN*

Aim: Knowledge is a key point in primary prevention in lung cancer. We consider two different classes of factors in this prevention, depending on the possibility of intervention or not. In a group of hospital staff smokers attending a tobacco cessation clinic we asked about their knowledge on tobacco and radon as lung cancer etiologic factors.

Methods: 197 smokers attending a 6 months hospital-based tobacco cessation programme were included in our study. They belonged to a university teaching tertiary hospital and were part of the staff. It included doctors, nurses and auxiliary personnel. We specifically asked about cancer risk of tobacco, radon knowledge and cancer risks of radon. Subgroups of smokers knowing these risks were analyzed and also some potential variables that could explain these differences were studied.

Results: 63 smokers (32%) finally succeed at 6 months follow up point. At the initial inclusion 140 smokers (70%) knew about the risk of lung cancer related to the cigarettes. 35 smokers (18%) had heard about radon. 2 smokers (1%) knew about the radon related lung cancer risk.

Conclusion: There is still room to insist in tobacco cessation specially arguing on lung cancer risks in nature or home environment that are sometimes difficult to modify. Even in a hospital setting there's a significant proportion of smokers ignoring the lung cancer risk related to tobacco.

Disclosure: All authors have declared no conflicts of interest.

119PD

CARCINOMAS OF LUNG & TOBACCO USE: SUPPORTIVE CARE NEEDS IN ASIAN COMMUNITY TO BRING DOWN MORTALITY/MORBIDITY

V.P. Shankpal *Community Medicine, Health Alert Organisation of India, Dhule/INDIA*

Issues: This is Phase-IV continuation of our NGO-Project in Indian-adolescents. Studied influence of counseling on reduction in tobacco-smoking eventually reducing lung-cancer-incidence. 218 deaths/year due to lung-cancer. Crude-Tobacco-smoking socially accepted in rural/tribal India. From May 2007 our NGO conducts project "BIDI [Locally made crude-Indian-tobacco] OR HEALTH". Aims to reduce tobacco-products-consumption & provide de-addiction guidance/counselling.

Methodology: 11 villages from rural India included. Total-participants 511, age 14-24. Tobacco-addicts graded clinically. Counseling-effect monitored for four-months. Counseled for cause tobacco-use, educational/social factors. Conducted 20 follow-up-sessions during course of study.

Results: Of 511 tobacco-users 493 continued to participate. [18 drop-outs]. 32% COPD & respiratory disorders, 12% Tuberculosis. 8 health-care personals from rural-Govt-clinics trained in counseling with community-leaders. 431 participants showed positive-attitude towards quitting tobacco use. Of these 431, 410 smokers quit habit of tobacco. 21 able to abstain for short-period but eventually restarted habit. Post-project-surveillance showed need for community help & Rehabilitation. Of 431 who responded positively majority [394] adolescents started using tobacco due to peer-pressure [84%], imitation of tobacco-advertising on media/films/TV [11%].

Conclusion: NGO-activists with scientific knowledge/expertise are only available resource for influencing cancer incidence in India. They act as channel to implement Supportive cancer care/prevention-programmes. NGOs should utilize this approach to reduce cost-factor in cancer-control-strategies & better de-addiction-facilities in rural/tribal areas where qualified Oncologists are rarity.

Recommendations: Developing-nations have little manpower/resources/technologies in de-addiction. Nicotine replacement therapies are expensive & available in metro-cities only. Government must carry out supportive-care-programmes with NGO-counsellors to bring down mortality/morbidity of lung-cancer. Anti-tobacco-activists trained in counseling provide better cancer care with reduced cost. We intend to form an Umbrella group of anti-cancer activists to workout more planned approach to this issue at 2nd European Lung Cancer Conference Geneva 2010.

Disclosure: All authors have declared no conflicts of interest.

120PD

USEFULNESS OF A FAST ACCESS INVESTIGATION UNIT FOR LUNG CANCER DIAGNOSIS

J. Sanz-Santos[1], F. Andreo[1], E. Monso[1], J. Bechini[2], M. Llatjós[3], E. Castella[3], I. Guasch[1], P. Lopez de Castro[1], F. Caro[4] *[1]Pneumologia, Hospital Universitari Germans Trias i Pujol, Badalona/SPAIN, [2]Radiologia, Hospital Universitari Germans Trias i Pujol, Badalona/SPAIN, [3]Anatomia Patologica, Hospital Universitari Germans Trias i Pujol, Badalona/SPAIN, [4]Pulmonologia, Hospital Maria Ferrer, Buenos Aires/ARGENTINA*

Aim: To evaluate the usefulness of a fast-track diagnosis unit for lung cancer after 42 months of being established.

Patients and method: Patients with suspected lung cancer (who could be investigated in a outpatient setting) were recruited from the e-department, hospitalization or from their GP and them referred to the unit (by fax, phone or e-mail). Within a week they were seen by a pulmonologist. After a first evaluation diagnosing and staging test were carried out in a quick access. Once the patients were diagnosed they were referred to oncology, radiotherapy and/or thoracic surgery department after being reviewed in a multi-disciplinary-weekly meeting. Time from the first visit to diagnosis as well as histologic type, diagnostic method, age, gender, tobacco exposure and TNM classification were recorded.

Results: 678 patients were seen from Oct 2005 to Apr 2009. Of these, 361 (54.7%) were found to have a thoracic malignancy. For the group of patients having lung cancer (337 cases) the mean age was 65.3 yrs (SD± 10.5), mostly men (87%), smokers or ex-smokers (91.8%) with a mean smoking exposure of 54.6 packs/yr. Adenocarcinoma was the most common histologic type accounting for 118 (33.5%) of the total with no differences on gender and smoking status. Second histologic type was squamous cell carcinoma: 89 (25.3%) cases. The most common diagnosis methods were: fiberoptic bronchoscopy (48.1%), endobronchial ultrasound bronchoscopy (EBUS) (20.2%), surgery (14.8%) and transthoracic needle aspiration (8.8%). For the cases of NSCLC, in a third part (36.3%) were found to be resectable (stage I and II) and for a quarter of them (26.6%) to have distant metastasis.

The median time to diagnosis was 12.5 days (IQR:5-27). Delays were related to stage (advanced stages were diagnosed earlier) and with the diagnosis method: fiberoptic bronchoscopy was the fastest method (mean time 8 days, IQR 4-14), and surgery was the slowest (mean time 65 days, IQR 47-109).

Conclusion: Although there is not evidence that delays in the diagnosis of lung cancer are related to prognosis there are other reasons for what delays have to be avoided. In our experience, a fast access investigating unit for lung cancer diagnosis improves management centralizing efforts and avoiding redundant tests.

Disclosure: All authors have declared no conflicts of interest.

121PD

CHARACTERISTICS OF THORACIC MALIGNANCIES OCCURRING AFTER SOLID ORGAN TRANSPLANTATION

C. Genebes[1], L. Brouchet[2], B. Lepage[3], N. Kamar[4], L. Rostaing[4], A. Didier[1], J. Mazières[1] *[1]Department of Pneumology, Larrey Hospital, CHU Toulouse, Toulouse/FRANCE, [2]Department of Thoracic Surgery, Larrey Hospital, CHU Toulouse, Toulouse/FRANCE, [3]Department of Statistics, CHU Toulouse, Toulouse/FRANCE, [4]Department of Nephrology, Rangueil Hospital, CHU Toulouse, Toulouse/FRANCE*

Background: Chronic immunosuppression after solid organ transplantation is associated with an increased risk of developing malignancies. The purpose of this study was to determine the clinical characteristics and the outcome of thoracic malignancies in patients who underwent solid organ transplantation.

Methods: Among a cohort of 2780 patients transplanted in our institution and followed between 1984 and 2009, 24 patients (0.86%) developed a lung cancer. Demographic characteristics, risk factors for lung cancer, cancer characteristics and transplantation characteristics were analyzed. A survival analysis was done.

Results: Twenty-four patients were included (21 men and 3 women, median age 61.2 year). Twenty-two patients were smokers. The most frequent anatomopathologic types were squamous cell carcinoma (46%) and adenocarcinoma (37%). The median time period between transplantation and the diagnosis of lung cancer was 6.6 years. Ten lung malignancies occurred after kidney transplantation (0.5%), 8 after liver transplantation (1.3%) and 6 after heart transplantation (2.8%). Seven patients underwent surgery, 3 radiotherapy, 4 chemotherapy and 5 radio-chemotherapy. The median survival was 1.2 years ranging from 6 months for stage IV to 3.7 years for stage I.

Conclusion: Solid organ transplantation is associated with a high risk of lung cancer. Survival of lung cancer in our study population is not inferior from the one in non transplanted patients. Screening lung cancer in this high-risk population should be considered to make an earlier diagnosis. In our study surgery allows to obtain favorable survival results.

Disclosure: All authors have declared no conflicts of interest.

122P

THE RISK OF LIFELONG DNA DAMAGE CAUSED BY LUNG CANCER AMONG RURAL MALE SMOKERS WHO BEGIN AT TEENAGE

E.O. Odiase *Tobacco Control, SmokeFree Foundation, Abuja/NIGERIA*

Goals: To examine the effect of smoking on lung cancer risk and entire DNA damage in a relatively large number of rural men, many of whom are poor and started smoking as teenagers.

Methods: We followed 50,232 men, ages 25 to 50 years, through a community-based tobacco control outreach programme with questionnaires both in English and the local language to the North western and North eastern Nigerian Cohort Study in 2002/2003, through December 2007. We estimated relative risk (RR) of lung cancer associated with different measures of smoking initiation, duration, and intensity adjusting for confounding variables. We conducted analyses on the entire study population, among men who had smoked for at least 15 years, among non drinkers, and separately for each geo-political zone.

Results: Altogether, 10,240 men were diagnosed with lung cancer. Compared with never smokers, men who smoked for at least 15 years and who smoked 10 cigarettes or more daily had a higher RR. In contrast, men who had smoked for at least 15 years, but started after their 19th birthday, did not experience an increased lung cancer risk. The increased RR associated with smoking was observed among nondrinkers of alcohol, men with and without a family history of lung cancer in both geo-political zones in Nigeria.

Conclusion: Our results support the notion that men who start smoking as teenagers and continue to smoke for at least 15 years may increase their lung cancer risk with dramatic and lifelong DNA damage.

Disclosure: The author has declared no conflicts of interest.

123P

POLYMORPHISMS IN MICRORNA BIOSYNTHETIC GENES AND LUNG CANCER RISK: A MULTI-STAGE CASE-CONTROL STUDY

G. Jin, J. Kim[1], H. Jeon[1], J.Y. Park[2] *[1]Department of Biochemistry and Cell Biology, Kyungpook National University School of Medicine, Daegu/KOREA, [2]Department of Internal Medicine, Kyungpook National University, School of Medicine, Deagu/KOREA*

Based on the important role of microRNA (miRNA) biosynthesis genes in carcinogenesis, we hypothesized that polymorphisms in the miRNA biosyn-

thesis genes may modulate susceptibility to lung cancer. To test this hypothesis, we conducted a two-stage study to evaluate the associations between single nucleotide polymorphisms (SNPs) in the miRNA biosynthesis genes and the risk of lung cancer. In stage 1 of the study, 24 SNPs in the 11 miRNA biosynthesis genes (DROSHA, DGCR8, RAN, XPO5, DICER, AGO1, AGO2, HIWI, GEMIN3, GEMIN4, and TRBP) were genotyped in 100 lung cancer patients and 100 healthy controls using a sequenome mass spectrometry-based genotyping assay. One promising SNP (AGO1 rs636832A>G) was selected for stage 2 of the study, and genotyped by a melting-curve analysis using fluorescence-labeled hybridization probes in an independent set of 552 cases and 552 controls. The AGO1 rs636832A>G exhibited highly consistent results between the two stages of the study. In combined analysis, the 636832A>G was associated with a significantly decreased risk of lung cancer in a dose-dependent manner ($P_{trend} = 6.0 \times 10^{-4}$). Individuals with at least one rs636832G allele were at a significantly decreased risk of lung cancer compared with those with the AA genotype (adjusted odds ratio = 0.67, 95% confidence interval = 0.53-0.84, $P = 4.0 \times 10^{-4}$). This finding suggests that the AGO1 rs636832A>G might be a useful marker for determining the susceptibility to lung cancer and that the AGO1 gene might be involved in the development of lung cancer.

Disclosure: All authors have declared no conflicts of interest.

124P

GENETIC POLYMORPHISMS IN ATM, ERCC1, APE1 AND IASPP GENES AND LUNG CANCER RISK IN A POPULATION OF SOUTHEAST CHINA

Q. Deng, L. Sheng, D. Su, S. Ma *Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou/CHINA*

Polymorphisms in DNA repair and apoptosis genes are suspected to alter the individual susceptibility to develop lung cancer. We investigated the relationship between polymorphisms in ATM (A60G), ERCC1 (Asn118Asn), APE1 (Asn148Glu), and iASPP (A67T) and the risk of developing lung cancer. A case-control study was conducted with 315 lung cancer patients and 315 cancer-free controls, matched on age and sex. Genotypes were detected using the ABI 7500 real-time PCR system. The association between genotype and lung cancer risk was evaluated by computing the odds ratios (ORs) and 95% confidence intervals (CIs) from multivariate unconditional logistic regression analysis with adjustment for gender, sex and smoking status. The T/T homozygote in ERCC1 (Asn118Asn) was correlated with a strong statistically significant increased risk of developing lung cancer (adjusted OR=2.44; 95% CI=1.13-5.28; P=0.023), especially lung adenocarcinoma (adjusted OR=3.18) and small cell lung cancer (adjusted OR=6.08). For iASPP (A67T), smokers with at least one T allele (A/T + T/T) were more likely to develop lung cancer compared to those who did not carry the T allele (95% CI, 1.07-2.84, P=0.026). Subjects carrying the G allele in APE1 (Asn148Glu) had a decreased risk of lung cancer ($P<0.05$), which showing a protective effect. Our results suggest that polymorphism Asn118Asn in ERCC1 increases the risk of lung cancer. The effect is especially for lung adenocarcinoma and small cell lung cancer. The iASPP A67T polymorphism may contribute to the early-onset of lung cancer in smokers. However, polymorphism of the APE1 (Asn148Glu) plays an important role in protecting against developing lung cancer, especially for smokers.

Disclosure: All authors have declared no conflicts of interest.

125P

IDENTIFICATION OF GENETIC ALTERATIONS IN LUNG CANCER PATIENTS IN SOUTH INDIAN POPULATION, INDIA

V. Balachandar[1], S. Mohanadevi[1], M. Arun[1], A. Karthick Kumar[1], P. Manikantan[1], P. Velmurugan[1], K. Sasikala[1], S. Sudha[2], S.N. Dharwatgar[3] *[1]Human Molecular Genetics Laboratory, Department of Zoology, Bharathiar University, Coimbatore/INDIA, [2]Department of Biotechnology, Karpagam University, Pollachi/INDIA, [3]Department of Biotechnology, KLE Medical University, Bangalore/INDIA*

Lung cancer (LC) is the leading cancer in incidence and mortality worldwide. Tobacco smoking is a major established risk factor for lung cancer, contributing to 10-fold or higher risks in long-term smokers. The aim of the present study was to identify the chromosomal alterations (CA) in LC patients and compare with their smoking status. In our study, a total of 34 LC patients have been selected (36 to 61 years) with known smoking status and equal number of normal, healthy controls. After signing a consent form, both groups (patients and controls) provided a blood sample (5 ml) to establish cell culture. In 25 patients random numerical and structural aberrations were identified. Structural aberrations predominated, consisted of deletions, translocation, inversion and mosaicism of various chromosomes. Our study has detected 1, 3, 4, 5, 7, 13, 18 and 21 suggested that these chromosomal scratches are prevalent in LC patients. In comparison to the patients, control subjects expressed very low levels of major CA ($P<0.005$). Statistically significant results were observed in smokers compared with non smokers. In the present study, the high frequency of chromosomal rearrangements designates a potential role for mitotic indiscretion coupled with the centromere in lung cancer patients. Therefore, the survival rate of chromosome alterations in lymphocytes might be used as a biomarker to identify populations at high risk for lung cancer. Identification of chromosome alterations may be helpful in devising better therapeutic strategies in future.

Disclosure: All authors have declared no conflicts of interest.

126P

METABOLOMIC PROFILING OF LUNG ADENOCARCINOMA

C.D. Hoang[1], M. Wu[2], Y. Xu[1], G. Peltz[1], R. Merritt[1], R. Whyte[1], J. Shrager[1] *[1]Cardiothoracic Surgery, Stanford University, Stanford/USA, [2]Anesthesia, Stanford University, Stanford/USA*

Objective: We hypothesized that accumulation of specific metabolites precedes morphologic changes in lung tumors during malignant transformation, and that this may be exploited to develop a lung cancer biomarker.

Methods: We performed metabolomic profiling on 9 fresh-frozen specimens from patients with proven adenocarcinoma. The following tissues from each patient were analyzed: tumor, adjacent-to-tumor tissues, and normal lung. The metabolites were extracted by a methanol chloroform technique and separated liquid chromatography. They were analyzed using a 6520 hybrid Q-TOF mass spectrometer (Agilent). Mass Profiler Professional software was used for statistical analysis and metabolite profiling. To identify a metabolite of interest, the retention time and elemental composition data were searched against databases: METLIN Personal Metabolite. After multiple data filtering steps we derived a lung carcinoma-specific metabolomic fingerprint. We performed metabolic network analysis to assess which gene(s) may be associated with the metabolomic biosignatures.

Results: We detected 2232 unique metabolites in the tumor specimens, 1795 in the adjacent-to-tumor specimens, and 1613 in the normal lung. Comparing tumor and normal lung samples, 201 metabolites were significantly over-expressed and 105 were under-expressed in the tumor tissue. The metabolic biosignature for the tumor group was highly distinct from the other lung regions by several fold change. The metabolites

within the tumor-specific signature included the following families: lactate, amino acids, phospholipids, eicosanoids, and glycine derivatives. In particular, multiple phosphatidylethanolamines showed dramatic differential expression in tumor tissues compared to normal lung. Metabolic network analysis suggests that the altered metabolite levels could affect critical cellular functions, including: cell signaling, growth and invasiveness.

Conclusion: Metabolomic analysis identified metabolites that were uniquely found in human lung adenocarcinomas. The specific metabolic biosignature of lung adenocarcinoma could suggest novel biomarkers for use in diagnosis, as well as suggest altered molecular pathways contributing to the pathogenesis of lung cancer.

Disclosure: All authors have declared no conflicts of interest.

127P

THE CLINICAL CHARACTERISTICS OF FAMILIAL LUNG CANCER (FLC) BY POPULATION SCREENING

A. Vanags, I. Strumfa, A. Gardovskis, V. Borosenko, A. Abolins, G. Trofimovics, J. Gardovskis *Hereditary Cancer Institute, Riga Stradins University, Riga/LATVIA*

Introduction: Although smoking is the main risk factor of lung cancer (LC), there is increasing evidence of the role of hereditary factors. While the search for the responsible mutations is going on, the diagnostics of FLC depends on clinical data.

Aim: To test the possibility of diagnosing FLC by clinical criteria in population screening (PS) approach.

Materials and methods: PS was carried out in a territorial unit of Latvia, reaching 18642 (76.6%) participants. Adult persons filled out the questionnaire reporting the presence, localisation and age of diagnostics of malignant tumours in kinsmen. Hereditary cancer syndromes were sought for according to international assessment criteria. Adjustment consultations were carried out. The FLC was diagnosed on the basis of 3 LC cases and suspected on the basis of 2 cases in mutually first-degree relatives. Descriptive statistics was performed by CIA software.

Results: The applied criteria revealed 13 cases of FLC and 93 – of suspected FLC (sFLC) corresponding to population frequency 0.07% [95% confidence interval = 0.04-0.12] and 0.50% [0.41-0.61], resp. The FLC/sFLC pedigrees had high frequency of LC (table), higher proportion of early-onset cases (15.0% [11.1-20.3] vs. 8.3% [7.1-9.6] in the population), low spouse correlation of 2.5% [0.7-8.6%], tumour anticipation. FLC/sFLC constituted 12.9% [11.5-14.6] but FLC – 2.4% [1.8-3.2] of all reported LC cases.

Conclusions: The clinical criteria based on the number of LC cases among blood relatives ensure the identification of reasonable number of families subjected to high LC load. The LC frequency in sFLC affected in single generation is lower than in FLC, although high. FLC/sFLC show higher frequency of early-onset cases but age as a diagnostic criterion does not identify group with higher LC frequency.

Disclosure: A. Vanags: This work was supported by ESF project 2009/0147/1DP/1.1.2.1.2./09/IPIA/VIAA/009 and Interreg IIIB NI-008; A. Gardovskis: This work was supported by Interreg IIIB NI-008; V. Borosenko: This work was supported by Interreg IIIB NI-008; J. Gardovskis: This work was supported by ESF project 2009/0147/1DP/1.1.2.1.2./09/IPIA/VIAA/009 and Interreg IIIB NI-008 All other authors have declared no conflicts of interest.

Table. Frequency of Lung Cancer in FLC/sFLC Pedigrees by Selection Criteria

Group	Frequency/ FLC	95% CI/ FLC	Frequency/ sFLC	95% CI/ sFLC
Basic	25.5	19.3–32.8	17.2	15.0–19.7
Single generation	28.6	18.9–40.7	15.4	12.3–19.1
Multiple generations	23.4	16.0–32.9	18.7	15.6–22.2
Early-onset pedigrees defined by presence of at least 1 case of lung cancer before the age of 50	27.5	18.9–38.1	17.7	14.3–21.8
Pedigrees lacking lung cancer cases before the age of 50	23.4	15.3–34.0	16.8	14.0–20.1
Early-onset cancer in single generation	31.3	19.9–45.3	15.5	10.9–21.4
Early-onset cancer in multiple generations	21.9	11.0–38.8	19.6	14.9–25.5
Late-onset cancer in single generation	20.0	7.0–45.2	15.4	11.5–20.3
Late-onset cancer in multiple generations	24.2	15.2–36.2	18.0	14.2–22.6

Abbreviations: FLC, familial lung cancer; CI, confidence interval; sFLC, suspected familial lung cancer.

128P

THORACIC TUMOURS ELECTRONIC DATABASE: A PORTUGUESE PROJECT

A.M. Figueiredo[1], M.T.A.S. Almodovar[2], S. Valente[3], V. Hespanhol[4], F. Barata[5] *[1]Pneumologia, Centro Hospitalar de Coimbra, Coimbra/PORTUGAL, [2]Serviço Pneumologia, Instituto Portugues de Oncologia, Lisboa/PORTUGAL, [3]Pneumologia, Centro Hospitalar Cova da Beira, Covilhã/PORTUGAL, [4]Pneumologia, Hospital S. João, Porto/PORTUGAL, [5]Pneumologia Oncológica, Centro Hospitalar de Coimbra, Coimbra/PORTUGAL*

Background: Lung cancer is the most deadly cancer in the world due to high incidence and poor response to treatment. Epidemiologic data are essential to compare treatments and outcomes in these patients. The oncologic section of the Portuguese Respiratory Society (PRS) exists for 25 years gathering together Portuguese doctors and other health professionals working with lung cancer patients.

Description: In order to improve the epidemiologic, demographic and clinical data collection, and to assist the treatment decisions, an on-line electronic database was developed, in compliance with current legislation regarding data protection. This password protected base can be accessed through the PRS website (http://tumorestoracicos.sppneumologia.pt/). The database is intended to achieve two main goals: To provide each Centre dealing with thoracic tumours a user-friendly standardized registry of the epidemiologic and clinical data, from diagnosis to death. The clinician is allowed to add data at any time after the initial registry of the patient (treatments performed, progression, follow-up and death). This database also provides descriptions of the staging criteria, node maps, makes an automatic staging of the patient and provides links to the main guidelines. It also allows automatic reports of every patient and provides automatic or personalized statistical treatment of all the data. The second goal is to gather the data from all the Centres and provide an epidemiologic overview of all the patients treated in Portugal with thoracic tumours. New fields can be added to integrate new data whenever justified.

Results: This project was established at the end of 2007 and the database was released in October 2009. This base has by now been approved by 18

Institutions and the patients are already being registered. We expect this registration to become systematic in 2010.
Conclusions: Our project aims to improve data collection on lung cancer while helping to uniform treatment decisions.
Disclosure: All authors have declared no conflicts of interest.

129P

AN EPIDEMIOLOGIC COMPARISON STUDY OF LUNG CANCER IN THE SAN JOAQUIN VALLEY OF CALIFORNIA BY GENDER, RACE AND HISTOLOGICAL SUBTYPES

A.M. Emtiazjoo, M.W. Peterson, P.K. Mills *Department of Medicine, University of California at San Francisco, Fresno Medical Education program, Fresno/USA*

Background: Both genetic and environmental factors influence lung cancer risk, however, the impact of these variables on histological subtypes of lung cancer is less studied. We compared the incidence of lung cancer in San Joaquin Valley of California (SJV) with the rest of the state by gender, race/ethnic groups and histological subtypes. We chose SJV for comparison to the rest of California due to its known poor quality of air, and agricultural related pollution.
Methods: A descriptive epidemiologic analysis of lung cancer was conducted using data from the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results program (SEER) for the diagnosis years 2000-2006. Age adjusted lung cancer incidence rates (AAIR) and associated 95% confidence intervals were calculated for lung cancer histological subtypes for the San Joaquin Valley of California (SJV) compared to the rest of the state. Comparisons between the two geographic regions were made based upon gender, race/ethnicity, and histological subtypes.
Results: A total of 121,365 incident lung cancers were included in the analysis. Overall, the AAIR was higher in the SJV than the rest of the state. Rates were higher in males than females and in Blacks compared to other race/ethnic groups and these patterns persisted for squamous cell carcinoma and adenocarcinoma of the lung. However, white males (WM) experienced the highest AAIR for small cell lung cancer (SCLC) compared to any other subgroup and this was particularly true among WM in the SJV. In addition, the AAIR of bronchoaveleolar lung cancer were lower in the SJV compared to the rest of the state and were found to be higher in both white females (WF) and black females (BF) compared to other gender and race/ethnicity subgroups.
Conclusion: There is a significant difference in the incidences of lung cancer and its histological subtypes among the different genders, race/ethnicity and geographical zones. This study strongly suggests the presence of a different set of risk factors for the different histological subtypes of lung cancer.
Disclosure: All authors have declared no conflicts of interest.

130P

EARLY DETECTION OF LUNG CANCER IN THE REPUBLIC OF KOSOVO

B. Osmani, G. Zhuri, Z. Bujupi, R. Mehmeti, P. Rashiti *Oncology, Clinic for Lung Diseases, Prishtina/ALBANIA*

Despite rapid development of diagnostic and therapeutics methods, lung cancer still remains a big challenge of contemporary medicine. According to various recent studies, results shows that a higher number of people die from lung cancer than any other kind of cancer.
Our results: Clinic for Lung Disease is reference institution for lung cancer in the Republic of Kosovo. Within a period of 2 years 245 patients were diagnosed with lung cancer and treated. 191 patients or 78% were with non small cell lung cancer (NSCLC) 54 patients or 22% were with small cell lung cancer (SCLC). Patients age is as follows: 40 years old – 3 patients 41–60 years old – 106 patients > 60 years old – 82 patients.
Histopathologic types: Squamous carcinoma 158 (83%) Adenocarcinoma 30 (16%) Large Cell 3 (1%) STAGING II – 17 patients IIIA – 24 patients IIIB – 113 patients IV – 37 patients.
Treatment protocols: Surgical treatment – 15 (8 %) Chemotherapy – 154 (80%) No treatment (symthomatic) – 23 (12%). Small cell lung cancer: 54 Patients: Male – 48 Female – 6 According to localization: Right sided – 31 Left sided – 23. Age: 40 years old – 2 patients (4%) 41–60 years old – 26 patients (48%) 60 years old – 26 patients (48%) As limited disease – 18 As spread disease – 36.
Treatment: – Surgical – No treatment, Chemotherapy 49 (91%), Symptomatic therapy 5 (9%).
Disclosure: All authors have declared no conflicts of interest.

131P

THE INFLUENCE OF MALIGNANCY AND REFERRING DEPARTMENT ON SMOKING CESSATION SUCCESS

P.M. Putora[1], F. Baty[2], P. Ludwig[2], G. Rogenmoser[3], L. Plasswilm[4], M. Brutsche[2] *[1]Klinik Für Radio-onkologie, Kantonsspital St. Gallen, St. Gallen/SWITZERLAND, [2]Department of Pneumology, Kantonsspital St. Gallen, St. Gallen/SWITZERLAND, [3]Lungeliga, Lungenliga St. Gallen, St. Gallen/SWITZERLAND, [4]Kantonsspital St. Gallen, Department of Radiation-Oncology, St. Gallen/SWITZERLAND*

Background: Smoking cessation programs are often under-utilized. This is usually the case with patients with malignant disease including lung cancer. Possibly, some physicians deem cancer patients less fit for smoking cessation programs, perhaps due to life expectancy issues. Our aim was to analyse whether cancer patients did differently in smoking cessation programs.
Method: We retrospectively analysed 635 patients that had at least one smoking cessation consultation at the Kantonsspital St. Gallen between 2006 and 2009. Factors that were analysed included their diagnosis list, whether the patients had a malignancy and specifically whether patients had lung cancer. Another factor we included in the analysis was the referring department. Using logistic regression and Pearson's Chi-squared test, we tested the influence of these factors on the success of the smoking cessation program.
Results: Of evaluable patients 8% (42/546 pts) had lung cancer and 12% (53/441 pts) had a other malignant disease. The 1-month quit rate was 54%, 55%, 44% for patients with non-malignant disorders, lung cancer and other malignancy respectively (Chi-square test: $p = 0.73$). Malignancy as a parameter also had no effect on the success rate: 48% with and 54% without cancer (Chi-square test: $p = 0.72$). Of the 441 patients, where a referring department could be identified, only 5% (21 pts) were referred from the oncology department. As expected, a difference could not be determined. There was no difference in the success rate between patients from medical and surgical departments. A factor that stood out was the motivational stage. In the Prochaska stage "active", the success rates were much higher than in the low-motivated patients (OR: 12.3 [2.6 - 89.9]).
Conclusion: We could demonstrate that lung cancer patients do not do worse in a smoking cessation program than patients with other malignancies or non-malignant diseases. Also, the referring department had no effect on the smoking cessation success rate. Our conclusion is that the diagnosis of lung cancer is no reason to expect the patient doing worse in a smoking cessation program. Therefore we recommend all treating physicians in pneumo-oncology to consider smoking cessation programs for all of their patients.
Disclosure: All authors have declared no conflicts of interest.

132P

QUIT-TOBACCO: A DECADE OF ABSOLUTE DEDICATION IN LUNG CANCER PREVENTION IN RURAL INDIA

P.D. Shankpal, V. Shankpal *Community Care, HAOI, Dhule/INDIA*

Issues: Indian farmers/adolescents use crude-tobacco leading to high incidence of inflammatory airway-diseases. It is a priority issue due to high mortality/morbidity. Developing nations have less expertise in tobacco-de-addiction. We used community volunteers to reduce tobacco consumption de-addiction (QUIT-tobacco project).

Methodology: Eleven villages from rural India are included in the program; n=320, age 14–37.

Tobacco-addicts were graded clinically in this 16-months project. Users were counseled about tobacco consumption, educational/social factors. Traditional faith-healers community-leaders were incorporated for better impact.

Results: 16 dropped out of the project. Volunteers from our NGO are trained in counseling. A total of 289 participants showed a positive attitude towards quitting tobacco and 250 subjects quit tobacco. We noticed that 39 subjects were able to abstain for a short period but eventually restarted the habit. Post-project surveillance showed the need for community help rehabilitation. Of 289 who responded positively, the majority [261] of adolescents started using tobacco due to peer pressure [84%], imitation of tobacco advertising in the media [14%], or were influenced by movies, TV [58%].

Conclusion: Community-NGO volunteers are a channel to implement a tobacco-control program. Other NGOs should utilize our approach to reduce the cost in tobacco control and achieve better impact in rural/tribal areas where qualified oncologists are rare.

Recommendations: Developing nations have little manpower/resources/technologies for tobacco control. Government/NGOs could address inflammatory airway-diseases interventional programs within available resources and by above approach.

Disclosure: All authors have declared no conflicts of interest.

133P

RISK OF RECURRENCE AND OVERALL SURVIVAL OF SURGICALLY RESECTED NON SMALL CELL LUNG CANCER IN ELDERLY PATIENTS

B. Al-Alao[1], E.N. Mc Govern[1], V.N. Young[1], K. O'Byrne[2] *[1]Cardiothoracic, St. James's Hospital, Dublin/IRELAND, [2]Oncology, St James Hospital, Dublin/IRELAND*

Introduction: Surgery is a valid option for fit elderly patients with lung cancer, but risk factors for overall survival and disease free survival after surgical resection are not well described. We report the outcomes in elderly patients (older than 70 years) with stage I-III non small cell lung cancer (NSCLC) after surgical resection.

Methods: This is a retrospective study of patients diagnosed with NSCLC after surgical resection at major cancer centre from 1998 to 2008. Demographic, pathologic, treatment, and follow-up data were collected. Recurrence rates and overall survival were calculated by the Kaplan-Meier method.

Results: Of the 593 patients included in the study, 204 were older than 70 years at diagnosis. In this elderly cohort, the median age was 74 years (range, 70-104 years) and 74 of them were women (36.3%). Clinical and pathologic characteristics were not statistically different between the elderly and younger cohorts, with the exception that older patients were more likely to have Lobectomy and Sub-lobar resections (90.7% versus 75.1%, $p < 0.0001$) and less likely to have multiple lymph nodes involved (19.1% versus 26.2%, $p = 0.03$) compared with the younger cohort. The Median follow-up of elderly cohort, the median overall survival and the median disease free survival were 2.9 years, 2.3 years and 2 years, respectively. While the overall 5-year survival rate was not statistically significant (23% versus 33%, $p < 0.062$), elderly patients had significantly lower 4-year disease free survival rate (16% versus 30%, $p=0.002$) when compared to the younger cohort.

Conclusions: Although overall survival rate was similar to younger patients, elderly patients had higher rate of limited surgical resection, more single lymph node involvement and higher rate of disease recurrence after complete resection.

Disclosure: All authors have declared no conflicts of interest.

TRANSLATIONAL RESEARCH

134O

ANALYSIS OF BIOMARKERS (BMS) IN THE AVAIL PHASE III RANDOMISED STUDY OF FIRST-LINE BEVACIZUMAB (BV) WITH CISPLATIN-GEMCITABINE (CG) IN PATIENTS (PTS) WITH NON-SMALL CELL LUNG CANCER (NSCLC)

M. Reck[1], S.L. de Haas[2], S.E. Evers[3], P.D. Delmar[4], C. Manegold[5], S.J. Scherer[6], N.B. Leighl[7] *[1]Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf/GERMANY, [2]PDEO, F. Hoffmann-La Roche Ltd., Basel/SWITZERLAND, [3]Molecuzlar Medicine Laboratories, F. Hoffmann La Roche, Basel/SWITZERLAND, [4]PDIM, F. Hoffmann La Roche, Basel/SWITZERLAND, [5]Department of Surgery, Thoracic Oncol., Heidelberg University, Mannheim/GERMANY, [6]Biomarker and Experimental Medicine, F. Hoffmann La Roche, Basel/SWITZERLAND, [7]Medical Oncology, Princess Margaret Hospital, Toronto/CANADA*

Background: Two phase III trials, E4599 and AVAiL, have shown that addition of Bv to platinum-based chemotherapy improved outcomes in pts with untreated advanced NSCLC. In study E4599, analysis of several BMs showed that intracellular adhesion molecule-1 (ICAM-1) levels may be predictive of response to therapy and prognostic of survival, whereas pts with high baseline vascular endothelial growth factor (VEGF) levels may have a higher response rate to Bv. A similar exploratory BM analysis was performed on baseline samples of the AVAiL trial.

Methods: In AVAiL 1,043 pts with untreated locally advanced, metastatic or recurrent non-squamous NSCLC, ECOG PS 0/1, were randomised to CG q3w for up to 6 cycles plus either Bv 7.5mg/kg (n=345), Bv 15mg/kg (n=351) or placebo (n=347). PFS was the primary endpoint. Baseline plasma samples were collected and analysed for VEGF, ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), E-selectin and basic fibroblast growth factor (bFGF) by ELISA. Samples were available for 358 pts. The use of median levels across the samples to categorise them as low and high was pre-specified as a cut-off. Simple and multiple regression approaches as well as subgroup analyses were used to correlate BM levels to PFS and OS.

Results: Baseline characteristics of pts with available BM samples appeared to be balanced between the 3 treatment arms. Analysis of ICAM, VCAM, bFGF and VEGF suggested that high baseline levels of these markers were associated with a shorter OS compared with low levels. When comparing PFS between the 15mg/kg Bv and placebo arms, a trend towards a larger treatment effect was observed in pts with low ICAM-1 levels compared with pts with high ICAM-1 levels. Comparing OS between the 7.5mg/kg Bv and placebo arms, a trend towards a larger treatment effect was observed in pts with high bFGF levels compared with pts with low bFGF levels.

Conclusions: This exploratory analysis showed that BMs involved in angiogenic pathways may play a prognostic role in pts with advanced NSCLC. The role of angiogenic BMs in predicting response should be further evaluated in ongoing trials with Bv in NSCLC.

Disclosure: M. Reck: Honoraria: Hoffmann-La Roche, Lilly, Merck, Astra-Zeneca; Advisory Board: Hoffmann-La Roche, Lilly, Merck, Astra-Zeneca S.L. de Haas: I am an employee of F.Hoffmann-La Roche, which has funded the conduct of the AVAIL study and biomarker analysis.

S.E. Evers: Stefan Evers is an employee and stock owner of F. Hoffmann-La Roche Ltd.
P.D. Delmar: I am regular full time employee of F. Hoffmann-La Roche Ltd.
S.J. Scherer: I am an employee of F.Hoffmann-La Roche, which has funded the conduct of the AVAIL study and biomarker analysis.
N.B. Leighl: none known - Roche has provided clinical trial funding for an unrelated investigator-initiated trial to the University Health Network in 2007
All other authors have declared no conflicts of interest.

135O

SOLUBLE LEVELS OF VEGF-A AND VEGFR-2 IN PATIENTS WITH ADVANCED NSCLC

R. Sirera[1], E. Sanmartin[2], E. Jantus[2], A. Blasco[3], C. Caballero[4], S. Gallach[5], P. Olmo[4], N. del Pozo[6], R.M. Bremnes[7], C. Camps[8] *[1]Molecular Oncology Laboratory, University General Hospital, Valencia/SPAIN, [2]Molecular Oncology Laboratory, Fundacion para la Investigacion del Hospital General Universitario de Valencia, Valencia/SPAIN, [3]Medical Oncology, Cosorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [4]Oncology Service, University General Hospital, Valencia/SPAIN, [5]Molecular Oncology Laboratory, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia/SPAIN, [6]Oncology Sevice, University General Hospital, Valencia/SPAIN, [7]Department of Oncology, Institute of Clinical Medicine, University of Tromsø, Tromsø/NORWAY, [8]Oncology Service, Hospital General Universitario de Valencia, Valencia/SPAIN*

Introduction: Angiogenesis is an early and crucial event in NSCLC pathogenesis. VEGF-A is an important proangiogenic factor for novel tumor blood vessel formation. The expression of VEGF-A in tumor cells and in tumor micro-vessels has been reported in 30–100% of NSCLC patients. VEGFR-2 is the main pro-angiogenic receptor for VEGF-A, and seems to play a key role in tumor-induced angiogenesis. An increased expression of angiogenic factors in tumor or serum/plasma is associated with metastasis and poor prognosis. The aim of this study is to investigate the usefulness of the quantification of soluble VEGF-A and VEGFR-2 as biomarkers in advanced NSCLC.
Patients and methods: 458 patients with advanced NSCLC (stages IIIB-IV) treated with cisplatin and docetaxel and 89 healthy age-matched controls were studied. Pre-treatment blood samples were collected, and plasma was obtained. VEGF-A and VEGFR-2 protein levels were quantified using an ELISA assay. Statistical analysis was performed using SPSS 15.0. Tests were considered significant at $p < 0.05$.
Results: Soluble levels of VEGF-A and VEGFR-2 were significantly higher in patients than controls; VEGF-A: 105.92 ± 5.30 pg/ml vs 26.17 ± 5.35 pg/ml, respectively; $p < 0.0001$; and VEGFR-2: 8346± 120 pg/ml vs 6903± 144 pg/ml, respectively; $p < 0.0001$). The areas under the ROC curve were 0.858 for VEGF-A and 0.744 for VEGFR-2, indicating that both variables are suitable diagnostic-biomarkers, allowing the discrimination between controls and patients. Patients with high VEGFR-2 plasma levels (75 percentile) show a significantly longer time to progression (TTP, $p=0.029$). On the other hand, high levels of soluble VEGF-A (75 percentile) correlates with a poor overall survival (OS, $p=0.026$). A subgroup characterized by a combination of high levels of soluble VEGF-A and low levels of soluble VEGFR-2 had the worse prognosis regarding TTP ($p=0.042$) and OS ($p=0.003$), when compared with other possible combinations of markers.
Conclusions: Soluble levels of VEGF-A and VEGFR-2 are significantly higher in NSCLC patients than in age-matched controls. The combination of both variables, allow the identification of a NSCLC subgroup with a poorer prognosis, which may benefit from additional anti-angiogenic therapy.
Disclosure: All authors have declared no conflicts of interest.

136O

EXPRESSION OF VEGF LIGANDS AND RECEPTORS IN TUMOR VERSUS STROMAL CELLS IN NSCLC: PROGNOSTIC VALUE

E. Jantus[1], E. Sanmartin[1], R. Sirera[2], A. Blasco[3], R. Guijarro[4], T. Donnem[5], S. Al-Saad[6], L. Busund[7], R.M. Bremnes[8], C. Camps[9] *[1]Molecular Oncology Laboratory, Fundacion para la Investigacion del Hospital General Universitario de Valencia, Valencia/SPAIN, [2]Molecular Oncology Laboratory, University General Hospital, Valencia/SPAIN, [3]Medical Oncology, Cosorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [4]Thoracic Surgery, Consorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [5]Institute of Clinical Medicine, Uniersity of Tromso, Tromso/NORWAY, [6]Institute of Medical Biology, Universitu of Tromoso, Tromso/NORWAY, [7]Institute of Medical Biology, University of Tromso, Tromso/NORWAY, [8]Department of Oncology, Institute of Clinical Medicine, University of Tromsø, Tromsø/NORWAY, [9]Oncology Service, Hospital General de Valencia, Valencia/SPAIN*

Background: In tumor angiogenesis there is a complex interplay between endothelial, stromal, and tumor cells. One of the most important signalling pathways in angiogenesis is initiated by binding of VEGF ligands to its receptors. This study analyses correlations between the expression of VEGF ligands and receptors in tumor cells and tumor stroma in samples from resectable non-small cell lung cancer (NSCLC) patients.
Methods: Primary tumor tissues (n=84) from NSCLC patients (I -IIIA) were used in this study. The most representative areas of tumor, stroma and normal tissue were carefully selected. RNA was extracted from 2 sampled cores (0.6 mm) using a standard protocol and RT-PCR was performed using TaqMan® probes. Relative quantification was calculated using actin-b as endogenous control. Results were normalized against a calibrator sample (NCI-H23 cell line). Normalization against normal tissue is under study. Statistical analysis were considered significant at $p<0.05$.
Results: Significant differences between tumor and stroma expression were found for VEGFR-1, −3 and neuropilin-1 (NRP-1). Analysis according to histological subtypes [squamous (SCC) vs. adenocarcinoma], show significant differences in expression for: PlGF and VEGFR-2 (in tumor) and VEGF-A, VEGFR-2, −3, NRP-1 (in stroma). Survival analyses revealed that patients co-expressing lower levels of VEGFR-2 in tumor and higher stromal levels of VEGF-A had significantly worse prognosis ($p= 0.017$).
Conclusions: Our results show the importance of tumor-stroma interactions in the angiogenic process in this type of cancer. There are "angiogenic profiles" that could be used as prognostic markers in NSCLC and may help in the selection of patients that will better benefit of the anti-angiogenic therapies. (Supported by ISCIII grant)
Disclosure: All authors have declared no conflicts of interest.

137O

PREDICTIVE SIGNIFICANCE OF EGFR SOMATIC MUTATIONS AND GENE COPY NUMBER IN NSCLC PATIENTS TREATED WITH SINGLE AGENT TYROSINE KINASE INHIBITORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

S. Murray[1], E. Evangelou[2], H. Linardou[3], I.J. Dahabreh[4,6], P. Kosmidis[5], D. Bafaloukos[3], J.P.A. Ioannidis[2,6] *[1]Department of Molecular Biology and Genetics, Metropolitan Hospital, Athens/GREECE, [2]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina/GREECE, [3]1st Oncology Department, Metropolitan Hospital, Athens/GREECE, [4]Department of Pathophysiology, Medical School, National University of Athens/GREECE, [5]2nd Department of Oncology Hygeia Hospital, Athens/GREECE, [6]Biomedical Research Institute, Foundation for Research*

and Technology – Hellas Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Department of Medicine, Tufts University School of Medicine, Boston/USA

Background: The presence of somatic mutations of in the TK of EGFR and gene copy number gain in patients with NSCLC are good candidate predictive biomarkers for response to monotherapy with TKIs. We aimed to characterize the predictive effect of these aberrations on survival outcomes and response by systematic review and meta-analysis

Methods: We performed a computerized search of MEDLINE and Cochrane library to identify the association between EGFR gene status and response or survival to the TK inhibitors gefitinib and erlotinib. Study eligibility: single agent TKI in unselected patients with advanced NSCLC. Between-study heterogeneity was assessed with the Q statistic and inconsistency with the I^2 statistic; small study effects were assessed using the Harbord/ Egger test. Both fixed and random effects models were considered for the summary effects. Data on OS, PFS, TTP and response rates were extracted. Random effects meta-analyses were used to calculate summary hazard ratios and bivariate random effects meta-analysis was used to calculate likelihood ratios for predicting response.

Results: Of 4873 studies, 85 were eligible for at least one outcome. For somatic EGFR mutations 20 (1373), 22 (1685), 43 (2412), 65 (3101) and for EGFR gene gain 5 (294), 10 (822), 20 (1689), 21 (1539) studies were evaluable for TTP, PFS, OS and response respectively. Random effects analysis showed somatic EGFR mutations to be superior predictors of TTP/PFS compared to gene copy gain (HR=0.38; 95%CI, 0.29-0.49 vs 0.6; 95%CI, 0.46-0.79) compared to wild type. Superiority was observed for OS (HR=0.49; 95%CI, 0.42-0.57 for mutations; 0.78; 95%CI, 0.66-0.93 gene copy). Likelihood ratios of response supported the superiority of EGFR mutations: +LR=5.6, -LR=0.25 vs +LR=2.1, -LR=0.55 for gene gain. Effects were consistent across subgroups

Conclusions: These comprehensive meta-analyses provide large-scale empirical evidence that the improved responses observed in patients harboring somatic mutations in EGFR are matched by survival outcomes. The data also suggests that there is less benefit obtained by stratifying for EGFR gene copy number

Disclosure: S. Murray: Consultant or Advisory role: S Murray, AstraZeneca, Macclesfield, United Kingdom. AstraZeneca are proprietors of Iressa® (gefitinib). P. Kosmidis: Consultant or Advisory role: P Kosmidis, AstraZeneca, Macclesfield, United Kingdom. AstraZeneca are proprietors of Iressa® (gefitinib). All other authors have declared no conflicts of interest.

138O

INCREASED THYMIDYLATE SYNTHASE (TS) GENE COPY NUMBER IN NSCLC

M.W. Wynes[1], R. Dziadziuszko[2], S. Singh[3], D. Christoph[4], J. Ranger-Moore[5], B. Szostakiewicz[6], K. Dziadziuszko[7], W. Eberhardt[8], J. Jassem[9], F.R. Hirsch[10]
[1]Medicine-division of Medical Oncology, University of Colorado Denver, Aurora/USA, [2]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND, [3]Translational Diagnostics, Ventana Medical Systems Inc., Tucson/USA, [4]Internal Medicine, University Hospital of Duisburg-Essen, Essen/GERMANY, [5]Biostatistics and Data Management, Ventana Medical Systems Inc., Tucson/USA, [6]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND, [7]Department of Radiology, Medical University of Gdansk, Gdansk/POLAND, [8]Department of Internal Medicine (cancer Research), West German Cancer Centre Universitätsklinikum Essen, Essen/GERMANY, [9]Oncology and Radiotherapy, Medical University, Gdansk/POLAND, [10]Medicine-Oncology, University of Colorado Cancer Center, Aurora/USA

Background: High TS expression may associate with poor prognosis and confer resistance to antifolates, particularly pemetrexed. TS is essential for DNA synthesis and for de novo production of dTMP. This study determined TS gene copy number in NSCLC, especially with regard to histology, and evaluated the prognostic influence of TS gene copy number.

Methods: TS was evaluated on a tissue microarray containing triplicate samples from 189 patients (pts) who underwent surgery using an experimental silver in situ hybridization (SISH) assay (Ventana Medical Systems, Inc., Tucson, AZ). Results were obtained for 124 pts (66%). This group included 83% males, 60% squamous cell carcinomas (SCC) and 25% adenocarcinomas (AC). The pathological stages were I: 39%, II: 25% and III: 30%, IV: 5% and unknown: 1%. A certified pathologist counted signals in 50 nuclei/core and determined the mean TS copies/nucleus/core. The average of the triplicate cores was compared to the highest core of same pt. The highest core was used for further analyses due to better relationship to parameters tested.

Results: Median gene copy number in the population was 2.5 (1.4-9.6) while mean was 2.7 (±1.0). Nine cases (7%) had ≥4 genes/nucleus and 1 had clusters. Gene copy number significantly differed (p=0.04) by histology: AC median 2.2 (1.6-4.5) mean 2.5 (±0.7); SCC 2.5 (1.4-9.6), 2.8 (±1.2); NOS/other 2.9 (1.5-3.4), 2.7 (±0.6). Using 2.5 as a cut-off, 32% of ADs, 50% of SCCs and 68%of NOS/others were positive. For TS ≥4, 7/9 pts were SCC and 2/9 AD. Kaplan-Meier analysis using median cut-off revealed no relationship between TS copy number and PFS (p=0.45) or OS (p=0.40). Similar results were obtained using adjusted Cox regression analysis and examining TS as a continuous variable; PFS (HR 0.96, p=0.77) or OS (HR 0.94, p=0.70). No relationship between TS and PFS (p=0.56) or OS (p=0.37) was found after stratification by histology (SCC vs. non-SCC).

Conclusions: TS gene copy number is increased in primary tumors from NSCLC pts. Many SCC tumors had high TS gene copy number, but others did not. TS gene copy number is not associated with prognosis. Ongoing studies will test whether TS gene copy number predicts clinical benefit from pemetrexed and preliminary data are planned to be presented.

Disclosure: S. Singh: This author is an employee of, and has stock ownership in Ventana Medical Systems Inc. J. Ranger-Moore: This author is an employee of Ventana Medical Systems Inc. F.R. Hirsch: Advisory Boards: AstraZeneca, Merck Serono, BMS/Imclone, Syndax, Pfizer, Boehringer-Ingelheim, Lilly Oncology, GSK, OSI/Genenetech/Roche Research Funding: AstraZeneca, OSI, Genentech, Syndax, Biogen-Idec, Ventana-Roche, Merck, Genmab. All other authors have declared no conflicts of interest.

139O

INFLUENCE OF EVEROLIMUS AND PEMETREXED ON THYMIDYLATE SYNTHASE EXPRESSION AS WELL AS ON PROLIFERATION AND SURVIVAL OF NON-SMALL CELL LUNG CANCER CELLS

B. Markova[1], P.S. Hähnel[2], S. Herbertz[3], M. Schuler[4], F. Breitenbuecher[1]
[1]Innere Klinik/tumorforschung, Westdeutsches Tumorzentrum, Universitätsklinikum Essen, Essen/GERMANY, [2]3rd Medical Department, Johannes Gutenberg University, Mainz/GERMANY, [3]Business Unit Oncology, Novartis Pharma GmbH, Pulheim/GERMANY, [4]Innere Klinik und Poliklinik (tumorforschung), University of Essen, Essen/GERMANY

Pemetrexed is a potent inhibitor of thymidylate synthase (TS) and additional folate-dependent enzymes, effective in treatment of non-squamous non-small cell lung cancer (NSCLC). Preclinical data indicate that overexpression of TS correlates with reduced sensitivity of NSCLC cells to pemetrexed. A recent study in chemotherapy-naÃ¯ve patients demonstrated that the baseline expression of the TS gene and protein were significantly higher in squamous cell carcinoma as compared to adenocarcinoma. Against this background we hypothesized that the allosteric mTOR inhibitor everolimus (RAD001) could increase the efficacy of pemetrexed in squamous NSCLC by lowering TS levels. To this end, we used a panel of cell lines representing squamous- and adenocarcinoma histology. Thymidylate synthase mRNA and protein levels were measured by qRT-PCR and western bloting, respectively. Biological end points

were proliferation, apoptosis and clonogenic survival of the cells. Surprisingly, no correlation between histology and TS expression levels was observed. Treatment with pemetrexed significantly induced TS mRNA and protein levels. RAD001 treatment did not modulate TS mRNA expression, but protein levels were reduced. RAD001 was able to prevent pemetrexed-induced upregulation of TS mRNA in some cell lines. However, the antiproliferative activity of pemetrexed was not enhanced in co-treatment experiments with RAD001. Surprisingly, combining pemetrexed and RAD001 considerably reduced pemetrexed-induced apoptosis. These results were further supported by colony formation assays, which revealed increased clonogenic survival under treatment with RAD001 and pemetrexed as compared to pemetrexed alone. These data indicate that strategies based on RAD001 and pemetrexed combinations require careful preclinical assessment.

Disclosure: S. Herbertz: Employed by Novartis Pharma GmbH. All other authors have declared no conflicts of interest.

140O

DETECTION OF CIRCULATING TUMOUR CELLS (CTCS) IN NON-SMALL CELL LUNG CANCER (NSCLC) BY CELLSEARCH AND ISET TECHNOLOGIES

M. Krebs[1], R. Sloane[1], L. Priest[1], L. Lancashire[2], J. Hou[3], G. Clack[4], A. Hughes[4], C. Dive[3], F. Blackhall[5] *[1]Clinical and Experimental Pharmacology Group, Paterson Institute for Cancer Research, Manchester/UNITED KINGDOM, [2]Cep, PICR, Manchester/UNITED KINGDOM, [3]Clinical & Experimental Pharmacology, Paterson Institute for Cancer Research, Manchester/UNITED KINGDOM, [4]Discovery Medicine, AstraZeneca, Manchester/UNITED KINGDOM, [5]Department of Medical Oncology, Christie Hospital NHS Trust, Manchester/UNITED KINGDOM*

Background: Circulating tumour cells (CTCs), a key intermediary in metastasis offer potential utility as prognostic, predictive and/or pharmacodynamic biomarkers. We compared the ability of CellSearch and ISET (Isolation by Size of Epithelial Tumours) technologies to enumerate and characterise CTCs in NSCLC patients.

Methods: CellSearch enriches CTCs by EpCam based immunomagnetic capture. Permeabilised cells were labelled with DAPI and antibodies to cytokeratins and CD45. ISET CTC detection is by size exclusion and CD45 negative selection. Baseline clinical samples, processed to GCLP standards, were collected from stage III/IV, chemo-näive patients according to ethically approved clinical protocols. Parallel blood samples were analysed by both technologies.

Results: 26 patients were analysed (4 stage IIIA, 8 stage IIIB, 14 stage IV disease). 6/26 patients (23%) had ≥2 CTCs/7.5ml blood (CTC#) by CellSearch. Median CTC# was 0 (mean±sd 5±16, range 0-78). Mean CTC # detected by stage is shown in Table1 By ISET, 20/26 (77%) patients had ≥2 CTC#. Median CTC# was 29 (mean±sd 90±206, range 0-1045). Mean CTC# by stage is shown in Table1. Ten patients (6 Stage IV, 4 Stage IIIB patients) had evidence of circulating tumour microemboli (CTMs), not identified by CellSearch. CTCs/CTMs were confirmed as malignant by positive staining for EpCam, cytokeratin, epidermal growth factor receptor and/or TTF1.

Conclusions: CTCs were identified in NSCLC patients by both technologies but with higher frequency and prevalence by ISET. CTM identification by ISET supports conceptualised mechanisms of tumour invasion. The prognostic significance of circulating cells enriched by ISET is unclear and will be explored regarding clinical outcome. Combinations of technologies are clearly needed to detect heterogeneous circulating cells and the potential to identify predictive biomarkers and understand further the biology of metastasis is highlighted.

Table 1

	CellSearch		ISET	
	No. pts with ≥2 CTC/ 7.5ml Blood	Mean±sd CTC Number	No. pts with ≥2 CTC/ 7.5ml Blood	Mean±sd CTC Number
Stage IIIA (n=4)	0	0.5 ± 0.6	2	19 ± 35
Stage IIIB (n=8)	1	0.6 ± 1.1	7	61 ± 74
Stage IV (n=14)	5	10 ± 22	11	127 ± 274

Disclosure: All authors have declared no conflicts of interest.

141PD

CLINICOPATHOLOGIC CHARACTERISTICS AND SURVIVAL OUTCOMES OF THREE RARE SUBTYPES OF ADENOCARCINOMA (PAPILLARY CARCINOMA, ACINAR CARCINOMA, SIGNET-RING CELL CARCINOMA) THAT HAVE BEEN ASSOCIATED WITH HISTOLOGICAL CHARACTERISTICS OF EML4-ALK NSCLC

S.H. Ou[1], A. Ziogas[2], J.A. Zell[1] *[1]Medicine-Hematology/Oncology, Chao Family Comprehensive Cancer Center, UC Irvine Medical Center, Orange/USA, [2]Epidemiology, University of California Irvine, Irvine/USA*

Background: Several rare subtypes of adenocarcinoma including signet-ring cell carcinoma (SRCC), acinar carcinoma (AC), and papillary carcinoma (PC) have been described in the EML4-ALK positive NSCLC. We investigated the clinicopathologic characteristics and survival outcome of these adenocarcinoma subtypes.

Methods: Retrospective population-based analysis of 3 adenocarcinoma subtypes diagnosed histologically in the California Cancer Registry (CCR) between 1989 and 2006 with comparison to adenocarcinoma of the lung.

Results: 1241 cases of PC, 379 cases of AC, and 262 cases of SRCC are compared to 50089 cases of adenocarcinoma of the lung. The median age of SRCC patients is significantly younger than adenocarcinoma patients (64 vs. 67; $p < 0.0001$). More than half of PC and AC patients are females. Close to half of AC patients (48.6%) present with stage I disease while 49.2% of SRCC patients present with stage IV disease. There is no significant difference in the distribution of AC and SRCC among the 4 major ethnicities but Asians have a higher proportion among PC as compare to adenocarcinoma. Among patients with known smoking status, SRCC patients have the highest proportion of never-smokers (30.8%) while only 11.0% of adenocarcinoma patients are never-smokers. The median overall survival (OS) for AC patients is 68 months, 20 months for PC patients, 10 months for adenocarcinoma patients, and 6 months for SRCC patients. Multivariate analyses reveal AC and PC histologies are independent favorable prognostic factors for OS while SRCC histology is an independent unfavorable prognostic factor when compare to adenocarcinoma. AC remained a favorable prognostic factor among stage I patients and SRCC histology remains an unfavorable prognostic factor among stage IV patients when compared to adenocarcinoma.

Conclusions: PC, AC, and SRCC are all rare subtypes of adenocarcinoma of the lung and have different clinicopathologic features and survival outcomes. Signet-ring cell carcinoma of the lung seems to share the most common characteristics associated with EML4-ALK NSCLC.

Disclosure: All authors have declared no conflicts of interest.

142PD

PROGNOSTIC VALUE OF CIRCULATING ENDOTHELIAL CELLS EXPRESSION MARKERS IN ADVANCED NSCLC

R. Sirera[1], S. Gallach[2], A. Blasco[3], E. Jantus[2], E. Sanmartin[2], N. del Pozo[4], A. Iraola[4], R.M. Bremnes[5], A. Berrocal[6], C. Camps[6] *[1]Molecular Oncology Laboratory, University General Hospital, Valencia/SPAIN, [2]Molecular Oncology Laboratory, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia/SPAIN, [3]Medical Oncology, Cosorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [4]Oncology Service, University General Hospital, Valencia/SPAIN, [5]Department of Oncology, Institute of Clinical Medicine, University of Tromsø, Tromsø/NORWAY, [6]Oncology Service, Hospital General de Valencia, Valencia/SPAIN*

Introduction: Angiogenesis is an important process for tumor development, growth and dissemination. Abnormal numbers of circulating endothelial cell (CEC) and circulating endothelial progenitor cell (EPC) are present in cancer, but their relationship with prognosis is unclear. CECs are a minute subset of peripheral blood cells, characterized by the expression of several surface markers like: CD146, CD31, CD133, Tie2 and CD34 (in the case of EPCs). The aim of the study was to quantify markers associated to CECs and EPCs by RT-PCR and to correlate them with clinicopathological variables, response to treatment and prognosis in advanced NSCLC patients.

Patients and methods: Patients with advanced NSCLC (n= 53), stage IIIB-IV, were studied. They were treated with a combination of cisplatin and docetaxel. Blood samples were collected before and after 3 cycles of chemotherapy in PAXgene Blood RNA Tubes and stored at −80°C until RNA isolation. mRNA was reverse transcribed and quantification of CD146, CD31, CD34, CD133 and Tie2 genes by RT-PCR was performed using TaqManâ primers/probes. Relative expression was calculated by Pfaffl formulae, using GUSB as endogenous control. Differences were considered significant at $p < 0.05$.

Results: We found no correlation between the expression of the analyzed markers and clinico-pathological variables. Compared to pre-treatment levels, post-treatment expression levels of CD31 and Tie2 were significantly reduced after chemotherapy ($p<0.0001$ and $p=0.003$, respectively). Considering only adenocarcinomas, we found that those patients with basal low CD146 expression had significant better progression-free ($p=0.024$) and overall survival ($p=0.001$).

Conclusion: This study shows that it is possible to detect and quantified CEC-associated markers in peripheral blood samples. The expression of CD146 can possibly be used as biomarker of prognosis in advanced NSCLC.

Disclosure: All authors have declared no conflicts of interest.

143PD

PRX1 PROVIDES RESISTANCE TO DOCETAXEL-INDUCED APOPTOSIS IN LUNG CANCER CELLS

H. Kim, S. Yang, E. Jeong *Internal Medicine, College of Medicine Wonkwang University, Iksan/KOREA*

Prx1 is a major 2-Cys peroxiredoxin family member and is frequently elevated in several human cancers including lung, oral, prostate, and breast cancers, and this seems to confer increased treatment resistance. Although Prx1 suppresses radiation-induced c-Jun NH2-terminal kinase (JNK) activation and apoptosis in non-small cell lung cancer (NSCLC), the precise mechanism of chemoresistnace is not clearly known. In this study, we investigated the role of Prx1 in docetaxel-induced apoptosis of A549 lung cancer cells. We generated shRNA targeting Prx1 in A549 cells to test the sensitivity to docetaxel treatment. We found that Prx1 knock-down increased apoptotic potential through activation of caspase cascade. In addition, inhibition of Prx1 by shRNA suppressed the phosphorylation of Akt and FoxO1a, a substrate of Akt, by docetaxel treatment in A549 cells. Furthermore, PI3K inhibitor LY294002 inhibited the phosphorylation of FoxO1a and increased the cytotoxicity of docetaxel in A549 cells. These findings suggest that Prx1 may modulate the chemosensitivity of lung cancer A549 cells to docetaxel through suppressing FoxO1a–induced apoptosis.

Disclosure: All authors have declared no conflicts of interest.

144P

THE MMP1, MMP2 AND VEGF GENETIC POLYMORPHISMS AS PROGNOSTIC FACTORS IN NON-SMALL CELL LUNG CANCER

R. Suwinski[1], D. Butkiewicz[2], A. Drosik[3], M. Gawkowska-Suwinska[1], E. Nowara[4], M. Rusin[2] *[1]Radiotherapy Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND, [2]Tumor Biology, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND, [3]Clinical Oncology, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND, [4]Radiotherapy Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Glliwice/POLAND*

Purpose: To evaluate the effect of four functional MMP1, MMP2 and VEGF gene polymorphisms on overall survival (OS) of non-small cell lung cancer (NSCLC) patients.

Material and methods: The study included 135 patients with NSCLC treated with radio-chemotherapy or radiotherapy alone. Genomic DNA was isolated from frozen peripheral blood and the polymorphisms were detected with standard PCR-RFLP. Survival in relation to genotypes was evaluated using the Kaplan-Meier method and assessed with log-rank test. Uni- and multivariate Cox proportional hazards model was also used.

Results: Out of four polymorphisms studied, the MMP1 −1607 and VEGF −634 significantly influenced OS in NSCLC patients. Carriers of one or two MMP1 2G alleles showed better survival compared to 1G1G homozygotes ($P = 0.043$). Carriers of at least one VEGF −634 C allele had higher risk of death than GG homozygotes ($P = 0.008$). When clinical stage was considered, only in IIIA-IIIB subgroup the influence of the polymorphisms on OS was observed – the VEGF −634 GG homozygotes showed better survival than GC+CC carriers. Also, in patients with T3-T4 primary tumour stage, the VEGF −634 GC+CC genotype correlated significantly with an increased risk of death ($P = 0.010$), whereas the MMP1 −1607 2G allele was slightly associated with better survival. Moreover, there was statistically significant influence of the VEGF −634 genetic polymorphism on survival among patients who received radiotherapy only ($P = 0.016$). Multivariate analysis revealed that VEGF −634 genetic polymorphism was an independent prognostic factor in the studied group.

Conclusion: Our results demonstrate that MMP1 −1607 2G and VEGF −634 G alleles are associated with better overall survival in NSCLC patients, especially among those with locally advanced disease, and suggest that MMP1 −1607 and VEGF −634 polymorphisms may serve as prognostic biomarkers in NSCLC.

Disclosure: All authors have declared no conflicts of interest.

145P

PDGF LIGANDS AND RECEPTORS: EXPRESSION IN TUMOR CELLS AND STROMA IN NSCLC

E. Jantus[1], E. Sanmartin[1], A. Blasco[2], R. Sirera[3], R. Guijarro[4], T. Donnem[5], S. Al-Saad[6], L. Busund[7], R.M. Bremnes[8], C. Camps[9] *[1]Molecular Oncology Laboratory, Fundacion para la Investigacion del Hospital General Universitario de Valencia, Valencia/SPAIN, [2]Medical Oncology, Cosorcio Hospital*

General Universitario de Valencia, Valencia/SPAIN, [3]Molecular Oncology Laboratory, University General Hospital, Valencia/SPAIN, [4]Thoracic Surgery, Consorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [5]Institute of Clinical Medicine, Uniersity of Tromso, Tromso/NORWAY, [6]Institute of Medical Biology, Universitu of Tromoso, Tromso/NORWAY, [7]Institute of Medical Biology, University of Tromso, Tromso/NORWAY, [8]Department of Oncology, Institute of Clinical Medicine, University of Tromsø, Tromsø/NORWAY, [9]Oncology Service, Hospital General de Valencia, Valencia/SPAIN

Background: Tumor angiogenesis is a complex process in which tumor, endothelial and stromal cells are involved. The ligands and receptors of PDGF family play an important role in this process. The aim of this study was to analyze the expression of PDGF ligands and receptors in tumor cells and tumor stroma in resectable non-small cell lung cancer (NSCLC) samples and to correlate them with clinicopathological variables and prognosis.

Methods: We studied 84 resectable NSCLC samples (stage I -IIIA). The most representative areas of tumor cells, tumor stroma and normal lung tissue were carefully selected for building tissue microarrays (TMA) blocks. RNA extracted from 2 cores pieces from each area. RTqPCR were performed to analyze genes of PDGF family by TaqMan ® primers/ probes. Relative quantification was calculated by Pfaffl formula using actin-b as endogenous control. Results were normalized against a calibrator sample (cDNA from NCI-H23). Normalization against normal lung tissue is under study. TTP and OS were calculated from the date of diagnosis to the date of disease progression, death or last follow up.Statistical analysis were considered significant at $p<0.05$.

Results: Significant differences between tumor and stroma expression were found for PDGF-B, PDGFR-α and -β. We observed a statistical association between lower levels of expression of PDGFR-α in tumor and relapse. Moreover, we also found a significant correlation between lower expression of PDGF-C, PDGFR-α and -β in tumor and a poor differentiation grade. Survival analyses in the SCC subgroup revealed that patients showing a combination of high stromal PDGF-A and low tumor PDGFR-α levels have shorter overall survival than the others ($p= 0.019$).

Conclusions: Our results show a possible prognostic role of the stroma in tumor angiogenesis in NSCLC. There are "angiogenic profiles" that could be used as prognostic markers and may help in the selection of patients that will better benefit of the anti-angiogenic therapies (Supported by ISCIII grant).

Disclosure: All authors have declared no conflicts of interest.

146P

REGULATORY T-LYMPHOCYTE-ASSOCIATED MARKER EXPRESSION IN RESECTABLE NSCLC: PROGNOSTIC VALUE

R. Sirera[1], M. Usó[2], S. Gallach[3], A. Blasco[4], E. Jantus[5], E. Palomares[6], R. Guijarro[7], C. Caballero[6], J. Galbis[8], C. Camps[9] *[1]Molecular Oncology Laboratory, University General Hospital, Valencia/SPAIN, [2]Molecular Oncology Laboratory, Fundación para la investigación del Hospital General de Valencia, Valencia/SPAIN, [3]Molecular Oncology Laboratory, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia/SPAIN, [4]Medical Oncology, Cosorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [5]Molecular Oncology Laboratory, Fundacion para la Investigacion del Hospital General Universitario de Valencia, Valencia/SPAIN, [6]Oncology Service, University General Hospital, Valencia/SPAIN, [7]Thoracic Surgery, Consorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [8]Thoracic Surgery Service, University General Hospital, Valencia/SPAIN, [9]Oncology Service, Hospital General de Valencia, Valencia/SPAIN*

Introduction: Regulatory T-lymphocytes (Tregs) play a critical role in immune tolerance to tumor cells. Several molecules, including CD4, CD25, CD127, CTLA-4, IL-10 and TGFβ1 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 Treg-associated markers by RT-PCR and to correlate them with clinicopathological and prognostic variables in NSCLC.

Patients and methods: RNA was obtained from frozen lung specimens (tumor and normal lung) from early-stage NSCLC patients (n=135). RT-PCR was performed to analyze the expression of: CD4, CTLA-4, FoxP3, IL10, CD25, CD127 and TGFβ1. Relative expression was normalized by an endogenous gene (GUS-B) using the Pfaffl formulae. Statistical analyses were done by SPSS 15.0 and considered significant at $p<0.05$.

Results: Compared to normal lung tissue, tumor samples had significantly higher expression of CD25 (x2.1) and lower expression of CD127 (x0.42), reflecting a Treg phenotype infiltrating the tumor. In concordance, those patients that relapsed presented significantly higher CD25 and lower CD127 levels in tumor ($p=0.05$ and $p=0.006$, respectively). Additionally, patients that did not relapse presented higher levels of CD4 and CD8 ($p=0.004$ and $p=0.037$, respectively), markers of infiltrating helper and cytotoxic lymphocytes, respectively. Survival analyses revealed that patients with high FoxP3 expression had reduced OS ($p= 0.028$) whereas those with high CD4 expression had improved PFS ($p=0.007$) and OS ($p= 0.047$).

Disclosure: All authors have declared no conflicts of interest.

147P

COMPREHENSIVE ANALYSIS OF DNA REPAIR GENE POLYMORPHISMS AND SURVIVAL IN PATIENTS WITH EARLY STAGE NON-SMALL CELL LUNG CANCER

J.E. Choi[1], S.Y. Lee[2], H.G. Kang[1], J.Y. Park[2] *[1]Department of Biochemistry and Cell Biology, Kyungpook National University School of Medicine, Daegu/KOREA, [2]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu/KOREA*

Background: This study was conducted to analyze a comprehensive panel of single nucleotide polymorphisms (SNPs) in DNA repair genes to determine the relationship between polymorphisms and survival outcome of patients with early stage non-small cell lung cancer (NSCLC).

Patients and methods: Three hundred ten consecutive patients with surgically-resected NSCLC were enrolled. Forty-eight SNPs in 27 DNA repair genes were genotyped and their associations with overall survival (OS) and disease-free survival (DFS) were analyzed.

Results: Individually, 6 SNPs exhibited significant associations with survival outcome. When the 6 SNPs were combined, OS and DFS were decreased as the number of bad genotypes increased ($P_{trend} < 0.0001$ for both). Patients with 3, and 4 or 5 bad genotypes had a significantly worse OS and DFS compared with those carrying 0 or 1 bad genotypes (adjusted hazard ratio [aHR] for OS = 3.53, P = 0.02, and aHR for DFS = 3.31, P = 0.006; and aHR for OS = 5.47, P = 0.002, and aHR for DFS = 4.42, P = 0.001, respectively).

Conclusion: These findings suggest that the 6 SNPs identified can be used as prognostic markers for patients with surgically-resected early stage NSCLC.

Disclosure: All authors have declared no conflicts of interest.

148P

POLYMORPHISMS IN THE APOPTOSIS-RELATED GENES AND SURVIVAL OF PATIENTS WITH EARLY STAGE NON-SMALL CELL LUNG CANCER

H.G. Kang[1], H. Jeon[1], S.S. Yoo[1], J.Y. Park[2] [1]*Department of Biochemistry and Cell Biology, Kyungpook National University School of Medicine, Daegu/KOREA,* [2]*Department of Internal Medicine, Kyungpook National University, School of medicine, Deagu/KOREA*

Purpose: This study was conducted to determine the association between single nucleotide polymorphisms (SNPs) in apoptosis-related genes and survival outcomes of patients with early stage non-small cell lung cancer (NSCLC).

Methods: Three hundred ten consecutive patients with surgically-resected NSCLC were enrolled. Twenty-five SNPs in 17 apoptosis-related genes were genotyped by a sequenome mass spectrometry-based genotyping assay. The genotype associations with overall survival (OS) and disease-free survival (DFS) were analyzed.

Results: Three SNPs (TNFRSF10B rs1047266, TNFRSF1A rs4149570, and PPP1R13L rs1005165) were significantly associated with survival outcomes in multivariate analysis. When the three SNPs were combined, OS and DFS were decreased as the number of bad genotypes increased (P_{trend} for OS and DFS = 7×10^{-5} and 1×10^{-4}, respectively). Patients with one bad genotype, and patients with two or three bad genotypes had a significantly worse OS and DFS compared with those with 0 bad genotypes (adjusted hazard ratio [aHR] for OS = 2.27, 95% confidence interval [CI] = 1.22-4.21, P = 0.01, aHR for DFS = 1.74, 95% CI = 1.08-2.81, P = 0.02; aHR for OS = 4.11, 95% CI = 2.03-8.29, $P = 8 \times 10^{-5}$; and aHR for DFS = 2.89, 95% CI = 1.64-5.11, $P = 3 \times 10^{-4}$, respectively).

Conclusion: Three SNPs in apoptosis-related genes were identified as possible prognostic markers of survival in patients with early stage NSCLC. The SNPs, and particularly their combined genotypes, can be used to identify patients at high risk for poor disease outcome.

Disclosure: All authors have declared no conflicts of interest.

149P

APPLICATION OF MASS SPECTROMETRY-BASED SERUM PROTEOME PATTERN ANALYSIS IN IDENTIFICATION OF LUNG CANCER PATIENTS

M.A. Pietrowska[1], Ł. Marczak[2], R. Suwinski[3], M. Stobiecki[2], J. Polańska[4], A. Polański[5], P. Widłak[1], M. Gawkowska-Suwinska[3], A. Drosik[6], A. Walaszczyk[1] [1]*Department of Experimental and Clinical Radiobiology, Center of Oncology Maria Sklodowska Curie Memorial Institute, Gliwice/ POLAND,* [2]*Plant Secondary Metabolites Biochemistry Group, Institute of Bioorganic Chemistry Polish Academy of Sciences, Poznań/POLAND,* [3]*Radiotherapy Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND,* [4]*Institute of Automatic Control, Silesian University of Technology, Gliwice/POLAND,* [5]*Institute of Computer Science, Silesian University of Technology, Gliwice/ POLAND,* [6]*Clinical Oncology, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/ POLAND*

Mass spectrometry-based analysis of the blood proteome is an emerging method of clinical proteomics and cancer diagnostics. Here we performed mass spectrometry-based serum proteome pattern analysis aimed at identifying features specific for patients with non-small cell lung cancer (NSCLC). Blood samples were collected before the start of therapy from 49 patients with locally advanced NSCLC, 39 patients with head & neck cancer and 36 patients with colon cancer, as well as in a group of age and sex-matched healthy controls (48 donors). Serum was isolated after blood clotting and the low-molecular-weight proteome fraction (2-14 kDa) was analyzed using MALDI-ToF mass spectrometry. Registered mass spectra were analyzed using bioinformatic tools created and optimized in our group. We have identified cancer classifiers built of multiple spectral components that differentiated sera from analyzed groups. Classifiers built of 16-18 components differentiated healthy persons and patients with NSCLC with about 90% specificity and sensitivity. Furthermore, we have compared similarity of proteome patterns specific for analyzed types of cancer. Peptide profiles characteristic of samples from blood of patients with NSCLC and head & neck cancer were the most similar, while samples of colon cancer were the most different. Spectral components that are the most characteristic of specific types of cancer have been also identified. MALDI-ToF MS-based serum proteome pattern analysis has an obvious potential to differentiate samples between NSCLC patients and healthy controls or patients with other type of cancers.

Disclosure: All authors have declared no conflicts of interest.

150P

ACTIVITY BASED PROTEIN PROFILING OF HUMAN LUNG ADENOCARCINOMA BIOPSIES

T. Wiedl[1], B. Roschitzki[2], J. Grossmann[2], S. Arni[3], A. Soltermann[4], S.N. Hillinger[5], R. Aebersold[6], W. Weder[7] [1]*Department of Surgery, Division of Thoracic Surgery, University Hospital Zurich, Zurich/SWITZERLAND,* [2]*Functional Genomics Center Zurich (FGCZ), UZH/ETHZ, Zurich/ SWITZERLAND,* [3]*Department of Surgery, University Hospital Zurich, Zurich/SWITZERLAND,* [4]*Institute of Pathology, University Hospital Zurich, Zurich/SWITZERLAND,* [5]*Department of Thoracic Surgery, University Hospital Zurich, Zurich/SWITZERLAND,* [6]*Department of Biology, Institute of Molecular Systems Biology (ETH) and Faculty of Science (UZH), ETH Zurich and University of Zurich (UZH), Zurich/SWITZERLAND,* [7]*Division of Thoracic Surgery, University Hospital Zurich, Zurich/SWITZERLAND*

Rationale Lung cancer is the leading cause of all cancer related deaths and treatment is still suboptimal. A promising option in the search for predictive biomarkers is a novel methodology termed Activity Based Protein Profiling (ABPP). This technology employs so-called Activity Based Probes (ABPs) that selectively bind to active sites of members of distinct enzyme superfamilies, thereby making a direct activity read-out of a given proteome possible. Using ABPs targeting serine hydrolases, a large and diverse class of enzymes that have previously been linked to lung cancer development, we introduced ABPP as a biomarker screening platform in a clinical setting. Methods A directed mass spectrometric approach was used for qualitative and quantitative analysis of ABP labeled proteomes. Samples were analyzed on an FTICR mass spectrometer (LTQ-FTMS, Thermo Finnigan, Bremen, Germany). Mass spectrometric data were searched against a recently updated human database (UniProt) using the Mascot search engine (version 2.2). SuperHirn v0.3 was used for label-free quantitation. Inclusion lists were generated based on data derived from discovery-driven experiments in data-dependent acquisition mode. Results Approximately 30 serine hydrolases – mostly esterases and proteases – were identified per investigated proteome of the human lung adenocarcinoma cell line CaLu-3. Certain enzymes like Fatty Acid Synthase (FASN) or Kallikrein-6 (KLK6) have previously been associated with lung cancer development or lung cancer diagnosis, respectively. However, other enzymes like Neutral cholesterol ester hydrolase 1 (NCEH1) have not been linked to lung cancer so far or even represent uncharacterized proteins (Abhydrolase domain-containing protein 10, ABHD10). Discussion ABPP allows a relative fast and semi-quantitative analysis of enzymatic activity profiles in cell lines and primary human specimen. We aim to apply the established methodology on >100 pairs of fresh-frozen human lung adenocarcinoma biopsies and corresponding normal lung tissues from our tumor bank and link activity profiles of serine

hydrolases to clinical follow-up data. The results of this study will ideally allow the discrimination of low-/ high-risk lung adenocarcinoma patients.
Disclosure: All authors have declared no conflicts of interest.

151P

FEASIBILITY STUDY OF GENE EXPRESSION ANALYSIS IN BRONCHOSCOPY SPECIMENS

M. Jarzab[1], T. Tyszkiewicz[2], M. Kowalska[2], A. Klusek[3], A. Drosik[4], E. Nowara[1], M. Gawkowska-Suwinska[5], M. Zielinski[6], J. Kozielski[7], R. Suwinski[5] *[1]Department of Clinical Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice/POLAND, [2]Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice/POLAND, [3]Lung Diseases Division, City Hospital, Chorzow/POLAND, [4]Clinical Oncology, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND, [5]Radiotherapy Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND, [6]Chest Disease Hospital, Zakopane/POLAND, [7]Department of Lung Diseases and Tuberculosis, Silesian Medical University, Zabrze/POLAND*

Numerous studies have shown the potential role of gene expression markers as prognostic or predictive factor in early lung cancer. Also, in advanced lung cancer the DNA-based analysis of EGFR mutations has been proven to be feasible. However, only single studies use material obtained from brochoscopy to determine gene expression-based molecular markers.

The aim of the previous study was to determine the feasibility of gene expression analysis of multiple mRNA markers in bronchoscopy-obtained lung cancer specimens and to verify the parameters influencing the technical quality of the result.

We analyzed gene expression of 19 genes in 110 lung cancer specimens, from which both RNA and DNA were isolated. Quantitative real time PCR was carried out by ABI 7900 HT machine, with Universal Probe Library (Roche) fluorescent probes. 11 potential prognostic/predictive markers were analyzed (ERCC1, EGFR, BRCA1, CSF1, CA9, DUSP6, STAT1, ERBB3, MMD, FN1, CDKN1B), with 6 reference genes and two subtype-specific genes.

Results: More than 50 ng of RNA was obtained in 81.3% of samples, but larger amount (>1 ug) only in 44%, with median isolation efficiency 800 ng. Very good RNA integrity (RIN 8-10) was obtained only in 12.3% of samples, with RNA degradation partially related to the learning curve of the cooperating physicians (correlation coefficient R=0.61). Six potential reference genes were tested, at least 3-gene set was necessary to obtain sufficient stability of geNorm normalization index (HADHA, EIF3S10 and UBE2D2). Majority of analyzed markers showed moderate expression, except of CDKN1B, with much larger expression amplitude. We found out that the panel of analyzed mRNAs showed significant differences when related to the expression of TTF1 and TP63 (representing differences between SCC and AC), but these two genes were not enough to reliably discriminate between AC and SCC specimens. Two genes, DUSP6 and BRCA1 showed distictly discordant pattern when compared to other analyzed genes.

Conclusions: Analysis of bronchoscopy-obtained markers demands extensive optimization and probably does not allow to directly utlilize markers selected by the analysis of bulk tissue. Study supported by N N403 290636 grant.

Disclosure: All authors have declared no conflicts of interest.

IMAGING AND STAGING

152O

NEGATIVE PREDICTIVE VALUE OF REAL-TIME ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION IN STAGING NON-SMALL CELL LUNG CANCER

J. Sanz-Santos[1], E. Monso[1], F. Andreo[1], M. Llatjós[2] *[1]Pneumologia, Hospital Universitari Germans Trias i Pujol, Badalona/SPAIN, [2]Anatomia Patologica, Hospital Universitari Germans Trias i Pujol, Badalona/SPAIN*

Aim: To evaluate the negative predictive value (NPV) of real-time endonbronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) in stagin non-small cell lung cancer (NSCLC) .

Material and methods: We performed a prospective study including patients who were referred for NSCLC staging through rtEBUS-TBNA between Ap 2005 to Mar 2009. A thoracic CT scan was performed prior to staging, mediastinal nodes with a short-axis diameter >10 mm were considered enlarged. In patients who underwent surgery we compared the results of rtEBUS-TBNA with post-surgical staging.

Results: 296 patients where included (mean age 63yr (SD±10)). 82 (61.5%) patients had enlarged nodes on the CT scan. Final diagnoses were adenocarcinoma in 124 (41.9%) patients, SCC 82 (27.7%), large-cell carcinoma 11 (3.7%) and NSCLC 79 (26./%).

A total of 803 sampling procedures were performed, 675 (84.1%) on mediastinal nodes and 128 (15.9%) on lobar nodes. The median (IQR) small-axis diameter of the sampled mediastinal and lobar nodes was 10 (7-10) mm and 8 (6-11) mm, respectively. The most sampled stations were number 7 390 (48.6%), number 4R 177 (22%) and number 4L 91 (11.3%). The result of the samples where: normal nodes (lymph tissue) in 470 (58.5%) cases and malignancy in 243 (30.3%). In 90 cases (11.2%) samples were unsatisfactory (blood,bronchial cells).

In 182 (61.5%) patients rt-EBUS TBNA detected N2/N3 disease , for the other 134 (38.5%) rt-EBUS TBNA didn't showed nodal metastasis over N0/N1. Off these patients, 78 patients underwent surgery Comparing the findings of postsurgical staging with rtEBUS TBNA, the absence of N2/N3 disease was confirmed in 66 (84.6%) cases. In the other 12 cases (15.4%) 6 cases were nodes inaccesible for EBUS, 3 had unsatisfactory samples and 3 nodes were malignant being considered normal on rtEBUS TBNA. In 72 cases where all nodes from stations 4R, 4L and 7 where sampled and proper material obteined, post-surgical staging only found N2 disease in 6 cases (8.3%).

Conclusion: In our study rt-EBUS TBNA showed a NPV of 84.6% for staging NSCLC. Whenever satisfactory samples could be obteined and all nodes from stations 4R, 4L and 7 could be sampled NPV reached up to 91.7%.

Disclosure: All authors have declared no conflicts of interest.

153O

AN INVESTIGATION OF METABOLIC DIFFERENCES IN VARIOUS HISTOLOGICAL TYPES OF LUNG CANCER AND THE POTENTIAL IMPLICATIONS ON TREATMENT AND PROGNOSIS

J. Singh, J. Feeback, J. Peck, R. Shah *Division of Oncology, The Cancer Center at Research Medical Center, Kansas City/USA*

Background: Positron emission tomography (PET) scanning has become increasingly useful and important in the initial staging and diagnosis of solid tumors, and has been studied extensively in lung cancer. The purpose of this retrospective study was to determine whether tumors of varying histologies can be differentiated based on PET data.

Method: 140 patients with lung cancer were identified from the Research Medical Center tumor registry, and data elements on these patients were abstracted from the medical records. Demographic information, disease characteristics, and PET SUVMAX for the largest lesion were collected.
Results: Of the 140 patients, 79 were female, and 61 were male. PET SUVMAX was obtained for 122 of these patients. AJCC staging was available for 98 patients. The most commonly reported histological types were adenocarcinoma (34%) and squamous carcinoma (33%). The mean SUV for adenocarcinoma patients was significantly lower than that of squamous or NSCLC that was not otherwise specified.
Conclusions: 1)Our results suggest that tumors of squamous histology exhibit higher metabolic uptake than those of adenocarcinoma histology, which is consistent with traditional studies of tumor doubling time. 2)The ability for PET scans to predict histology may prove useful when sufficient tissue cannot be obtained for pathology or when a patient is unable to tolerate a surgical staging procedure. 3)There is evidence to support the idea that PET scanning can be used to differentiate between lung tumors of various histology. Further research is necessary to determine the extent to which this information would be useful in practice.
Disclosure: All authors have declared no conflicts of interest.

154O
BASELINE (BL) RADIOGRAPHIC CHARACTERISTICS AND SEVERE PULMONARY HEMORRHAGE (SPH) IN BEVACIZUMAB (BV)-TREATED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PT): RESULTS FROM ARIES, AN OBSERVATIONAL COHORT STUDY (OCS)

P. Kumar[1], N.A. Fischbach[2], J.R. Brahmer[3], D.R. Spigel[4], S. Beatty[5], S.L. Teng[5], E.D. Flick[6], A.P. Sing[7], T.J. Lynch[8] *[1]Hematology, Oncology, & Transplantation, University of Minnesota, Minneapolis/USA, [2]Oncology, Oncology Associates of Bridgeport PC, Fairfield/USA, [3]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore/USA, [4]Oncology, Sarah Cannon Research Institute, Nashville/USA, [5]Biostatistics, Genentech, Inc, South San Francisco/USA, [6]Epidemiology, Genentech, Inc, South San Francisco/USA, [7]Biooncology, Genentech, Inc, South San Francisco/USA, [8]Oncology, Yale Cancer Center, New Haven/USA*

Background: BV (Avastin®) prolongs progression free and overall survival in advanced NSCLC pts. ARIES, a prospective OCS, evaluates BV clinical outcomes in a real world setting. Post hoc analyses from randomized controlled trials suggest location and cavitation as potential risk factors for SPH, a serious and often fatal adverse event (AE). ARIES presents a unique opportunity to independently evaluate BL tumor characteristics and correlate with SPH.
Methods: Pts with advanced nonsquamous NSCLC on 1st line chemotherapy and BV enrolled. No doses, regimens or assessments were prespecified. Data were collected electronically at BL and quarterly. SPH were reported expeditiously. BL CT scans were requested for all pts and reviewed by an independent review facility (IRF).
Results: NSCLC enrollment completed 06/2009. As of 09/2009, 1970 pts had median follow-up of 9.6 mo. The IRF reviewed BL scans of 1881 pts; 1470 (78%) had ≥1 BL measurable (meas) tumor (≥0.5cm) and 49% (718) were central; 67% had largest tumor size ≥3cm; 14% had cavities and 10% had >1 cavity. BL tumor characteristics were generally similar across subpopulations (age ≥70, PS ≥2, pts with CNS mets). Pts with a history (Hx) of hemoptysis (n=105) had more centrally located tumors, fewer numbers of meas tumor, and larger cavity size. There are 15 (0.8%) reported SPH events to date; 2 pts had no BL CT scan submitted and 2 pts with BL scans had no meas tumor (1 had Hx of hemoptysis). Of the remaining 11 pts with SPH: 8 had central tumors; 1 had cavitation (1.2cm); 0 were on anticoagulants at BL; largest tumor size ranged from 1.8-11.6cm. There was 1 SPH in pts with ≥1 cavity (0.5%) and 8 in pts with central tumors (1.1%).
Conclusions: ARIES has the largest series of independently reviewed BL scans from advanced NSCLC pts, providing an opportunity to correlate radiographic factors with outcomes in BV treated pts. Although limited by small numbers, the data suggest that cavitation is not predictive of SPH. Correlation of BL radiographic characteristics with outcomes and risk factor analysis will be presented.
Disclosure: P. Kumar: Advisory role with Genentech (compensated) and have received honoraria from Genentech; J.R. Brahmer: Advisory role for Genentech (compensated); D.R. Spigel: Advisory role (Genentech; uncompensated); S.L. Teng: Employee of Genentech, with stock ownership in Roche; E.D. Flick: Employee of Genentech, with stock ownership in Roche; A.P. Sing: Employee of Genentech, with stock ownership in Roche; T.J. Lynch: Member of Board of Directors and stockholder: Infinity Pharma Advisory role (compensated): Genentech, Merck, Astra Zeneca, Boehringer Ingelheim Pharmaceuticals (BIPI).
All other authors have declared no conflicts of interest.

155O
EARLY RESPONSE MONITORING OF ERLOTINIB AND SORAFENIB BY 18F-FLUORODEOXYGLUOSE AND 15O-WATER POSITRON EMISSION TOMOGRAPHY IN NON-SMALL CELL LUNG CANCER

J.S.W. Lind[1], V. Frings[1], O.S. Hoekstra[2], R. Boellaard[1], A.C. Dingemans[3], H. Groen[4], E.F. Smit[5] *[1]Pulmonary Diseases, VUMC, Amsterdam/NETHERLANDS, [2]PET Centre, VU University Medical Centre, Amsterdam/NETHERLANDS, [3]Respiratory Medicine, Maastricht University Medical Center, Maastricht/NETHERLANDS, [4]Pulmonary Diseases, University Medical Center Groningen, Groningen/NETHERLANDS, [5]Pulmonary Diseases, VU University Medical Center, Amsterdam/NETHERLANDS*

Purpose: Response monitoring of molecularly targeted agents remains a challenge. This study prospectively evaluates the change in tumour metabolic activity and tumour perfusion, measured by ^{18}F-FDG- and $H_2{}^{15}$O-PET, in patients with advanced/metastatic non-small cell lung cancer (NSCLC) receiving combined anti-angiogenic (sorafenib) and anti-epidermal growth factor receptor (erlotinib) treatment, as possible early predictors of response and outcome with targeted therapy.
Patients and methods: ^{18}F-FDG- and $H_2{}^{15}$O-PET were performed at baseline and 3 weeks after starting treatment. The percentage change in tumour metabolic activity (SUV) and blood flow (BF) were calculated. Metabolic response (>25% decrease in SUV) and perfusion response (>20% decreased in BF) after 3 weeks and RECIST after 6 weeks of treatment were correlated with progression-free survival (PFS) and overall survival (OS) using log-rank statistics.
Results: Complete ^{18}F-FDG- and $H_2{}^{15}$O-PET sets were available for 35 and 12 patients respectively. At week 3 the mean decrease in SUV was 26% (±31.4%), p<0.0001. Median PFS was longer in metabolic responders (5.5 months) compared to metabolic non-responders (3.0 months), p=0.037. There was no difference in median OS. The mean percentage change in BF was +38% (±60), p=0.17. BF response was not associated with PFS or OS. RECIST responders at week 6 tended towards a longer median PFS compared to non-responders (14.2 versus 4.3 months, p=0.052). There was no difference in OS.
Conclusion: After only 3 weeks of treatment tumour metabolic response was predictive for PFS in patients with NSCLC receiving sorafenib and erlotinib. RECIST at week 6 showed only a trend. ^{18}F-FDG-PET may, thus, allow earlier response evaluation than RECIST. Blood flow, measured by $H_2{}^{15}$O-PET, was not predictive for outcome.
Disclosure: All authors have declared no conflicts of interest.

156O

DYNAMIC CONTRAST-ENHANCED CT IN PATIENTS TREATED WITH SORAFENIB AND ERLOTINIB FOR NON-SMALL CELL LUNG CANCER: A NEW METHOD TO MONITOR TREATMENT?

J.S.W. Lind[1], M.R. Meijerink[2], A.C. Dingemans[3], C. van Kuijk[2], M. Ollers[4], D. De Ruysscher[5], P.E. Postmus[6], E.F. Smit[7] *[1]Pulmonary Diseases, VUMC, Amsterdam/NETHERLANDS, [2]Radiology, VUMC, Amsterdam/NETHERLANDS, [3]Respiratory Medicine, Maastricht University Medical Center, Maastricht/NETHERLANDS, [4]Radiotherapy, Maastro Clinic, Maastricht/NETHERLANDS, [5]Department of Radiation Oncology (Maastro Clinic), Maastricht University Medical Center + GROW Research Institute, Maastricht/NETHERLANDS, [6]Pulmonary Diseases 4a50, VU University Medical Center, Amsterdam/NETHERLANDS, [7]Pulmonary Diseases, VU University Medical Center, Amsterdam/NETHERLANDS*

Purpose: We investigated the feasibility of serial dynamic contrast-enhanced computed tomography (DCE-CT) in patients with advanced/metastatic non-small cell lung cancer (NSCLC) receiving anti-angiogenic (sorafenib) and anti-epidermal growth factor receptor (erlotinib) treatment, and correlated tumour blood flow (BF) with treatment outcome.

Methods: DCE-CTs were performed at baseline and 3 and 6 weeks after starting treatment. Tumour BF, calculated with the maximum-slope method, and percentage change were measured in 23 patients (14 males; median age 59 years). Tumour BF at baseline and weeks 3 and 6 were compared using the Wilcoxon signed-rank test; relation with RECIST and Crabb responses was assessed using the Mann-Whitney test and associations with progression-free survival (PFS) using log-rank statistics.

Results: Mean tumour perfusion decreased from 39.2 ± 29.9 ml/100g/min at baseline to 15.1 ± 16.5 ml/100g/min at week 3 ($p<0.001$) and 9.4 ± 15.4 ml/100g/min at week 6 ($p<0.001$). Tumour perfusion was lower in responders versus non-responders at week 3 (4.2 ± 7.8 versus 17.7 ± 13.4 ml/100g/min, $p=0.03$) and week 6 (0 ± 0 versus 13.4 ± 16.9 ml/100g/min, $p=0.04$). This was also found when incorporating tumour cavitation into response assessment. Patients with a decrease larger than the median of 91% at week 6 tended towards a longer PFS than those with a smaller decrease (7.1 versus 5.7 months, $p=0.06$).

Conclusion: Serial DCE-CTs are feasible in patients with NSCLC and demonstrated a significant decrease in tumour BF following sorafenib and erlotinib therapy. Moreover, early changes in tumour BF correlated with objective response and showed a trend with PFS.

Disclosure: All authors have declared no conflicts of interest.

157O

EARLY PREDICTIVE VALUE POST CHEMOTHERAPY OF METABOLIC RESPONSE ASSESSMENT USING FLUORDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY (FDG-PET) IN NON SMALL CELL LUNG CANCER

T. Meniawy, A. Davidson *Medical Oncology, Royal Perth Hospital, Perth/AUSTRALIA*

Background: Recently there has been interest in the prognostic value of baseline FDG PET SUV measured in primary tumours as well as the predictive value of response assessment using PET metabolic response criteria (PRESIST criteria). The last published review was in 2006.

Objectives: To assess the predictive value on survival of changes in standardised uptake value (SUV) measured on fluordeoxyglucose positron emission tomography (FDG-PET) before and after treatment of non-small cell lung cancer, at either cycle 1 or 2 SEARCH.

Methods: We searched MEDLINE (January 1966 to September 2009) and EMBASE (January 1985 to September 2009). In addition, reference lists were hand searched for any other relevant trials.

Selection criteria: Randomised and non-randomised studies evaluating metabolic response using at least two FDG-PET studies performed at baseline and after one or two cycles of chemotherapy for non small cell lung cancer, and reporting survival data for metabolic responders compared to non-responders. Trials published after 2000 only were chosen to reduce the effect of technological changes over time on the results.

Data collection and analysis: Two authors independently assessed trial quality and extracted data. We performed a meta-analysis of the difference in median overall survival between metabolic responders and non-responders as defined by the cut-offs for metabolic response in individual studies. A subgroup analysis of patients treated with radical or palliative interventions was also performed

Results: Nine studies involving 426 patients were included. Six studies involved 305 patients treated with radical radiotherapy or surgical resection, whereas three studies involved 121 patients predominantly treated with palliative chemotherapy. There was some heterogeneity between studies with regards to patient characteristics, treatments received and criteria for PET metabolic response assessments. Meta-analysis of included studies demonstrated that metabolic responders had a median overall survival that was significantly longer than non-responders by 13.34 months (95% CI 6.12, 20.56). Subgroup analysis also demonstrated a median overall survival that was 19.05 months longer in metabolic responders than in non-responders (95% CI 6.81, 31.38) in patients treated radically, and 5 months longer (95% CI 1.82, 8.17) in metabolic responders treated with palliative intent.

Authors' conclusions: Metabolic response assessment using changes in standardised uptake value measured on FDG-PET are predictive of treatment response and long-term survival in non-small lung cancer. The shown differences in survival would suggest that early identification of response to treatment would have clinical implications for early trial design and personalised patient treatment management . Limitations of data and analyses include small patient numbers, heterogeneity in PET raw data analyses, metabolic response criteria and therapeutic interventions leading to many caveats on the validity of the results. There is individual trial specific limitations on statistical power to establish the predictive value of PET response as an independent marker when other variables such as age, stage, performance status and histology are considered. We aim to conduct a systematic review and meta-analysis of individual patient data to allow multivariate analyses and subgroup analyses across studies. (note there is also the forrest plot of the meta-analysis).

Disclosure: All authors have declared no conflicts of interest.

158O

THE IMPACT OF STAGE MIGRATION ON SURVIVAL IN THE UICC 7 TNM-CLASSIFICATION OF LUNG CANCER

J.P. van Meerbeeck[1], K. Chansky[2], P. Goldstraw[3] *[1]Department of Respiratory Medicine, University Hospital, Ghent/BELGIUM, [2]Cancer Research and Biostatistics, Cancer Research and Biostatistics, Seattle/USA, [3]Department of Thoracic Surgery, Royal Brompton Hospital, London/UNITED KINGDOM*

Background: Change of staging classification has been associated with improvements in stage specific survival without improvement of overall survival (Feinstein, 1985). Aim: to estimate in patients with non-small cell lung cancer (NSCLC), included in the IASLC staging database (Goldstraw, 2006) 1. the magnitude and direction of stage migration between the 6th and

7th edition of the UICC-TNM classification, and 2. its impact on stage specific outcome.

Methods: Untreated NSCLC cases were extracted from the IASLC database and classified according to the 6th and 7th edition of UICC-cTNM. Cases with prior lung cancer were excluded from the set; only substages A and B for stage III were detailed. Migration was estimated by calculating the rate of patients classified in any higher or lower UICC-7 c-stage over the corresponding UICC 6 c-stage. Outcome was estimated by the Kaplan-Meier method and expressed as median survival rate (mSR) with lower and upper 95% confidence intervals (95% CI).

Results: stage distribution of 11,536 cases, classified according to UICC 6 and 7, with corresponding overall and stage specific mSR are in the table. 5 year survival rate is 21% (20-22). Overall, 1068 cases (9%) migrate, of whom 899 (8%) to a higher and 177 (%) to a lower stage. There are no substantial changes in mSR.

Conclusion: in this data set of untreated NSCLC cases, the change of TNM staging classification from UICC6 to 7 results in a net migration of out of cases, to a higher stage in most of them. The impact on outcome is however not substantial, making a Will Rogers phenomenon unlikely.

	UICC 6	UICC 7	Net Migration
Total	11,536 (100%)		1068 (9%)
m SR	13.9 (13.5–14.3) m		0 m
c I	2673 (23%)	2115 (18%)	—
m SR	43.5 (40.9–47.9) m	49.9 (45.2–55.2) m	+6.4 m
c II	2176 (19%)	2731 (24%)	57 (5%)
m SR	18.3 (17.4–19.8) m	19.6 (18.2–21.0) m	+1.3 m
c IIIA	3005 (26%)	3175 (28%)	170 (1%)
m SR	14.1 (13.3–15.0) m	14.3 (13.5–15.2.) m	0.2 m
c IIIB	1224 (11%)	758 (7%)	10 (<1%)
m SR	9.8 (9.1–10.6) m	9.7 (8.6–10.4) m	−0.1 m
c IV	2458 (21%)	2757 (24%)	318 (3%)
m SR	5.8 (5.6–6.0) m	6. (5.7–6.2) m	+0.2 m

Disclosure: All authors have declared no conflicts of interest.

159P

THE PROGNOSTIC SIGNIFICANCE OF FDG-PET IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

S.H. Bae[1], H.M. Ryoo[2] *[1]Oncology/Hematology, Daegu Catholic University Hospital, Daegu/KOREA, [2]Internal Medicine, Daegu Catholic University Medical Center, Daegu/KOREA*

Background/Aims: Positron emission tomography with [18F] fluorodeoxyglucose (FDG-PET) shows various levels of FDG uptake in patients with non-small cell lung cancer (NSCLC). This study was conducted whether the maximal standardized uptake value (SUVmax) of the primary tumor by PET at the time of diagnosis has prognostic significance in patients with advanced NSCLC.

Methods: A retrospective review identified 59 patients with pathologically proven stage IIIB and IV NSCLC who underwent FDG-PET at the time of diagnosis. All patients received systemic chemotherapy. The Cox proportional hazards model was used with SUVmax and clinical data including age, performance status, histologic cell type, hemoglobin, and number of metastatic sites.

Results: The median overall survival of all patients was 18.3 months (95% CI 16.0-20.6). The median survival of the 16 patients with the primary tumor having an SUVmax $\leq$ 7 was not reached, whereas the median survival of the 43 patients with the primary tumor having an SUVmax $>$ 7 was 16.6 months (95% CI 8.7-23.6). In the univariate and multivariated analysis, performance status and SUVmax were significant predictors of overall survival. These finding were replicated in progression free survival.

Conclusions: The amount of FDG uptake of the primary lesions in patients with advanced non-small cell lung cancer have a significant relation with survival.

Disclosure: All authors have declared no conflicts of interest.

160P

PROGNOSTIC POTENTIAL OF F-FLURODEOXYGLUCOSE UPTAKE IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH RADICAL RADIOTHERAPY OR CONCOMITANT CHEMO-RADIOTHERAPY

M.Y. Lin[1], M. Wu[1], S. Brennan[1], M.P. Campeau[1], D. Binns[2], M. Mac Manus[1], B. Solomon[3], R. Hicks[2], D. Ball[1] *[1]Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne/AUSTRALIA, [2]PET Centre, Peter MacCallum Cancer Centre, East Melbourne/AUSTRALIA, [3]Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne/AUSTRALIA*

Purpose: The aim of this retrospective study is to investigate the potential of Standarized Uptake Values (SUVs) derived from F-2-deoxy-D glucose (FDG) Positron Emission Tomography (PET) or PET/CT (computed tomography) scans, to predict outcome in patients with non-small cell lung cancer (NSCLC) treated with radical radiotherapy (RT) alone or concurrent chemo-radiotherapy (CCRT).

Methods: Patients were eligible if they: had histological or cytological evidence of NSCLC; were treated with radical RT or CCRT as their primary treatment between January 2000 and December 2006; had pre-treatment staging PET/ PET-CT scans; had no recent history of other malignancies; had no prior treatment for NCSLC. Other known or potential prognostic factors including UICC stage group, tumor histology and differentiation, smoking status, performance status, recent weight loss and simplified co morbidity score (SCS) were recorded. The maximum SUV (SUVmax) was defined as the maximum pixel SUV value retrieved from the primary tumor. SUV max was analyzed as a dichotomous variable for survival using a selected cut point of 9.

Results: 121 NSCLC patients met the eligibility criteria for the study, including 39 stage I patients, 13 stage II, 65 stage III, and 4 stage IV. The mean SUVmax in stage I patients was significantly lower than that in stage II to IV patients (11.8 versus 17.2, $p=0.002$). In univariate analysis, with a median follow-up of 48.7 months (range 21.8 to 79.1 months), progression-free survival (PFS) was 32.5 months for patients with SUVmax less or equal to 9 and 11.3 months for patients with SUVmax more than 9 ($p=0.023$). Disease-specific survival (DSS) was 50.2 months if SUVmax was less or equal to 9 and 24.3 months if SUVmax was more than 9 ($p=0.028$).

Conclusion: In this cohort of patients, higher levels of FDG uptake were associated with worse outcomes, but also with more advanced stage. Further studies are required to determine if SUV is an independent prognostic factor for survival in patients treated by non-surgical means.

Disclosure: All authors have declared no conflicts of interest.

161P

USE OF PET/CT FOR RADIATION THERAPY PLANNING IN LOCALLY ADVANCED LUNG CANCER: DEFINITION OF GTV AND DOSIMETRIC ANALYSIS

B. Meduri[1], G.N. Mantini[2], F. De Rose[1], M.N. Balducci[2], V.N. Frascino[2], N.N. Dinapoli[3], M.L. Calcagni[4], G.N. Corbo[5], T.N. Pirronti[6], V.N. Valentini[4] *[1]Radiotherapy, Polyclinic, Rome/ITALY, [2]Radiotherapy, Polyclinic A Gemelli, Rome/ITALY, [3]Radiotherapy, Polyclinic Gemelli, Rome/ITALY, [4]Radiology, Polyclinic, Rome/ITALY, [5]Pneumology, Polyclinic Gemelli, Rome/ITALY, [6]Radiology, Polyclinic Gemelli, Rome/ITALY*

Purpose: FDG-PET/CT is more accurate than CT alone in determining the extent of non-small-cell lung cancer (NSCLC); this study was performed to evaluate the impact of functional imaging on radiation therapy (RT) Gross Tumor Volume (GTV) definition in patients with Stage III NSCLC.

Methods: Each patient underwent sequential CT and PET/CT simulation using the same immobilization devices. Both the CT and PET/CT image data sets were transferred to the RT treatment planning workstation for contouring. For each patient, two conformal treatment plans were made: one with a CT-based GTV (GTV-CT) and one with a PET/CT based GTV (GTV-PET). A qualitative visual method for contouring GTV-PET was used. Dosimetric factors and volumes of each plan were analyzed and compared. For each patient, both GTV-CT and GTV-PET were contoured independently by a second observer.

Results: Fifteen patients with Stage III NSCLC were studied. A clinically significant (>20%) treatment volume modification was observed between GTV-CT and GTV-PET in 7/15 (46%) cases. Four cases resulted in a reduction in GTV-PET volume vs GTV-CT because PET/CT was more accurate in distinguishing tumor from atelectasis. MLD (mean lung dose), lung V20 (the percentage of lung volume receiving 20 Gy) and lung V30 decreased in favour of PET-CT ($p=0.5$). Three cases showed an increase in GTV-PET volume vs GTV-CT because of an unsuspected nodal disease detected by PET. The increase in target volumes led to a respective increase in MLD, lung V20, lung V30. The interobserver GTV variability decreased from a mean volume difference of 18 ± 10 cc when evaluating CT-based treatment plans to 4 ± 2 cc when the evaluation was made on PET/CT-based treatment plans ($p<0.001$).

Conclusion: In this group of clinical stage III NSCLC patients, fused PET/CT and CT images in RT planning reduced the radiation exposure of lung because it resulted in a more accurate distinction of tumor from atelectasis or reduced risk of geographic misses detecting unsuspected nodal disease; moreover, the use of PET/CT, reducing interobserver variability, improved homogeneity in GTV delineation. The results of this study confirmed that PET/CT planning increased therapeutic ratio in RT.

Disclosure: All authors have declared no conflicts of interest.

162P

COMPARISON OF INSPIRATION AND EXPIRATION BREATH-HOLD FOR NSCLC IMRT

M.Q. Hatton, B. Tahir, C. Bragg, S. Lawless, R. Ireland *Department of Clinical Oncology, Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield/UNITED KINGDOM*

Background: To compare target coverage and lung tissue sparing between inspiration and expiration breath-hold intensity modulated radiotherapy (IMRT) plans for patients with non-small cell lung cancer (NSCLC).

Methods and materials: In a prospective study, seven NSCLC patients gave written consent to undergo both a controlled 1L inspiration and an end expiration breath-hold computed tomography (CT), which were used to generate 5-field IMRT plans. Dose was calculated with a scatter and inhomogeneity correction algorithm. The percentage of planning target volume (PTV) receiving 90% of the prescription dose (PTV90), the volume of total lung receiving ≥ 10 Gy (V10) and ≥ 20 Gy (V20) and the mean lung dose (MLD) were compared by the Student's paired t test.

Results: Compared with the expiration plans, the mean±SD reductions for V10, V20 and MLD on the inspiration plans were $4.0\pm3.7\%$ ($p=0.031$), $2.5\pm2.3\%$ ($p=0.028$) and 1.1 ± 0.7 Gy ($p=0.007$), respectively. Conversely, a mean difference of $1.1\pm1.1\%$ ($p=0.044$) in PTV90 was demonstrated in favour of expiration.

Conclusions: When using IMRT, inspiration breath-hold can reduce the dose to normal lung tissue while expiration breath-hold can improve the target coverage. The improved lung sparing at inspiration may outweigh the modest improvements in target coverage at expiration. Acknowledgments Supported by a Postdoctoral Award from the UK National Institute of Health Research, Weston Park Cancer Charity and Sheffield Hospitals Charitable Trust.

Disclosure: All authors have declared no conflicts of interest.

163P

EXPERIENCE IMPROVES TRAINEE YIELD IN THE FIBREOPTIC BRONCHOSCOPIC (FB) DIAGNOSIS OF PRIMARY LUNG CANCER

M.M. Wilczynska, J. Bennett, B. Sutton *Respiratory Medicine, Glenfield Hospital, Leicester/UNITED KINGDOM*

Introduction: FB remains a significant tool in the diagnosis of primary lung cancer. Our audit from 2006 demonstrated a significant difference in bronchoscopic yield between consultants and trainees. This study aimed to reassess the same group of operators' yield two years later.

Methods: All FBs requested via the lung cancer MDT in 2008 were investigated. Collected data included: operator grade, macroscopic appearance and diagnostic yield. The CHI-SQUARE distribution was used for data analysis.

Results: 149 FBs were requested via the lung cancer MDT. 130 patients were diagnosed with primary lung cancer of whom 97 had a cancer diagnosis confirmed pathologically from FB biopsies whilst the remaining 33 required further investigations for pathological verification. All FBs were preceded by staging Computed Tomography (CT) scan. There were 26 different FB operators (most of whom were the same operators as in 2006) with consultants performing 57% of FB (n=75). Over all hit rate for consultants and trainees was 71%. There was no significant variation in positive diagnostic yield between consultants and trainees ($p=0.694$) (table 1). Macroscopically abnormal mucosa was reported in 85 FB with 80% positive yield (n=68) compared to a 77% yield in 2006. Hit rate for macroscopically visible tumour was not significantly different ($p=0.44$) between consultants and trainees.

Fibreoptic Bronchoscopy	Consultants	Trainees	Total	P value
2006				
Positive	59	48	146	0.009
Negative	12	27		
2008				
Positive	55	42	130	0.694
Negative	20	13		

Conclusions: Closer consultants' supervision during bronchoscopy sessions as well as experience gained during further 24 months in specialty training improved trainees' skills in obtaining positive samples via FB for primary lung cancer. Given the changes in specialist training and the European Working Time Directive, rigorous training in procedures is required and we

believe that it would be advisable to develop new guidelines for respiratory medicine trainees in the form of mandatory logbooks to demonstrate an appropriate level of ability.
Disclosure: All authors have declared no conflicts of interest.

164P
THE IMPORTANCE OF TRANSBRONCHIAL BIOPSY CONTROLLED BY ROENTGEN-SCOPE IN THE DIAGNOSIS OF LUNG CANCER

V. Radosavljevic, M. Obradovic, V. Milovanovic *Pulmology, KBC "Bezanijska Kosa", Belgrade/SERBIA AND MONTENEGRO*

The aim of the study was to examine importance of transbronchial biopsy controlled by roentgen (RO) scope in the diagnosis of lung cancer. About 30% of lung cancer presents with central localisation, and the rest (about 70%) with peripheral. A lot of skill is needed to take a good quality biopsy tissue for pathological exam from periphery of the lung.
Material and method: Patients with suspected radiological finding of peripheral lesions were divided in two groups. In both groups CT scan was also performed. The first group included 30 patients in whom blind transbronchial biopsy was performed, based on experience and CT localisation. The second group also included 30 patients but in whom transbronchial biopsy was performed and controlled by roentgen-scope.
Result: In the 1st group there were 5 (16.6%) patients with positive pathohistological findings (3 patients with adenocarcinoma and 2 with planocellularl carcinoma). In the 2nd group there were 12 (40%) patients with positive pathohistological findings (7 patients with adenocarcinoma and 5 with planocellular carcinoma).
Conclusion: Our result suggests that transbronchial biopsy leaded by RO scope has an important advantage compared to the blind method. However higher percentage of positive pathohistological findings is needed. Our study showed that transbronchial biopsy leaded by RO scope is a good diagnostic method of peripheral lung lesions.
Disclosure: All authors have declared no conflicts of interest.

165P
THE CLINICAL VALUE OF MEDIASTINOSCOPY IN PREOPERATIVE STAGING OF NON-SMALL CELL LUNG CANCER

D. Kim[1], H. Seok Jin[2], P. Hyochae[2] *[1]Thoracic and Cardiovascular Surgery, Eulji University Hospital, Daejeon/KOREA, [2]Thoracic and Cardiovascular Surgery, Kangnam Severance Hospital, Seoul/KOREA*

Objective: Mediastinoscopy is generally performed to confirm mediastinal lymph node metastasis and to find optimal neoadjuvant therapy candidate in lung cancer patients. It still remains controversial whether mediastinoscopy should be performed in all patients with resectable non-small cell lung cancer (NSCLC). We studied the clinical value of mediastinoscopy in preoperative staging in NSCLC.
Methods: We retrospectively studied 111 NSCLC patients who underwent radiological evaluation and mediastinoscopy followed by surgical resection from March 2002 to December 2004. Sensitivity, specificity, and accuracy of each evaluation method were assessed and compared.
Results: Sensitivity, specificity, and accuracy of radiologic evaluation and mediastinoscopy and were 62.9%, 75.8%, 64.9% and 54.3%,100%, 76.6% respectivley. Specificity and accuracy was superior to those of radiological evaluation ($p<0.01$, $p=0.015$), but absolute sensitivity of radiological evaluation is higher rather than mediastinoscopy although there was no significant difference in sensitivity ($p=0.58$). Especially, the sensitivity of mediastinoscopy was 23.1% in 38 patients with radiological N0/1 disease and 72.7% in 73 patients with radiological N2/3 disease.
Conclusion: Considering its invasiveness, the difficulty to reach certain node stations, and its low sensitivity in radiological N0/1 disease, mediastinoscopy should be selectively performed in radiological N2/3 disease rather than in all radiological cancer stages.
Disclosure: All authors have declared no conflicts of interest.

166P
THE FEASIBILITY OF MEDICAL THORACOSCOPY FOR THE DIFFERENTIAL DIAGNOSIS OF MALIGNANT EFFUSION IN THE TUBERCULOSIS ENDEMIC COUNTRY

D. Kim, J.J. Hwang, K. Kim *[1]Thoracic and Cardiovascular Surgery, Eulji University Hospital, Daejeon/KOREA*

Objective: The high sensitive and accurate diagnosis is necessary to prevent misconceiving malignant effusion as tuberculosis pleurisy in the tuberculosis endemic country. The thoracoscopic pleural biopsy is thought ideal diagnostic tool, but it did not gain general concept because the procedure is necessary general anesthesia. Medical thoracoscopy has as high sensitivity as conventional throacoscopy, and performed under local anesthesia. We thought medical thoracoscopy was ideal diagnostic tool for differential diagnosis of malignant effusion in the tuberculosis endemic country.
Methods: 248 patients transferred to evaluate undetermined pleural effusion. 216 patients underwent medical thoracoscopy, cytology, and chest CT except 32 patients refused medical thoracoscopy. We analyzed safety of medical thoracoscopy and compared sensitivity, specificity, and accuracy among three diagnostic tools.
Results: There was no mortality, and nor morbidity. Only two cases were impossible to perform medical thoracoscopy due to severe dyspena. The final diagnosis is malignant effusion 30.1% (n=65), tuberculosis pleurisy 28.3% (n=61), parapneumonic effusion 40.7% (n=88), and others 0.9% (n=2). The sensitivity of cytology, radiologic evaluation, and medical thoracoscopy were 22.6%, 78.5%, 93.8% respectively, and the specificity were 99.3%, 91.4%, 100% respectively, and the accuracy were 75.9%, 87.5 %, 98.4% respectively. Especially, Sensitivity and accuracy of medical thoracoscopy are significantly higher than cytology and radiologic evaluation ($p<0.05$).
Conclusion: The medical thoracoscopy is safe and feasible as a routine diagnostic tool of undetermined pleural effusion. And the sensitivity and specificity is superior to other diagnostic tools, especially it is useful to differential diagnosis between malignant effusion and tuberculosis pleurisy.
Disclosure: All authors have declared no conflicts of interest.

EARLY NSCLC

167O
PREVALENCE, CORRELATIONS, AND PROGNOSTIC SIGNIFICANCE OF THE PRESENCE OF MICROSCOPIC VASCULAR INVASION FOLLOWING COMPLETE RESECTION OF STAGE I NON-SMALL CELL LUNG CARCINOMA. AN UNDERESTIMATED FACTOR?

E. Ruffini[1], P.L. Filosso[1], S. Asioli[2], L. Buffoni[3], A. Oliaro[1] *[1]Thoracic Surgery, University of Torino, Torino/ITALY, [2]Pathology, University of Torino, Torino/ITALY, [3]Clinical Oncology, S. Giovanni Battista Hospital, Torino/ITALY*

Objective: The significance of microscopic invasion of blood vessels (Microscopic Vascular Invasion, MVI) in patients with non-small cell lung carcinoma (NSCLC) remains controversial. The aim of this study was to

evaluate prevalence, correlations and the prognostic significance of MVI in patients following complete resection of Stage I NSCLC.

Methods: From 1/1998 to 10/2008 1521 patients received resection for NSCLC at our Institution, of whom 737 were at pathological Stage I after surgery. There were 323 adenocarcinomas (ADK) (44%), 322 squamous cell carcinomas (SCC) (44%), 53 bronchioloalveolar carcinomas (BAC) (7%), 29 large cell anaplastic carcinomas (LCC) (4%). Histologic grading was: 114 G1 (15%), 279 G2 (38%) and 344 G3 (47%). Mean tumour dimension was 36 mm. MVI was ascertained using routine histopathological workup. Immunohistochemical staining with antibody anti-CD34 was done to evaluate blood vessels on a selective basis. Prevalence differences, logistic regression and survival analysis were used for analysis.

Results: MVI was observed in 228 patients (31%). Prevalence was significantly higher in ADK (131/323, 41%) than in SCC (80/322, 25%, p=0.002). A significant correlation was found between the presence of MVI and ADK (OR 0.8, 95% CI 0.7-0.9) and increased tumour dimension (OR 1.1, 95% CI 1.01-1.24). Univariate survival analysis indicates that the presence of MVI was associated with a significantly reduced 5-year survival overall (65% vs. 52%, p=0.0003) and in ADK (68% vs. 54%, p=0.0002) but not in SCC (58% vs. 49%, p=0.25). In a multivariate survival analysis, the presence of MVI was a significant indicator of poor survival overall (HR 1.61, 95% CI 1.30–2.15) and in ADK (HR 2.02, 95% CI 1.36–3-02).

Conclusions: The finding of MVI in completely resected Stage I NSCLC is not infrequent. MVI is strongly correlated with adenocarcinoma histotype and increased tumour dimensions. The presence of MVI is an independent negative prognostic factor, which is particularly significant in adenocarcinomas. The use of adjuvant chemotherapy might be taken into consideration in these patients.

Disclosure: All authors have declared no conflicts of interest.

168O

MOLECULAR EXPRESSION OF ANGIOGENIC MARKERS IN EARLY-STAGE NSCLC: EVALUATION OF THE PROGNOSTIC ROLE

E. Jantus[1], A. Cabrera[2], R. Sirera[3], M. Usó[4], S. Gallach[5], A. Blasco[6], A. Berrocal[7], M. Taron[8], R. Rosell[9], C. Camps[10] *[1]Molecular Oncology Laboratory, Fundacion para la Investigacion del Hospital General Universitario de Valencia, Valencia/SPAIN, [2]Molecular Oncology Laboratory, Fundacion para la Investigación del Hospital General Universitario de Valencia, Valencia/SPAIN, [3]Molecular Oncology Laboratory, University General Hospital, Valencia/SPAIN, [4]Molecular Oncology Laboratory, Fundación para la investigación del Hospital General de Valencia, Valencia/SPAIN, [5]Molecular Oncology Laboratory, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia/SPAIN, [6]Medical Oncology, Cosorcio Hospital General Universitario de Valencia, Valencia/SPAIN, [7]Oncology Service, University General Hospital, Valencia/SPAIN, [8]Medical Oncology Service, Institut Catala d'Oncologia, Badalona, Barcelona/SPAIN, [9]Medical Oncology Service, Catalan Institute of Oncology, Badalona/SPAIN, [10]Oncology Service, Hospital General Universitario de Valencia, Valencia/SPAIN*

Background: NSCLC is a major cause of cancer related death worldwide. While treatment with conventional chemotherapy has improved during the last decade, 5 year survival is still modest. It is known that angiogenesis is an essential event for solid tumour growth and angiogenic factors, such as different ligands and receptors of vascular endothelial growth factor (VEGF), seem to play a key role. Our objective was to evaluate the mRNA expression of the family of VEGFs and VEGFRs and correlate them with disease outcome in resectable NSCLC patients.

Methods: We performed quantitative analysis (RTqPCR) to assess the expression of VEGF-A, -B, -C, -D, PlGF, VEGFR-1, −2 and −3 in 135 frozen lung cancer specimens from untreated NSCLC patients who had undergone surgical resection. RNA was extracted using Trizol® and RTqPCR was performed using TaqMan® probes. Relative quantification was evaluated using GUS-B (endogenous control gene) for normalization. We correlate the expression of the angiogenic genes with clinico-pathological and survival variables. All statistical analysis were considered significant at $p<0.05$.

Results: We found an overexpression of PlGF in tumor vs normal tissues, being higher in squamous cell carcinomas (SCC). There was no correlation between VEGF-A, VEGFR-1 and VEGFR-2 with the histology or tumor stage in our cohort. A strong positive correlation between the expression of VEGF-A and VEGFR-1 in tumour samples ($p<0.000$, Spearman's test) was found. Using the median as a cut-off value for VEGF-A and VEGFR-1, cases were splited as high (H) or low (L) accordingly. 71.5% of patients (108/151) have concordant results in both variables. Kaplan Meier plots show that the group of patients expressing higher levels of VEGF-A and VEGFR-1 (HH) had a worse prognosis (OS: p=0.066, PFS: p=0.098, log-rank test) than the other groups (HL or LL).

Conclusion: In NSCLC tumour samples, PlGF is overexpressed, specially is SCC. In addition, determination of VEGF-A and VEGFR-1 genes by RTqPCR would be a useful clinical test to assess prognosis in NSCLC, due to the fact that higher levels of expression of both genes correlates with shorter OS. Supported by ISCIII grant.

Disclosure: All authors have declared no conflicts of interest.

169O

LUNG VOLUME REDUCTION SURGERY IN PATIENTS WITH LUNG CARCINOMA

M. Tutic[1], D. Lardinois[2], P. Kestenholz[1], D. Schneiter[1], I. Opitz[1], K. Bloch[3], E.W. Russi[3], W. Weder[1] *[1]Thoracic Surgery, University Hospital Zurich, Zurich/SWITZERLAND, [2]Thoracic Surgery, University Hospital Basel, Basel/SWITZERLAND, [3]Pulmonology, University Hospital Zurich, Zurich/SWITZERLAND*

Introduction: The majority of patients with non-small cell lung cancer (NSCLC) are lifelong heavy smokers, a considerable part of them are functionally impaired by COPD. Complete surgical resection offers the best chances to cure patients with early-stage NSCLC and anatomic lobectomy with mediastinal lymph-node dissection is still considered the operation of choice. The aim of this study is to report the experience of a single center in patients with heavily impaired lung function due to COPD undergoing simultaneously lung cancer surgery and LVRS and to assess postoperative course, lung function and survival.

Methods: 33 patients (12 females), mean age (±SE): 68 ± 1,8, with marginal lung function due to advanced emphysema (mean FEV1: 34% ± 2,1) underwent resection of preoperatively detected lesions, which were suspicious and later proven for malignancy.

Results: Tumorresection and including Lung Volume Reduction Surgery (LVRS) was performed in 8, unilateral LVRS in 13, anatomical segmentectomy in 5, lobectomy in 5 and bilobectomy in 2 patients. The histology revealed an adenocarcinoma in 18 patients, a squamous cell carcinoma in 7, a large cell carcinoma in 4, a neuroendocrine tumor in 3 and a well-differentiated chondrosarcoma in 1 patient. The tumorstaging showed 19 patients with Stage IA, 7 with IB, 2 with II A and 1 with III A- Stage. The postoperative FEV1 improved up to 38% ± 2,3 (21-66%) at 3 months. In hospital mortality was 6 % (one due to intracerebral bleeding and one due to multiorgan failure). The 5 years survival was 60%.

Conclusion: Lung cancer surgery in selected high-risk patients with very severe emphysema and impaired lung function is feasible and safe in an experienced center. The in hospital mortality is low, the postoperative lung function may be improved and the 5- years survival is acceptable.

Disclosure: All authors have declared no conflicts of interest.

170O

STEREOTACTIC BODY RADIOTHERAPY VERSUS SURGERY FOR STAGE I NSCLC: A MARKOV MODEL BASED DECISION ANALYSIS

G. Rodrigues[1], A.V. Louie[1], M. Hannouf[2], G. Zaric[2], D. Palma[1], J. Mocanu[3]
[1]Radiation Oncology, London Regional Cancer Program, London/CANADA, [2]Epidemiology, University of Western Ontario, London/CANADA, [3]Business, University of Western Ontario, London/CANADA

Purpose: To compare the quality-adjusted life expectancy and overall survival in patients with stage I NSCLC treated with either stereotactic body radiation (SBRT) or surgery.

Methods and materials: We constructed a Markov model to describe health states after either SBRT or lobectomy for stage I non-small cell lung cancer (NSCLC) for a 5-year timeframe. Rates of recurrence and Markov state utilities, consistent with the four stages of the AJCC staging system, were extracted and adapted from the literature. We report various treatment strategy survival outcomes stratified by age, sex, and pack-year history of smoking and compared these to an external outcome prediction tool (Adjuvant! Online).

Results: Overall survival, cancer specific survival, and other causes of death as predicted by our model correlated closely with those predicted by the external prediction tool. Mean quality-adjusted life expectancy after surgery ranged from 3.47 to 4.00 years and 3.45 to 3.97 years for SBRT for our base cases. The SBRT associated utility threshold for preferring SBRT over surgery assuming 80% of patients who fail locally and/or regionally received standard salvage treatment ranged from 0.948 to 0.966 for our base cases. Outcomes were sensitive to the utility of initial treatment, the proportion of local and regional recurrences that were treated with standard versus palliative treatments, and the surgical and SBRT treatment related mortality.

Conclusions: The role of SBRT in the medically operable patient is yet to be defined. Our model indicates that SBRT may offer comparable survival and QALYs as compared to surgical resection. Well powered prospective studies comparing surgery versus SBRT in early lung cancer are warranted to further confirm the relative survival, quality of life and cost characteristics of both treatment paradigms in a multiinstitutional setting.

Disclosure: All authors have declared no conflicts of interest.

171O

RADIOLOGICAL AND CLINICAL PNEUMONITIS AFTER STEREOTACTIC LUNG RADIOTHERAPY: A MATCHED COMPARISON OF 3D-CONFORMAL AND VOLUMETRIC MODULATED ARC THERAPY TECHNIQUES

D. Palma[1], S. Senan[1], C.J.A. Haasbeek[1], W. Verbakel[1], A. Vincent[2], F.J. Lagerwaard[1]
[1]Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS, [2]Department of Biometrics, Netherlands Cancer Institute, Amsterdam/NETHERLANDS

Purpose: Lung fibrosis is common after stereotactic body radiotherapy (SBRT) for lung tumors, but the influence of treatment technique on rates of clinical and radiological pneumonitis is not well-described. After implementing volumetric modulated arc therapy (RapidArc™ [RA], Varian Medical Systems) for SBRT, we compared the early pulmonary changes seen with arc vs. conventional 3-dimensional SBRT (3D-CRT).

Methods: Twenty-five SBRT patients treated with RA were matched 1:2 with fifty SBRT patients treated with 3D-CRT. Dose-fractionations were based on a risk-adapted strategy. Clinical pneumonitis was scored using Common Terminology Criteria for Adverse Events, version 3.0. Acute radiological changes three months post-treatment were scored by three blinded observers. Relationships between treatment type, baseline factors, and outcomes were assessed using Spearman's correlation, Cochran-Mantel-Haenszel tests, and logistic regression.

Results: The RA and 3D-CRT groups were well-matched. 43 patients (57%) had radiological pneumonitis 3 months after treatment. 28 patients (37%) had CT findings of patchy or diffuse consolidation, and 15 patients (20%) had ground glass opacities only. Clinical pneumonitis was uncommon, with no differences seen between 3D-CRT vs. RA in rates of grade 2/3 clinical pneumonitis (6% vs. 4%, respectively; $p=0.99$), moderate/severe radiological changes (24% vs. 36%, respectively, $p=0.28$), or patterns of CT changes ($p=0.47$). Radiological severity scores were associated with larger planning target volumes ($p=0.09$) and extended fractionation ($p=0.03$).

Conclusions: Radiological changes after lung SBRT are common. However, no differences in clinical or radiological findings were observed 3 months after RA. Data with longer follow-up is awaited to exclude late changes.

Disclosure: D. Palma: Dr. Palma's research is supported by the Canadian Assoc. of Radiation Oncologists-Elekta Fellowship, the Ontario Institute for Cancer Research, and the Detweiler Fellowship. The VUMC has a research collaboration with Varian Medical Systems. All other authors have declared no conflicts of interest.

172O

TREATMENT UTILIZATION AND SURVIVAL FOR ELDERLY PATIENTS WITH STAGE I NSCLC: A POPULATION-BASED TIME-TREND ANALYSIS

D. Palma[1], O. Visser[2], F.J. Lagerwaard[3], S. Senan[4]
[1]Radiation Oncology, VU University Medical Centre, Amsterdam/NETHERLANDS, [2]Cancer Registry, Comprehensive Cancer Centre, Amsterdam/NETHERLANDS, [3]Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS, [4]Department of Radiation Oncology, VU University Medical Centre, Amsterdam/NETHERLANDS

Background: Treatment options for elderly patients with stage I NSCLC have changed dramatically in the past decade, mostly due to the introduction of stereotactic body radiotherapy (SBRT). Treatment patterns and overall survival (OS) in elderly patients (age ≥75) with stage I NSCLC were studied in a comprehensive population-based registry in North Holland (http://www.ikcnet.nl/IKA).

Methods: Population-based data was assessed for three eras: 1999-2001 (period A, pre-SBRT); 2002-04 (period B, some availability of SBRT) and 2005-07 (period C, full access to SBRT). Chi-square, Kaplan-Meier and Cox Regression were used to compare treatment patterns and OS between these periods.

Results: 842 elderly patients were diagnosed with stage I NSCLC in the study period. Primary treatment was surgery in 299 (36%), radiotherapy (RT) in 264 (31%) and neither in 279 (33%). The proportion of patients undergoing RT increased significantly (26% in period A vs. 36% in period C; $p=0.01$), which corresponded to a decrease in patients receiving no treatment. Median survival for all patients increased from 16 months in periods A and B to 21 months in period C. On multivariate analysis, factors predictive of improved OS were T1 disease (vs. T2, HR 0.55 95% CI 0.45-0.67), pathological confirmation of disease (vs. clinical diagnosis, HR 0.31; 95% CI 0.21-0.46), and treatment in period C (vs. period A, HR 0.68 95% CI 0.56-0.83). This improvement in OS was confined to patients treated with RT (HR 0.67 95% CI 0.47-0.97), but not observed in patients who received surgery or no treatment.

Conclusion: In this population-based study, a 10% increase in RT utilization in elderly patients was associated with improved OS in the SBRT era. However, improvements in OS were not observed in patients aged ≥75 who either underwent surgery or were untreated.

Disclosure: D. Palma: Dr. Palma's research is supported by the Canadian Assoc. of Radiation Oncologists-Elekta Fellowship, the Ontario Institute for Cancer Research, and the Detweiler Fellowship. The VUMC has a research collabora-

tion with Varian Medical Systems. All other authors have declared no conflicts of interest.

173O

EXTENDING THE BENEFIT OF STEREOTACTIC BODY RT (SBRT) TO STAGE II/III NSCLC: A TREATMENT PLANNING STUDY

E. Damen[1], A. Holt[1], A. Lakeman[1], J. Belderbos[2], J. Sonke[1] *[1]Radiation Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam/NETHERLANDS, [2]Radiotherapy, The Netherlands Cancer Institute, Amsterdam/NETHERLANDS*

Purpose: SBRT for stage I NSCLC results in local control rates of ~90%. Conventional (chemo-)radiation for stage II/III NSCLC results in high local recurrence rates, mainly at the site of the primary tumor. In this planning study we assessed the feasibility of extending the advantage of SBRT to stage II/III NSCLC by combining SBRT to the peripheral tumor with conventional fractionated RT to the pathologic lymph nodes.

Material: Nine patients were selected with stage II/III disease and primary tumors < 5 cm in diameter located > 2 cm from the main bronchial tree. The clinical plan consisted of an IMRT treatment plan delivering 24 × 2.75 Gy to the primary tumor and pathologic lymph nodes. A hybrid stereotactic/conventional plan was created delivering 3 × 18 Gy to the primary tumor and 24 × 2.75 Gy to pathologic lymph nodes. Dose to organs at risk (OAR) was converted to equivalent dose in fractions of 2 Gy (EQD2) using the LQ model with $\alpha/\beta = 3$ Gy (lung, esophagus, heart, and mediastinal structures (MS)) and 2 Gy (spinal cord), respectively. Planning constraints for OAR were: mean lung dose (MLD) ≤20 Gy, maximum dose (Dmax) to the spinal cord ≤ 50 Gy, volume of esophagus receiving 35 Gy or more (V35) ≤ 65%, mean heart dose (MHD) ≤ 46 Gy, and Dmax of the MS ≤ 94 Gy. In addition, V20 and V5 for lung were recorded.

Results: Clinically acceptable hybrid plans could be created for eight out of nine patients. Average changes in dose values for the OAR are listed in the table. There was no significant change in dose values for spinal cord, esophagus, heart, and MS when comparing the hybrid plan with the clinical plan. For lung, a significant decrease in V20 and V5 was seen for the hybrid plans, but the MLD showed a significant increase.

Conclusion: The novel hybrid stereotactic/conventional technique for stage II/III NSCLC is feasible with no increased risk to the OAR. We will introduce this hybrid technique in a phase II clinical trial in which the dose delivered to the primary tumor will be escalated gradually.

Disclosure: All authors have declared no conflicts of interest.

	Average Difference ± SD (Hybrid – Clinical)	p-Value (Paired t-Test)
Lung		
MLD (Gy)	2.0 ± 3	0.04
V20 (%)	−2.6 ± 3	0.02
V5 (%)	−5.8 ± 5	0.01
Spinal cord		
Dmax (Gy)	−4.3 ± 12	n.s.
Esophagus		
V35 (%)	−0.9 ± 3	n.s.
Heart		
MHD (Gy)	−1.3 ± 4	n.s.
MS		
Dmax (Gy)	1.7 ± 6	n.s.

174PD

A FOUR-GENE SIGNATURE THAT PREDICTS OUTCOME IN NON SMALL CELL LUNG CANCER PATIENTS

P. Cejas[1], C. Belda-Iniesta[2], J.J. Sanchez[3], R. Machado-Pinilla[4], V. Rodríguez-Fanjul[4], I. Ibañez de Cáceres[5], J. Feliu[1], M. Nistal[6], R. Perona[5], J. De Castro[7] *[1]Department of Medical Oncology, IdiPAZ, La Paz University Hospital. Madrid, Spain. IdiPAZ, Madrid/SPAIN, [2]Medical Oncology, IdiPAZ, La Paz University Hospital, Madrid/SPAIN, [3]Statistics, Autonomous University of Madrid, Madrid/SPAIN, [4]Traslational Oncology Unit, Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid/SPAIN, [5]Translational Oncology Unit, IdiPAZ, La Paz University Hospital. Madrid, Spain. IdiPAZ, Madrid/SPAIN, [6]Department of Pathology, IdiPAZ, La Paz University Hospital. Madrid, Spain. IdiPAZ, Madrid/SPAIN, [7]Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid/SPAIN*

Background: Cisplatin based adjuvant chemotherapy improves survival among patients with completely resected non small-cell lung cancer. However, objective response rates are in the range of 30% to 50% Thus, prediction of treatment response and outcome before CRT is a major challenge for clinicians.

Methods: In a first stage we perfomed a SAGE analysis on snap-frozen surgical specimens from three good responder and three bad responder patients. Response sensibility to cisplatin was evaluated using cytotoxicity assays in primary cultures of tumor cells from the surgical specimens. In a second stage we analyzed the expression of 22 genes and 2 controls using TaqMan low density arrays in snap-frozen surgical specimens from 51 operable stages non small cell lung cancer patients. Disease free survival was used as the endpoint of the study. All patients received Cisplatin based adjuvant chemotherapy. Multivariate Cox methods were applied to build an optimized predictor of outcome.

Findings: The combination of mTOR, TWIST1, AKCR1C2 and HSPB1 gene expression was able to predict clinical outcome in pretreated tissues. In addition, DFS analysis revealed that the gene signature-based score was the only statistically significant prognostic factor remaining in the multivariate analysis. Interpretation A basal 4-gene signature, obtained from surgical specimens of non small cell lung cancer, efficiently predicted clinical outcome in the patients. These preliminary results are very encouraging and, if they are validated in larger series, could have clinical implications.

Disclosure: All authors have declared no conflicts of interest.

175PD

IMPACT OF ADJUVANT CHEMOTHERAPY IN STAGE IB NON-SMALL CELL LUNG CANCER. AN ANALYSIS OF 112 CONSECUTIVELY TREATED PATIENTS

M. Dediu, O. Ion, R. Ion, A. Alexandru, D. Median, C. Gal, M. Gongu *Medical Oncology, Institute of Oncology, Bucharest/ROMANIA*

The impact of adjuvant chemotherapy (CT) in the management of radically resected stage IB non-small cell lung cancer (NSCLC) is highly debated. The aim of the study was to evaluate the outcome of this category of patients treated at our institution. We retrospectively analyzed the survival data of patients with pathologically staged IB NSCLC, who received at least 1 adjuvant CT cycle. CT was planned to be platinum-based and to be delivered for 6 cycles. During 1997–2007 a number of 135 consecutively resected patients were classified as stage IB. Twenty three patients were excluded from the analysis: 3 patients were deemed ineligible for adjuvant CT, 11 underwent tumor resection less than lobectomy/pneumectomy, and 9 patients had no mediastinal lymph nodes evaluated by the pathologist. The characteristics of the remaining 112 patients were as following: 83% male , 27% female , median age 60, lobectomy was performed in 87% of patients and pneumectomy in 13%. Median tumor dimen-

sion was 4 cm, and visceral pleural involvement was present in 58% of cases. Disease free (DSF) and overall survival (OS) rates after a median follow up period of 46 months are presented in table.

Months	12	24	36	48	60
DFS (%)	94	84	71	69	68
OS (%)	97	90	88	80	77

The median number of CT cycles was 6 (range 3-6), with 79% of patients receiving > 4 cycles. The median cisplatin (CDDP) dose intensity (DI) was 22 mg/m^2/week and the actually delivered vs. the predicted DI ratio was 0.85%. Median total CDDP dose/patient was 412 mg. A number of 28 (25%) relapses were recorded, of which 14% were local and 86% distant. In a multivariate analysis we found no significant interaction between OS and the following variables: gender, type of surgery, histology, tumor volume, visceral pleural involvement, number of lymph nodes evaluated. Our results compare favorable with the historical data evaluating the outcome of stage IB patients treated by surgery alone in a customary medical setting. Overall, our data support the use of adjuvant CT in stage IB NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

176P

OVER-EXPRESSION OF THE MAMMALIAN TARGET OF RAPAMYCIN (MTOR): A NOVEL BIOMARKER FOR POOR SURVIVAL IN RESECTED EARLY STAGE NON-SMALL CELL LUNG CANCER

T. Dhillon[1], M. Seckl[1], F. Mauri[2], G. Belleza[3], B. North[4], L. Cagini[5], M. Barbareschi[6] *[1]Oncology, Imperial College London, London/UNITED KINGDOM, [2]Pathology, Imperial College London, London/UNITED KINGDOM, [3]Pathology, University of Perugia, Perugia/ITALY, [4]Statistics, Imperial College London, London/UNITED KINGDOM, [5]Thoracic Surgery, University of Perugia, Perugia/ITALY, [6]Molecular Pathology, S Chiara Hospital, Trento/ITALY*

Introduction: The best hope of cure for patients with non-small cell lung cancer (NSCLC) is surgical resection. However, even in stage IA patients 30% die within 5 years. Further improvements in survival require a biomarker(s) which defines the subset of these patients destined to do badly so that they could be targeted for additional therapies. Here, we investigate whether the immunohistochemical expression of a key kinase implicated in lung cancer biology, the mammalian target of rapamycin (mTOR) can predict survival outcome in early stage resected NSCLC patients.

Materials and methods: 134 patients with resected early stage (IA-IIB) NSCLC were pathologically reviewed centrally prior to staining for mTOR. Multiple variables including age, sex, stage, angio-invasion, lymph node status and mTOR staining were assessed by univariate and multivariate analyses.

Results: Stage ($p = 0.044$), lymph node status ($p = 0.049$), angio-invasion ($p= 0.017$) and mTOR staining ($p = 0.007$) were significant univariate predictors of poor survival. However, only angio-invasion ($p= 0.016$) and mTOR staining ($p = 0.046$) remained significant following multivariate analysis. Moreover, mTOR staining was the only variable to predict poor outcome in patients who had either negative lymph-nodes ($p =0.016$) or were stage IA ($p = 0.0016$).

Conclusions: mTOR staining provides a new biomarker for poor outcome in early stage NSCLC and could enable resected stage IA patients to be selected for novel therapies possibly with an mTOR inhibitor.

Disclosure: All authors have declared no conflicts of interest.

177P

SINGLE NUCLEOTIDE POLYMORPHISMS OF ATM AND P53 AND ITS ASSOCIATION WITH RADIATION-INDUCED PNEUMONITIS

K. Iqbal *Oncology, Nuclear Medicine, Oncologyand Radiotherapy Institute, Islamabad/PAKISTAN*

Introduction: To explore the possible relationship between single nucleotide polymorphisms (SNPs) in candidate genes encoding DNA repair, apoptosis, and inflammatory cytokines with radiation-induced pneumonitis (RP) in patients with lung cancer.

Patients and methods: One hundred and twenty-seven non-small cell lung cancer patients and forty-three small cell lung cancer patients who were inoperable and underwent thoracic radiotherapy at Cancer Hospital of Peking Union Medical College (PUMC) and Chinese Academy of Medical Sciences between January 2004 and August 2006, were evaluated. All of them consented for blood sampling, SNP analysis and follow up. The primary endpoint was ≥ grade 2 radiation pneumonitis. We analyzed 37 SNPs in 20 DNA repair, apoptosis and inflammatory Cytokines genes, including ATM, TP53, ERCC1, XRCC1, XRCC3, XPD, XPC, XPG, NBS1, STK15, ZNF350, ADPRT, FAS, FASL, CYP2D6*4, CASP8, COX-2, TGF-β1, CD14 and ACE genes, using PCR-based restricted fragment length polymorphism (RFLP).

Results: One hundred and seventy patients with a median follow-up of 22 months were evaluated. Twenty-nine patients (17.1%) experienced ≥ grade 2 pneumonitis and the median occurrence time was 59 days from the first day of irradiation. ATM –111GA and –111AA genotypes were independently associated with the risk of RP (Hazards ratio (HR) = 3.27, 95% confidence interval (CI) = 1.09-9.78, P = .034) and TP53 72Arg/Pro and 72Pro/Pro genotypes had a trend to decrease the risk of RP (HR = 0.43, 95% CI = 0.17-1.12, P = .084). The presence of two risk genotypes (ATM –111A allele combined with TP53 72Arg/Arg genotype) showed an independent role for high risk for RP with HR of 4.75 (95% CI = 1.33-17.04, P = .017).

Conclusion: Genetic polymorphisms in ATM gene and TP53 gene contribute to the risk of radiation-induced pneumonitis. These could be used as putative predictive biomarkers for radiotherapy in the future.

Disclosure: The author has declared no conflicts of interest.

178P

RADIOLOGICAL PATTERNS IN PATIENTS WITH OPERABLE NON-SMALL CELL LUNG CANCER (NSCLC) IN MID-WESTERN IRELAND

K.I. Quintyne[1], N. O\'Leary[2], F. Wallis[3], P. Hession[3], R.K. Gupta[1] *[1]Medical Oncology, Mid-Western Regional Hospital, Limerick/IRELAND, [2]Mid-western Cancer Centre, Mid-Western Regional Hospital, Limerick/IRELAND, [3]Radiology, Mid-Western Regional Hospital, Limerick/IRELAND*

Introduction: Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. Within this group of patients with lung cancer, almost 20% are suitable to undergo a definitive surgical procedure. The ultimate outcome for these patients is usually associated to size of the primary tumour, degree of nodal involvement and clear resection margins. As such, we herein report our findings for patients with operable NSCLC with respect to their related radiological patterns and outcomes.

Methods: Study period: 01/01/03 – 31/12/05. Data was derived from (1) Mid-Western Cancer Centre (MWCC) Oncology Database (2) MWRH pathology and radiology records (3) individual case records.

Results: 35 patients were found, M: F (23:12). Mean age was 66.2 years (SD – 10.3 years). The mode for ECOG performance status (PS) at presentation to was 1. The majority of patients presented at Stage IIIA, with 15/35 (43%).

The mean survival based on pre-op stage revealed that IA, IB, IIA, IIB, and IIIA was 52.5, 30.5, 65, 8.5, and 20 months respectively. The mean survival by T-status is below.

T Status	T1	T2	T3	T4
Mean Survival (Months)	65.1	44.3	48.8	69.2

(Significant at p value < 0.05) The mean survival by N-status is below.

N Status	N0	N1	N2
Mean Survival (Months)	55.1	40.6	37.1

(Significant at p value < 0.05)

Conclusions: Male preponderance was noted, with most patients having a good ECOG PS to tolerate therapy.The higher the stage at onset, the poorer the overall survival.The smaller the T-status and the lower the N-status, the better the mean overall survival, these were both significant statistically. These results underscore the need to review patients as early in the course of their disease as possible, to ensure the best overall survival, and hence are potentially highlighting the potential need for screening programs.
Disclosure: All authors have declared no conflicts of interest.

179P

SURVIVAL OF CONSERVATIVELY TREATED PATIENTS WITH SECOND STAGE NON-SMALL CELL LUNG CANCER IN COMPARISON WITH THE SURGICALLY TREATED

G. Popovic[1], D. Bursac[1], N. Secen[2], A. Tepavac[1], D. Sazdanic Velikic[1], B. Zaric[2], B. Perin[2] *[1]Department for Lung Cancer Treatment, Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica/SERBIA AND MONTENEGRO, [2]Department for Interventional Pulmonology, Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Sremska Kamenica/SERBIA AND MONTENEGRO*

Background: Surgery is the treatment of first choice for patients with stage II of non-small lung cancer (NSCLC), however some patients with comorbidities are subject to conservative therapy. The aim was to determine effects of conservative treatment in patients with NSCLC.
Methods: Seventy patients with NSCLC who have been treated in the Institute for pulmonary diseases of Vojvodina from January 2004 to December 2006 were enrolled into the study. All of the patients have pathohistological or cytological confirmation and had TNM stage II of NSCLC. There were 30 surgically treated patients in first group and 40 patients in second group who were treated conservatively with chemotherapy or radiation therapy due to comorbidities. Patients were scheduled to receive 4 cycles of standard regimen with cisplatin (60mg/ m^2, day 1) and etoposide (100mg/m^2, days 1–3) and thoracic radiation therapy in dose of 40Gy.
Results: Sixty-four (91,4%) patients were male and 6 (8,6%) female. Median age was 60,1 years. Squamous cell carcinoma was pathohistologically or cytologically confirmed in 44 (62,8%) patients, adenocarcinoma in 25 (35,7%) and macrocellular carcinoma in 1 (1,5%). Our results have shown median survival of 17 months in conservatively treated patients compared with 21,5 months in surgically treated patients (p=0,0665). One-year survival in conservatively treated patients was 72,5% in comparison with 76,6% in surgically treated. Two-years survival in first group was 10% and in second group 43,3%. The median time to progression in conservative treated patients were 12,7 months and in surgically treated 15,4 months.
Conclusions: Patients with TNM stage II NSCLC who cannot be surgically treated should undergone conservative treatment with the modest results in comparison with surgical treatment.
Disclosure: All authors have declared no conflicts of interest.

180P

PREDICTED POSTOPERATIVE PRODUCT AND DIFFUSION INDEX IN PREOPERATIVE EVALUATION

J. Wang *Medicine Department, Taipei Medical University, Taipei City/TAIWAN*

Objectives: The purpose of this retrospective study is to evaluate whether abnormal predicted postoperative (ppo) variables and predicted postoperative product (PPP) are useful in predicting postoperative complications and whether an abnormal diffusion index (DI) is associated with increased postoperative complications.
Methods: Calculations of the ppo variables were performed using preoperative testing data and the extent of the resected bronchopulmonary segments. PPP was obtained by multiplying ppo FEV1 % predicted by ppo DLCO % predicted and measured product (MP) was obtained by multiplying FEV1 by DLCO. DI, was derived from measurements of the single-breath DLCO using the 3-equation method as a measure of the heterogeneity of the distribution of gas exchange in the lung.
Results: Patients with complications had lower ppo FEV1, lower ppo DLCO, lower ppo maximal oxygen uptake (VO2max/kg), and lower ppo mean increase in DLCO% predicted at 70% workload from resting DLCO% predicted ((70%-R)DLCO%). Patients with complications also had lower PPP, and lower MP. Interestingly, DI deteriorated with exercise in patients with complications but DI improved with exercise in patients without complications.
Conclusions: All variables including ppo variables, PPP, MP, and DI were potentially useful predictors for preoperative evaluation in lung resection pending further confirmation in larger studies.
Disclosure: The authot has declared no conflicts of interest.

LOCALLY ADVANCED NSCLC

181O

CORRELATION OF IMAGING AND HISTOPATHOLOGY IN COLD SPOTS ON FDG PET SCANS OF NON SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

C. Siedschlag[1], J. Belderbos[2], J. Sonke[3], J. Stroom[1], K. Gilhuijs[1], L.N. Boersma[4], J. van Loon[4], A. van Baardwijk[5], R. van Suylen[6], M. Rossi[3] *[1]Radiotherapy, Dutch Cancer Institute, Amsterdam/NETHERLANDS, [2]Radiotherapy, The Netherlands Cancer Institute, Amsterdam/NETHERLANDS, [3]Radiation Oncology, The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam/NETHERLANDS, [4]Radiotherapy, Maastro Clinic, Maastricht/NETHERLANDS, [5]Radiotherapy, MAASTRO Clinic, Maastricht/NETHERLANDS, [6]Pathology, Maastricht University Clinic, Maastricht/NETHERLANDS*

Introduction: Recent technical advances like intensity modulated radiotherapy (IMRT) enables us to adapt the radiation dose to anatomical and functional image information in lung tumors. The possibility to use FDG-PET uptake information raises the question how to deal with tumor inhomogeneities pre-irradiation. This question is particularly relevant in the light of ongoing efforts to optimize local control while limiting normal-tissue toxicity. The aim of this preliminary study was to correlate cold spots visible on FDG-PET imaging of NSCLC with histopathology.

Materials and methods: Sixty-one patients with operable non-small cell lung cancer scheduled for a lobectomy underwent FDG-PET within six weeks before surgery. The PET voxel size was 4x4x4 mm^3. The scans were visually inspected for cold spots within the tumor. After surgery, the excised lung lobes were cut into slices of 0.5 cm thickness. The tumor-bearing slices were microscopically analyzed; vital and necrotic tumor tissue was delineated, as well as inflammatory tissue. The annotated pathology slices were registered to the pre-operative PET/CT data.
Results: In seven out of 61 patients (11.5%) cold spots within the tumor on the FDG-PET scans were present. In five of these patients, necrosis was present at microscopic examinationin corresponding locations. The surgical specimens of the two patients with cold spots on FDG-PET but no necrosis at microscopy showed extensive inflammatory tissue around the tumor-bearing tissue.
Conclusions: The results of this preliminary study indicate that necrosis may be the most common cause for cold spots on FDG-PET scan in NSCLC patients. Another cause might be relatively high FDG uptake in nearby inflammatory tissue. When validated in larger cohorts of patients, these findings may justify reduced radiation dose in tumor regions with relatively low FDG uptake in order to optimize local control while limiting normal-tissue toxicity.
Disclosure: All authors have declared no conflicts of interest.

182O

PREDICTIVE VALUE OF PATIENT CHARACTERISTICS AND PULMONARY SYMPTOMS FOR RADIATION INDUCED LUNG TOXICITY

G. Borst[1], M. Rossi[1], E. Damen[1], W. Heemsbergen[1], S. Burgers[2], J. Belderbos[3] *[1]Radiation Oncology, Antoni van Leeuwenhoek Hospital - Netherlands Cancer Institute, Amsterdam/NETHERLANDS, [2]Pulmonology, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam/NETHERLANDS, [3]Antoni van Leeuwenhoekhuis - Netherlands Cancer Institute, Amsterdam/NETHERLANDS*

Purpose: Prediction of radiation induced lung toxicity (RILT) after radical radiotherapy or chemo-radiation for lung cancer remains challenging. The mean lung dose (MLD) is an important independent predictive factor for RILT albeit a limited specificity. This limitation may be related to the complexity and a limited patient specific sensitivity of diagnosing and scoring RILT. We prospectively evaluated the predictive role of patient characteristics and pulmonary symptoms before, during and after high dose irradiation on the incidence of RILT. The scoring differences of pulmonary symptoms between physicians and patients were also analyzed.
Patients and methods: 83 patients from a phase I/II dose escalation trial were included. At baseline the patient's medical history of COPD and heart disease was recorded. Complaints of dyspnea and cough were scored by the patients at baseline and at each visit during the follow-up using a validated questionnaire and by the physician according to NCI-CTC criteria. RILT was scored as radiation pneumonitis (RP) grade ≥ 2 according to NCI-CTC criteria.
Results: According to the questionnaire, 95% of the patients with more than one year follow-up (n=41) experienced an increase of dyspnea and/or coughing one year after irradiation. Of these patients 15% were scored by the physician as having grade $\geq$ 2 RP. Neither the medical history (COPD and/or heart disease), nor the scoring of dyspnea or coughing at baseline were significantly ($p>0.05$) predictive for the incidence of RILT whereas the MLD ($p<0.05$) was predictive. These results were independent of baseline symptoms scored by the physician and by the patients. The correlations between the scoring of the physician and the patients at baseline and during follow up were not significant for coughing ($p>0.05$) or dyspnea ($p>0.05$), respectively. At one year follow up, changes in dyspnea or coughing scored by the physician and patient were not significantly correlated.
Conclusion: Baseline clinical pulmonary symptoms and pulmonary/cardiac morbidity are not predictive for the incidence of RILT. Scoring of RILT remains challenging. The subjective symptoms of the patients need to be objectified by the physician in diagnosing RILT.
Disclosure: All authors have declared no conflicts of interest.

183O

INDUCTION CHEMOTHERAPY (I-CT) WITH VINORELBINE AND CISPLATIN FOLLOWED BY CONCURRENT CHEMOTHERAPY (CT-RT) AND DYNAMIC ACCELERATED HYPERFRACTIONATED RADIOTHERAPY (DAHR) (ZAMORA-MITSOURA REGIMEN) IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

J. Zamora-Moreno-Varaona[1], D. Gallardo-Rincon[1], E. Mitsoura[2], M. Blake[1], G. Calderillo[3], M. Schlienger[4], F. Baillet[5], O. Arrieta[3] *[1]Radiation Oncology, Instituto Nacional de Cancerologia, Mexico City/MEXICO, [2]Universidad Autonoma Del Estado De Mexico, Instituto Nacional de Cancerologia, Toluca, Mexico/MEXICO, [3]Medical Oncology, Instituto Nacional de Cancerologia, Mexico City/MEXICO, [4]Department of Radiotherapy Anf Physics, Tenon Hospital APHP, Paris, France/FRANCE, [5]Radiation Oncology, Hopital Pitié-Salpêtrière, Paris, France/FRANCE*

Background: Combined CT-RT is the standard treatment for locally advanced (LA) NSCLC. Hyperfractionated schedules have been implemented with success in early stage lung cancer, and reports of its use have been increasing in the last decade. In developing countries, radiotherapy schedules are saturated because of lack of linear accelerators, therefore it is necessary to design alternative treatment schedules, based on radiobiological knowledge, to reduce radiotherapy (RT) administration time without increasing toxicity or compromising tumor control.
Methods: Twenty seven patients were treated with 2 cycles of I-CT with vinorelbine 30 mg/m2 on days 1 and 8 and cisplatin at 80 mg/m2 on day 1, every four weeks; followed by 2 additional cycles concurrently with DAHR (Total Dose 35.5 Gy) during 2 weeks with same drug and dosage consolidation chemotherapy (CT) in patients with LA NSCLC.
Results: Stages IIIA-N2 and IIIB were 33.3% (9/27) and 66.7% (18/27). Median follow-up was 15.9 months (mo). One patient progressed during I-CT. Overall response was observed in 37% (10/27) and 53.8% (14/26) of patients following I-CT and after concurrent CT-RT, respectively. Local and distant progressions were present in 33.3% and 44.4%, correspondingly. Median progression-free survival (PFS) was 14 mo (95% Confidence Interval [95% CI], 8.4-19.6) and overall survival (OS) was 19.4 mo (95% CI, 13.8-25). Patients who responded to I-CT had a longer OS, 15.2 (95% CI, 12.2-18.3) vs. 36.3 mo (95% CI, 16.5-56) ($p= 0.02$). Grade III/IV global toxicity was 44.4% and 25.9% after I-CT and CT-RT, respectively. Grade I and II radiation pneumonitis was developed in 15.3% (4/26) and 7.6% (2/26), no grade III/IV was encountered. Grade I, II and III Esophagitis was reported in 15.3%, 7.6% and 11.5% (N=26) of patients, respectively.
Conclusions: This multimodal treatment using CT-RT with DAHR in LA NSCLC provides a short course of RT and confers satisfactory PFS and OS with an acceptable toxicity profile. Prospective trials with this fractionation are necessary to confirm these findings.
Disclosure: All authors have declared no conflicts of interest.

184O

PEMETREXED (PEM) AND CISPLATIN (CIS) IN CONCURRENT COMBINATION WITH HIGH DOSE OF THORACIC RADIATION (RT), AFTER INDUCTION CHEMOTHERAPY (CT), IN PATIENTS (PTS) WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A PHASE I STUDY

F. Mornex[1], J.M. Tourani[2], V. Wautot[1], N. Chouaki[3], A. Thareau Vaury[3], N. Bourayou[4], B. Coudert[5] *[1]Radiotherapy, Centre Hospitalier Lyon-Sud, Pierre Bénite, Lyon/FRANCE, [2]Medical Oncology, CHRU La Miletrie, Poitiers, Poitiers/FRANCE, [3]Medical Oncology, Eli-Lilly Laboratories, Suresnes/FRANCE, [4]Medical Oncology, Eli Lilly Laboratories. France, Suresnes/FRANCE, [5]Medical Oncology, Centre Georges François Leclerc, Dijon/France*

Background: Concurrent RT-CT is the current standard of care of pts with unresected stage III NSCLC. However, optimal CT regimen and schedule remain undefined. Pem has an established role in treatment of metastatic NSCLC and showed interesting data with variable RT doses and carboplatin in multitumors phase I trial (Seiwert et al. 2007). This work reports on the first Pem phase I trial targeting exclusively NSCLC pts and using Cis and fixed-high dose of RT after induction CT. Primary objective was to determine the Maximum Tolerated Dose of Pem.

Patients and methods: Pts with unresected stage III NSCLC, planned V20≤35% and FEV≥1.3 L, were treated every 21 days for 2 induction cycles: Pem 500 mg/m^2 plus Cis 75 mg/m^2, followed by 2 cycles of concurrent RT-CT: Pem at starting dose of 400 mg/m^2 and then escalated to 800 mg/m^2 per 100 mg/m^2 dose level (DL), Cis at fixed dose of 75 mg/m^2 and RT at 66 Gy/33 fractions over 7 weeks.

Results: Nine of 10 enrolled pts were entered on 3 DLs. Age range [46-68], 6 males, ECOG PS 0: 6; PS 1: 4, stage IIIA: 1; IIIB: 9, 6 adenocarcinoma, 3 squamous cell carcinoma, 1 large cell carcinoma. One pt received only induction CT due to disease progression. Dose escalation of Pem was conducted up to 600 mg/m^2 based on the independent safety monitoring board recommendation and available clinical data showing no dose-effect correlation beyond 500 mg/m^2 (Cullen et al. 2008). One Dose Limiting Toxicity (DLT) occurred at DL3: a grade (G) 4 septic shock. No G¾ radiation related toxicities. No toxic death.

DL Pem mg/m^2	Pts Entered in RT-CT	Pts Completed RT Dose	Pts Completed 4 Cycles of CT	Related G3 Toxicities (Nb of pts)	Related G4 Toxicities (Nb of pts)
400	3	2	2	1 Neutropenia 2 Lmphopenia	
500	3	3	3	2 Lymphopenia 1 Nausea 1 Vomiting	
600	3	3	2	2 Neutropenia 2 Leukopenia 1 Gastric pain 2 lymphopenia	1 Septic shock (DLT)

Conclusion: This is the 1st phase I report of Pem dedicated exclusively to NSCLC, with high dose RT. Pem at 500 mg/m^2, concurrently given with Cis and RT was well tolerated and appears to be the only 3rd generation agent that can likely be recommended safely at full dose, in future trials with concurrent RT.

Disclosure: F. Mornex: Study Coordinator; N. Chouaki: Clinical Research Physician, Eli-Lilly employee A. Thareau Vaury: Study Statistician, Eli-Lilly employee; N. Bourayou: Clinical Research Physician, employee Eli-Lilly; All other authors have declared no conflicts of interest.

185O

ACCELERATED OR HYPERFRACTIONATED RADIOTHERAPY (RT) VERSUS CONVENTIONAL RT IN NON METASTATIC LUNG CANCER (LC): INDIVIDUAL PATIENT DATA (IPD) META-ANALYSIS FROM 2279 PATIENTS (PTS)

C. Le Pechoux[1], A. Mauguen[2], S.E. Schild[3], M.I. Saunders[4], A. Turrisi[5], W. Sause[6], D. Ball[7], C.P. Belani[8], A. Zajusz[9], J.P. Pignon[10] *[1]Department of Radiotherapy, Institut Gustave Roussy, Villejuif/FRANCE, [2]Service de Biostatistique et D'epidémiologie, Institut Gustave-Roussy, Villejuif/FRANCE, [3]Department of Radiation Oncology, Mayo Clinic Arizona & NCCTG, Phoenix/USA, [4]Mount Vernon Hospital, Marie Curie Research Wing, Northwood/UNITED KINGDOM, [5]Radiation Oncology, Wayne State University, Detroit/USA, [6]Department of Radiation Oncology, Intermountain Medical group, Salt Lake City/USA, [7]Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne/AUSTRALIA, [8]Penn State Milton S. Hershey Medical Center, Penn State Cancer Institute, Hershey/USA, [9]Department of Radiotherapy, Center of Oncology Maria Sklodowska-Curie Memorial Institute Branch Gliwice, Gliwice/POLAND, [10]Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif/FRANCE*

Background: The role of and utility of modified RT fractionation for lung cancer continues to evolve. Randomized trials assessing hyperfractionated or accelerated RT offer conflicting results regarding its effect on progression-free survival (PFS) or overall survival (OS). The MAR-LC (Meta-Analysis of Radiotherapy in Lung Cancer) Collaborative Group was established to address this issue.

Methods: We performed an IPD meta-analysis in pts with non metastatic LC, that included trials comparing modified RT (accelerated, hyperfractionated or both) to a conventional RT (one 1.8- to 2-Gy fraction per day, 5 days a week and a minimum total dose of 40 Gy for small cell LC (SCLC) and 60 Gy for non-small cell LC (NSCLC).

Results: Eleven trials were identified; two were excluded due to lost data and one with factorial design was split into two trials (with and without chemotherapy). Ten trials were analyzed including 2279 pts. In NSCLC (8 trials, 1594 pts), modified fractionation improved OS as compared to conventional RT (hazards ratio HR=0.87, 95% confidence interval [0.79-0.97], p=0.009), resulting in an absolute benefit of 3% (8% to 11%) at 5 years. No heterogeneity between trials was found and no subgroup of pts benefited more or less from modified RT. This benefit is not seen on PFS (HR=0.94 [0.85-1.04], p=0.23). Even if not significant, modified RT may reduce non-lung cancer deaths (HR=0.79 [0.57-1.11], p=0.18) as well as lung cancer deaths (HR=0.89 [0.80-0.99], p=0.03). In SCLC (2 trials, 685 pts), similar survival results were found although not significant (OS: HR=0.87 [0.74-1.02], p=0.08; PFS: HR=0.88 [0.75-1.03], p=0.11). In both histological types, the use of modified RT increased the risk of acute esophageal toxicity (HR=2.11 in NSCLC and HR=2.46 in SCLC; p<0.001) but did not impact on the risk of acute hematological, pulmonary or cardiac toxicity.

Conclusion: Patients with non metastatic lung cancer benefit from accelerated or hyperfractionated RT, to a similar degree in NSCLC and SCLC. As expected, there was an increased acute esophageal toxicity. Supported by PHRC , LNCC, Sanofi-Aventis.

Disclosure: All authors have declared no conflicts of interest.

186O

A 4D SOFTWARE FOR BREATHING ADAPTED RADIOTHERAPY (BART) OF LUNG CANCER

N. Peguret[1], J. Vock[2], P. Fenoglietto[3], D. Azria[4], V. Vinh-Hung[1], R. Miralbell[1] *[1]Service de Radio-Oncologie, Hôpitaux Universitaires de Genève, Genève/SWITZERLAND, [2]Service de Radio-oncologie, Hôpitaux universitaires de Genève, Genève/SWITZERLAND, [3]Service de Radiothérapie, CRLCC Val d'Aurelle Paul Lamarque, Montpellier/FRANCE, [4]CRLC Val D'aurelle, Montpellier/France*

Background: Pulmonary lesions are subject to respiratory motion. These movements can be taken into account by respiratory gating, which enables delivering radiotherapy (RT) in a particular breathing phase. However, the moment to deliver RT with the best chance of cure without excess toxicity is not known.

Aim: To develop a 4D image processing software in order to determine this optimal phase in the respiratory cycle.

Patients and methods: Seven patients with lung cancer were studied. Each patient underwent a 4DCT which provides ten datasets related to ten phases of the respiratory cycle (0-100% of the cycle). We defined three morphological criteria for comparison of 4DCT images in different respiratory phases: ratio (tumour volume/lung volume), distance between tumour and spinal cord, distance between tumour and metastatic lymph nodes. Our 4D image processing software automatizes the calculations (around 300 calculations per patient) of these criteria for each respiratory phase and presents their visual comparison. This permits to determine the optimal moment for RT based on the defined criteria.

Results: Lower lobe tumours not attached to the diaphragm (patient 1, 6, 7) present an important respiratory motion. In these cases, our software identified a phase where the volume ratio is 17 to 33% smaller than in the reference phase (maximal inspiration). For a mediastinal tumour localized close to the spinal cord (patient 4), the analysis by comparing the distance spinal cord-tumour detected a phase where the distance to the cord is increased by 28%. Tumours adherent to the diaphragm or located centrally in the mediastinum are less mobile and the differences in the comparison criteria between the respiratory phases are less pronounced (patient 2, 3, 5).

Conclusion: Our software facilitates determination of an optimal moment for respiratory gated RT based on morphological criteria. It is easy to apply in daily routine. If these preliminary results are confirmed, our software might transform the theoretical benefit of 4DCT and respiratory gating into a real therapeutic gain for future patients.

Disclosure: All authors have declared no conflicts of interest.

187O

ACUTE ESOPHAGUS TOXICITY IN LUNG CANCER PATIENTS TREATED WITH INTENSITY MODULATED RADIOTHERAPY (IMRT)

M.H. Kwint[1], W. Heemsbergen[1], M. Wentink[1], W. Uyterlinde[2], J. Knegjens[1], B. Reichelt[1], E. Damen[1], S. Burgers[2], M.M. van den Heuvel[2], J. Belderbos[3] *[1]Radiation Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam/NETHERLANDS, [2]Pulmonology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam/NETHERLANDS, Amsterdam/NETHERLANDS, [3]Radiotherapy, The Netherlands Cancer Institute, Amsterdam/NETHERLANDS*

Background and purpose: The V35 (volume of the esophagus which receives 35 Gy) is a dosimetric predictor of acute esophageal toxicity (AET) in lung cancer patients treated with 3D-conformal-radiotherapy (3DCRT) [1]. Purpose of this study was to investigate the dose-effect relation between AET and dose-volume parameters in lung cancer patients treated with IMRT. The incidence of AET with 3DCRT was compared with the incidence of AET with IMRT.

Patients and methods: 36 patients were prospectively followed and analyzed. Radiotherapy with or without sequential chemotherapy (RTgroup) was given to 21 patients and 15 patients received concurrent chemo radiotherapy (CTRTgroup). Fractionation schemes were: 24x2.75Gy, 17x3Gy, or 25x2Gy. The esophagus constraint was V35 $<$ 65% [1]. Maximum AET was scored (CTC 4.0). Dose-volume histograms and dose-volume parameters V5 to V70, Dmean and Dmax of the esophagus were calculated. A logistic regression analysis was used to analyze the dose-effect relation between the different dose-volume parameters of the esophagus and AET $\geq$ grade 2 en $\geq$ grade 3. This was done separately for the RTgroup and CTRTgroup.

Results In the RTgroup, 5 out of 21 patients developed AET $\geq$ grade 2 of which 1 patient had grade 3 AET. In the CTRTgroup 14 out of 15 patients developed AET $\geq$ grade 2 of which 9 patients had grade 3. The analysis showed no significant dosimetric predictor for AET in the RTgroup. At univariate analysis in CTRTgroup, most significant dosimetric predictor of AET was the V60 ($p=0.032$). The Dmean was borderline significant ($p=0.055$). The incidence of AET in the RTgroup didn't change compared to previous reported data with 3D-CRT. Within the CTRTgroup the incidence of AET $\geq$ grade 3 toxicity was 60%, compared to 27% in previously published 3DCRT data [1].

Conclusion: The incidence of acute esophagus toxicity was increased in the CTRTgroup treated with IMRT compared to previous 3DCRT data. The V60 was a significant dosimetric predictor of AET and the Dmean was borderline significant. A larger group of patients will be analyzed in the near future.

1. J Belderbos et al. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. *Radiother Oncol* 2005; 75:157–164.

Disclosure: All authors have declared no conflicts of interest.

188O

PNEUMONECTOMY FOR LUNG CANCER IN NON-ACADEMIC COMMUNITY PRACTICE: QUALITY RECOMMENDATIONS FROM A LARGE U.S. METROPOLITAN AREA

M. Ninan *Thoracic Surgery, University of Tennessee Health Science Center, Memphis/USA*

Introduction: Pneumonectomy (PN) for non small cell lung cancer (NSCLC) has a mortality ranging from three to ten times that of lesser anatomic resections and requires careful selection. Many central tumors necessitate mediastinoscopy for accurate staging. Bronchoscopy by surgeon is mandatory to assess airway tumor extension. Documentation of extent of parenchymal, vascular , airway, mediastinal or nodal (PVAMN) tumor invasion is important to establish clinical and medico-legal necessity for PN. We studied these practices in a defined geographic area.

Methods: Retrospective review of all curative resections for NSCLC performed from 2004 to 2007 in all non-academic hospitals in the Greater Memphis Metropolitan Area (population 1 million), all were performed by ten board certified cardiothoracic surgeons.

Results: Of 806 resections for cure, 84 (10.4%) were PN procedures, and 3 (0.4%) were sleeve resections. Of the PNs, 29 were in pathologic Stage I NSCLC. A bronchoscopy performed by the surgeon was documented in 49 (58%) and a mediastinoscopy was performed in 25 (30%). The non-feasibility of sleeve resections was documented in 3 (3.5%) of PN. The extent of PVAMN invasion was documented in 33 patients (39%). Mediastinal nodal samples were submitted in 52 (62%) of PN. The 30 day mortality for PN was 15.5% and the 3 Year Survival Estimate (Kaplan Meier) was 0.38 ($SE=0.06$).

Conclusions: 1. Many patients undergoing PN for NSCLC have no bronchoscopy documented by the operating surgeon in community practice in our region. 2. Non-feasibility of rarely performed sleeve resections are often undocumented. 3. Exact anatomic reasons for PN are documented only in a minority of cases. 4. We have developed a checklist for community surgeons to adhere while performing a PN Table 1 Documentation check-list for PN 1. Discussed in multi-disciplinary conference 2. Pulmonary function tests 3. Bronchoscopy by surgeon 4. Mediastinoscopy 5. PVAMN extension 6. Why sleeve resection not possible. 7. Mediastinal nodal stations dissected.

Disclosure: The author has declared no conflicts of interest.

189O

PET-CT DOES NOT IMPROVE THE OUTCOME OF LUNG CANCER SURGERY

K.K.W. Lau[1], J.E. Jacques[1], M. Javed[1], A. Nakas[1], D. Waller[2] [1]*Department of Thoracic Surgery, Glenfield Hospital, Leicester/UNITED KINGDOM,* [2]*General Thoracic Surgery, Glenfield Hospital, Leicester/UNITED KINGDOM*

Objective: To evaluate the impact of routine pre-op PET-CT staging on incidence of resected N2 disease and subsequent outcome.

Methods: We compared patients in the 2 years prior to the introduction of staging PET-CT (2003-4, 'pre-PET') with patients following the introduction of routine PET-CT (2005-6, 'PET'). We explored the impact of PET-CT on resected N2 disease in a tertiary surgical referral unit.

Results: During the study period, 266 patients (156M : 110F, mean age 66 years) underwent anatomical lung cancer resection with systematic nodal dissection in a single 3-surgeon institution (110 pre-PET vs. 156 PET with no difference in patient demographic or pathological characteristics). The incidence of resected N2 disease reduced significantly by 54% with the introduction of routine PET-CT (20 (18%) vs 13 (8%), p=0.015). The overall median post-operative survival was similar between the two periods (38 months vs 34 months, p=0.71). Median survival of the subgroup of patients with resected N2 disease was also similar (34 months vs 20 months, p=0.90), even when adjusted for clinicopathological factors and adjuvant treatment (HR 0.839, 95% CI 0.23 – 3.04, p=0.79). The proportion of resected N2 which was single-station disease was similar in both groups (17 (90%) vs 10 (77%), p=0.37).

Conclusion: The introduction of routine PET-CT staging in potential surgical patients has significantly reduced the incidence of resected N2 disease. However, this was not accompanied by an improvement in overall post-operative survival, or in those with resected N2 disease. This may be explained by the relatively low incidence of resected N2 disease and a similar proportion of single-station N2 disease in both groups.

Disclosure: All authors have declared no conflicts of interest.

190PD

CONCURRENT CHEMORADIATION TREATMENT FOR INOPERABLE, NONMETASTASIC, UNFIT NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

F. Pons[1], E.S. Nadal[1], M. Plana[1], R. Palmero[1], J.M. Solé[2], I. Brao[1], R. Castany[1], S. Padrones[3], M.M. Arnaiz[4], F. Cardenal[1] [1]*Medical Oncology Department, Institut Català d'Oncologia, L'Hospitalet (Barcelona)/SPAIN,* [2]*Radiotherapic Oncology Department, Institut Oncològic del Vallès, Sabadell (Barcelona)/SPAIN,* [3]*Pneumology Department, Hospital de Bellvitge, L'Hospitalet (Barcelona)/SPAIN,* [4]*Radiotherapic Oncology Department, Institut Català d'Oncologia, L'Hospitalet (Barcelona)/SPAIN*

Background: There is no consensus treatment for inoperable, nonmetastatic NSCLC patients (pts) too vulnerable for standard concurrent chemoradiation. Concurrent carboplatin plus vinorelbine with thoracic radiotherapy (TRT) has proved to be safer than the sequential treatment with the same drug combination in a poor-risk patient population (Cardenal F; 2006, 31th ESMO Congress). We present the results in the routine clinical setting of a simple chemoradiation platform applied without the strict selection constraints of a clinical trial.

Patients and methods: From August 2006 to November 2009, 64 pts were treated with carboplatin AUC 2.5 plus vinorelbine 15mg/m2 days 1, 8, 22 and 28, concurrent with TRT: 70 Gy in 7 weeks with no elective lymph node irradiation. All pts were staged with FDG-18 PET/TC scan and were considered inoperable by a chest cancer board meeting. Pts were deemed suitable for high dose standard radiation, but unfit for investigational or routine chemoradiation protocols (based on SWOG 9019).

Results: Male/Female: 95%/5%, Median age 74 years (y) (range: 51-82). Older than 75 y: 34%. ECOG PS 0-1/2 70%/30%; current/former/never smokers 37.5%/60%/1.6%; squamous/undifferenciated/adenocarcinoma 69%/28%/3.1%; stage I-II/IIIA/IIIB: 14%/37%/48%. Median FEV1 1690 ml (range: 920-3660). Forty-eight percent of pts had a simplified comorbidity score (SCS), reported by Colinet >9. Seventy-three percent of pts received the four doses of both drugs. The median radiation dose was 70 Gy (range: 0-78). One patient developed grade 3 pneumonitis. Three pts (4.7%) died from respiratory failure (grade 5 pneumonitis the most likely diagnosis). Two pts (3%) developed grade 3 esophagitis. With a median follow-up for living pts of 10.6 months (mo), 36 pts have progressed and 23 pts have died. Median progression-free survival was 10.2 mo (95% CI: 7.7–12.6) and median survival was 20.2 mo (95% CI: 15.2–25.3).

Conclusions: This simple chemoradiation platform was safe and feasible in routine clinical practice. Survival outcomes were rather longer than those currently reported for poor-risk patient populations.

Disclosure: All authors have declared no conflicts of interest.

191PD

RADIOPROTECTION OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER BY AMIFOSTINE – HISTOPATHOLOGICAL FEATURES

J. Stejskal[1], M. Kubecová[2], D. Dvořáková[1], V. Ulrych[1], I. Kolářová[1], M. Kheck[3], J. Va´asek[1] [1]*Radiation Oncology, Regional Hospital Pardubice, Pardubice/CZECH REPUBLIC,* [2]*Radiation Oncology, University Hospital Prague, Praha/CZECH REPUBLIC,* [3]*Pathology, Regional Hospital Jihlava, Jihlava/CZECH REPUBLIC*

Purpose: Locally advanced non-small cell lung cancer (LA NSCLC) represents a disease with poor prognosis. Radiochemotherapy with dose escalation is an effective treatment for LA NSCLC. This management can be limited by acute and late toxicities, especially radiation pneumonitis (RP). Amifostine could reduce the incidence of induced acute and late toxicities.

Methods: Between 2000 and 2007, a total of 36 patients with LA NSCLC (IIIA, IIIB) were treated. All patients were treated with neoadjuvant chemotherapy (4 cycles) followed by concomitant RT-CT (2 cycles) plus amifostine – group A (n=18) and without amifostine – group B (n=18). Chemotherapy consisted of paclitaxel and cisplatin, both day 1, every 3 weeks. All patients were irradiated using 3D CRT. Lung tissue had been sampled from two different sites. The first sample came from the area of PTV 2 (A_{max}, B_{max}) while the second sample was taken from the intact lung outside the PTV 1 (A_{ref}, B_{ref}).

Results: Median 3D CRT dose was 67.4 Gy (63.8 - 72.8 Gy). Symptoms of RP grade 3/4 (CTC v 2.0) occurred in 4 pts in group A vs. 9 pts in group B. Histopatological examination of lung tissue showed major differences between groups A and B in terms of the thickening of the alveolocapilary space. Characteristic histopathological features were: proliferation and thickening of alveolocapillary septa, interstitial septal edema, intensive expressing of collagen (short, loop, fragmentation of fibrillated collagen) and nuclei of fibroblasts. Fibroproliferative changes (interstitial fibrosis, perivascular fibrosis, pulmonary emphysema) are late changes, as impact of acute toxicity. Median thickness of the alveolocapillary space was 8.6 μm (range 2.1-11.2) and 3.2 μm (range 0.9-4.2) for the A_{max} and A_{ref} samples compared to 49.5 μm (range 10.2-71.4) and 2.8 μm (range 1.1-3.8) for the B_{max} and B_{ref} samples, respectively. The difference between A_{max} and B_{max} samples was statistically significant (p=0.0001).

Conclusions: The incidence of radiation pneumonitis was lower for patients receiving amifostine than for patients receiving radiochemotherapy alone. Significant differences of the thickness of alveolocapillary space may represent the effect of amifostine as a radioprotector.
Disclosure: All authors have declared no conflicts of interest.

192P
THE EFFECT OF P-AKT AT THE PROGNOSIS OF NON SMALL CELL LUNG CANCER

S. Karabulut Gul[1], A. Fatih Oruc[2], A. Mayadagli[2], A. Ozkan[2], M. Kocak[2]
[1]Radiation Oncology, Selcuk University, Konya/TURKEY, [2]Radiation Oncology, Kartal Education and Research Hospital, Istanbul/TURKEY

Akt, known as protein kinase B (PKB) is an intracellular signal transduction protein which was activated by growth hormones. Akt arranges some cellular functions such as cellular life continuation, cellular growth and differantiation. PKB/Akt became activated in some cancer types but its role in lung cancer evolution and progression has not been determined yet. The purpose of this study is to determine the prognostic value of Akt in lung cancer. Immunohistochemical expression of p-akt was observed at light microscope. Cases were evaluated by the strength and diffusiveness of the tumour cell's nuclear and cytoplasmic staining. For the diffusiveness degree, nuclear and cytoplasmic staining ratio of the staining tumour cells were considered. According to the intension degree, nuclear and cytoplasmic staining were considered as light, median and potent and cases without staining were considered as no staining. Between January 2003 and July 2008, 32 cases of non-small cell lung cancer patient samples were observed before therapy in our hospital. Samples staining characteristics were evaluated according age, sex, stage (T and N), response to therapy, histologyical type, and tumour size. In our study, no correlation was observed between staining and stage, nodal condition, and T stage. The relation between staining and histopathological condition, tumour size, and response to therapy was evaluable statistically. Squamous cell lung cancer histology ($p=0.03$), and tumours over 5cm ($p=0.03$) showed more staining and such patients expressed less complete response ($p=0.049$) and survival ($p=0.3$). Correlation shows direct proportion between the activation of Akt and squamous cell carcinoma histology, tumour size and therapy response in lung cancer patients. Activation of Akt in lung cancer patients affects prognosis negatively. We need further studies to show the relation between Akt activation and therapy response, and survival in lung cancer patients.
Disclosure: All authors have declared no conflicts of interest.

193P
TECHNICAL ASPECTS OF THE SURGERY OF T4 LUNG CARCINOMAS

J. Klein[1], C. Neoral[1], M. Szkorupa[1], T. Bohanes[1], T. Janaskova[2], D. Petras[3]
[1]The 1st Department of Surgery, University Hospital Olomouc, Czech Republic, Olomouc/CZECH REPUBLIC, [2]Department of Pneumology, Hospital Ostrava-V¡tkovice, Ostrava/CZECH REPUBLIC, [3]Department of Surgery, KNTB Zlin, Zlin/CZECH REPUBLIC

Objectives: Therapeutic strategy in advanced stages of lung carcinomas remains controversial. T4 lung carcinomas are a heterogeneous group of locally advanced tumours. In the past, resections of T4 tumours were not indicated due to high perioperative mortality, morbidity and poor 5-year survival rates. Recently however, a few long-term survivors after extended lung resections without any evidence of recurrence of the cancer have been reported. Carinal resection, superior cava vein resection, pericardium and left-atrial resection have become standard operations in lung cancer surgery with 5-year survival rates of about 10–25%, depending on the nodal status and completeness of the resection. Invasion of adjacent structures, however, often makes complete resection of T4 tumours impossible, but induction treatment can increase the number of successfully operated patients.
Methods: From 1997 to 2007, 37 patients underwent resection of primary non-small cell non- satellite T4 cancer. Resection was complete in 29 patients (78%). Lymph node involvement was stated as negative in 9 cases, whereas lymph node involvement was found in 28 cases. Actual survival time was calculated in both groups, and own technique of the resection of the superior cava vein or aorta is described.
Results: The 5-year survival was 27,0 % for patients with complete resection, and 2,7% for incomplete resections ($P = 0,05$). Overall 30-day mortality was 10,8%. ($P = 0,05$).
Conclusion: Extended resections of T4 carcinomas can be undertaken in highly selected patients with low morbidity and mortality. Despite described results of the procedure, the long-term results of such extensive surgery still remain unclear. Nevertheless, the final success of any oncology therapy has not as yet been achievable without precise local (surgical) control. This study was supported by grant IGA MZCR NS 10285.
Disclosure: All authors have declared no conflicts of interest.

194P
EARLY-ONSET CHEMOTHERAPY-INDUCED NEUTROPENIA DURING PERIOPERATIVE CHEMOTHERAPY IS ASSOCIATED WITH A LONG DISEASE FREE SURVIVAL IN PATIENTS WITH COMPLETELY RESECTED NON-SMALL-CELL LUNG CANCER

S.H. Jang[1], Y.I. Hwang[1], J.C. Lee[2], Y.Y. Lee[2], C. Choi[3], J. Chung[4], H.S. Chung[5]
[1]Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Anyang/KOREA, [2]Department of Internal Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological & Medical Science, Seoul/KOREA, [3]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, Seoul/KOREA, [4]Pathology, Seoul National University Bundang Hospital, Sungnam/KOREA, [5]Internal Medicine, Boramae Hospital, Seoul/KOREA

Background: Neutropenia during adjuvant chemotherapy was a significant predictor of disease free survival (DFS) in breast cancer. The purpose of this study was to examine the association between neutropenia during perioperative chemotherapy and prognosis in patients with completely resected non-small-cell lung cancer (NSCLC).
Methods: This is a retrospective analysis. Assessment of early onset neutropenia was based on the lowest recorded absolute neutrophil count (ANC) in cycle 1 or 2, and neutropenia was divided into two groups, grade 0-1 ($ANC \geq 1{,}500/mm^3$) vs. grade 2-4 ($ANC < 1{,}500/mm^3$).
Results: Seventy patients were treated with platinum based doublet chemotherapy (vinorebine, gemcitabine, paclitaxel, docetaxel or etoposide) in the neoadjuvant or adjuvant setting (median 4 cycles, range 2-9). A long DFS was associated with grade 2-4 neutropenia and early pathologic stage (stage $\leq$ IIB) ($P=0.085$ and $P=0.037$, respectively). The median DFS were 20.0 vs. 48.7 months in grade 0-1 vs. grade 2-4 neutropenia group. Overall survival (OS) was associated with neutropenia, performance and disease progression. Vinorelbine or gemcitabine containing regimens included drug infusion schedule on day 8, so they potentially had a lot of chance to detect lower ANC than the other regimens. Really, a total of 45.8% of the patients receiving vinorelbine or gemcitabine containing regimen fall into grade 2-4 neutropenia group compared with only 9.1% in the other regimens. If the analysis was confined to the patients receiving these regimens, grade 2-4 neutropenia was more clearly associated with better DFS (17.5 months vs. 48.7 months, $P=0.022$) and OS (30.6 months vs. 67.8 months, $p=0.017$). The adjusted HR for disease progression in grade 2-4 neutropenia group

compared with grade 0-1 neutropenia group was 0.415 (95% CI 0.191-0.903; P=0.027) in multivariate Cox-regression analysis. However, the adjusted HR for death was not significant (P=0.168).
Conclusion: Early onset neutropenia during perioperative chemotherapy was associated with a long disease free survival in patients with completely resected non-small cell lung cancer.
Disclosure: All authors have declared no conflicts of interest.

195P

IMRT VERSUS STANDARD CONFORMAL 3D RADIOTHERAPY FOR CENTRALLY LOCATED ADVANCED NON-SMALL CELL LUNG CANCER

A. Kowalczyk[1], R. Dziadziuszko[1], P. Szewczyk[2], E. Szutowicz-Zielinska[1], K. Konopa[1], J. Jassem[3] *[1]Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND, [2]Oncology and Radiotherapy Department, Medical University of Gdansk, Gdansk/POLAND, [3]Oncology and Radiotherapy, Medical University, Gdansk/POLAND*

Objective: The experience with intensity-modulated radiotherapy (IMRT) in lung cancer is very limited. We compared lung doses using IMRT and standard conformal treatment plans for 3D radiotherapy (3D CRT) for centrally located advanced non-small cell lung cancer (NSCLC).
Methods: Study group included four consecutive patients with locally advanced NSCLC referred for radical radiotherapy. Gross tumor volume (GTV), clinical treatment volume (CTV), planning target volume (PTV) and organs at risk (lungs, spinal cord, heart) were contoured on axial CT slices. GTV included lung tumor and involved mediastinal lymph nodes. The PTV dose was 66-72 Gy in 30-36 daily fractions. 3D CRT included 3 oblique fields technique using 6-12 MV photons and multileaf collimator (MLC) to minimize the dose to the critical organs. Six or seven-field techniques using 6 MV photons were used for IMRT. The dose-volume histograms (DVHs) for 3D CRT and IMRT treatment plans were compared.
Results: The mean lung dose (MLD), volume of lungs receiving ≥20 Gy (V20 Gy) and ≥5 Gy (V5 Gy) were compared. With IMRT MLD and V20 Gy for lungs were reduced by an average of 4% and 3.5% compared to 3D, respectively, whereas V5 Gy was higher by an average of 10%.
Conclusions: IMRT allowed for significant reduction in MLD and the V20 Gy at the expense of larger lung volume receiving smaller doses. The reduction in high dose volume of normal tissues may potentially translate into reduction in acute and late treatment-related toxicity, particularly in patients with borderline planning DVH parameters for definitive radiotherapy.
Disclosure: All authors have declared no conflicts of interest.

196P

EXPERIENCE IN THE TREATMENT OF UNRESECTABLE STAGE IIIA AND IIIB NON SMALL CELL LUNG CANCER (NSCLC) WITH COMBINED CHEMOTHERAPY AND RADIOTHERAPY IN A SINGLE INSTITUTION

M. Majem[1], C. Pallarés[2], N. Farre[1], N. Sala[1], G. Gomez de Segura[1], I. Gich[1], A. Barnadas[1] *[1]Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona/SPAIN, [2]Oncology Service, Hospital Sant Pau, Barcelona/SPAIN*

Background: The best combination of chemotherapy (CT) and radiotherapy (RT) for the treatment of unresectable stage III NSCLC remains unclear. There are no definitive data on the best schedule, drugs and dosage. We have prospectively recorded patients with unresectable NSCLC treated in our institution. In this study we describe our clinical experience in the treatment of unresectable stage III NSCLC.
Methods: We have prospectively collected data from 165 patients: demographic data, clinical characteristics, as well as the treatment received, the toxicity presented and the best response. Additionally, we have analyzed the prognostic value of different clinical characteristics according to the Cox regression model. A survival analysis using the Kaplan-Meier method has also been performed.
Results: Median age 65 (35-84); Sex: male 90%, female 10%. Smoking status: 49% active smokers or former smokers. Karnofsky Index: 90-100 42%, 80 30%, 70 21%. Stage: IIIA 13%, IIIB 87% Histology: Squamous cell carcinoma 50%, large cell carcinoma 36%, adenocarcinoma 14%. Combination of CT-RT: sequential 74%, concurrent 7%; 19% of patients did not receive RT. Type of CT in combined treatment: platinum doublet 85% (with gemcitabine 75%), non-platinum schedule 15%. The concurrent treatment was always with a platinum compound and a taxane. Total dose of RT: was > 60 Gy in 46%. Response to induction CT: Complete 1%, Partial 42%, Stable 39%, Progression: 18%. Final Response: Complete 25%, partial 36%, Stable 31%, Progression 8%. Most frequent toxicity to CT: G2 asthenia 32%, G1 haematological toxicity 32%. Late toxicity to RT at 6 m: G3-4 pneumonitis 10%-3%; late toxicity to RT at 12 m: G3-4 pulmonary fibrosis 8%-1%. The median overall survival and progression-free survival were 16.2m and 13.2m, respectively. The overall survival at 5 years was 12.5%.
Conclusions: the response rate and survival rate of unselected population with unresectable stage III NSCLC in our institution are comparable to the results obtained in clinical trials. The observed toxicity is acceptable and manageable.
Disclosure: All authors have declared no conflicts of interest.

197P

THE ROLE OF CHEMOTHERAPY IN DOWNSTAGING OF NON-RESECTABLE NSCLC (IIIA AND IIIB) INTO RESECTABLE NSCLC

V. Radosavljevic, M. Obradovic, *V. Milovanovic Pulmology, KBC "Bezanijska Kosa", Belgrade/SERBIA AND MONTENEGRO*

Chemotherapy is one of the most important therapy modality in the treatment of NSCLC. The purpose of the study was to examine the influence of chemotherapy on downstaging of non-resectable NSCLC (stages IIIa and IIIb) into resectable.
Material and method: The group consisted of 40 patients, (31 male = 77,5%, 9 female = 22,5%), aged between 44–64, ECOG rate: 0–22 patients (55%); 1–18 patients (45%); histology type: carcinoma planocellulare = 21 patients (52,5%), adenocarcinoma = 17 patients (42,5 %), large cell carcinoma = 2 patients (5,0%); clinical stage: IIIA = 18 patients (45%), IIIB = 22 (55%); side: left = 12 patients (30%), right 28 (70%); localization: periferial 26 patients (65%), central 14 (35%). There were two chemotherapy protocols applied: first group of 20 patients, MIC (Holoxan, Mitomycin, Cisplatin); the second group also with 20 patients, PE – cisplatin-etoposide in standard dosages. Standard statistical methods such as Hi2 test and Student's T test were used.
Results: The therapy response was the following: partial response = 17 patients (42,5%), stable disease = 16 patients (40%), complete response = 1 patients (2,5%), progressive disease = 6 patients (15,0%) Twelve of the patients (30%) were successfully operated, and 28 patients (70%) were not.
Conclusion: Chemotherapy as the only therapy modality has a significant effect on downstaging of non-resectable NSCLC (IIIA, IIIB) to resectable stages.
Disclosure: All authors have declared no conflicts of interest.

198P

PRELIMINARY REPORT OF A PILOT STUDY OF CONTINUOUS ACCELERATED IRRADIATION IN PATIENTS WITH STAGE III A OR III B NON-SMALL CELL LUNG CANCER AFTER INDUCTION CHEMOTHERAPY

K. Galwas-Kliber[1], S. Blamek[1], W. Bal[2], A. Zajusz[3], R. Suwinski[4] *[1]Department of Radiation Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice/POLAND, [2]Department of Clinical Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice/POLAND, [3]Department of Radiotherapy, Center of Oncology Maria Sklodowska-Curie Memorial Institute Branch Gliwice, Gliwice/POLAND, [4]Radiotherapy Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND*

Aim: The aim of this report is to evaluate the acute normal tissue reactions in patients with stage III A or III B non-small cell lung cancer treated with continuous accelerated irradiation (CAIR) after induction chemotherapy.

Material: 26 patients (21 men), age 43-72 (mean 58.5) were enrolled into the study. Nineteen patients had squamous cell carcionoma, 2 – adenocarcinoma and 5 non-small cell cancer of unspecified subtype.

Methods: The patients received 2-4 cycles of induction chemotherapy. After chemotherapy they were irradiated with 1.8 Gy per fraction to dose of 43.2 Gy from Monday to Friday and with 2 Gy per fraction during weekends to total dose of 67.2-71.2 Gy. Acute radiation reactions in esophagus, skin, lungs and heart were assessed weekly during treatment, and monthly during the follow-up. Blood cell count was analysed during and after treatment.

Results: 19 patients were irradiated according to study protocol. Four patients refused participation in the study, two had distant metastases on PET and were irradiated with palliative intent, one was assigned to surgery after an internal audit. No grade 3 or 4 acute radiation effects occurred, in one patient esophageal grade 2 toxicity since 3rd week of irradiation was recorded, in the remainder mild (grade 1) skin, lung and esophageal toxicities were noted. Statistical analysis did not reveal significant alterations in blood cell count during treatment.

Conclusions: The proposed protocol of continuous accelerated irradiation in patients with advanced non-small cell lung cancer after induction chemotherapy is well tolerated, suggesting its feasibility for phase III study with respect to acute tolerance.

Disclosure: All authors have declared no conflicts of interest.

199P

CARDIAC TOXICITY AFTER DEFINITIVE RADIOTHERAPY OF LOCALLY ADVANCED NSCLC

T. Schytte[1], O. Hansen[1], T. Stolberg-Rohr[2], C. Brink[2] *[1]Oncology, Odense Universityhospital, Odense C/DENMARK, [2]Laboratory of Radiation Physics, Odense Universityhospital, Odense C/DENMARK*

Background: Lung and oesophageal toxicity have been regarded as main toxicity in definitive radiotherapy (RT) of non-small cell lung cancer (NSCLC), whereas cardiac toxicity has not been offered much concern. This is probably due to the poor prognosis for patients with unresectable NSCLC. In this study we report the heart toxicities in locally-regionally advanced NSCLC (LA-NSCLC) patients (pts) treated with RT in our centre.

Methods and material: From 01.01.1995-30.11.2007, 287 pts with LA-NSCLC (stage IIB-IIIB) were treated with RT at our centre with planned dose 60-66 Gy. All RT was applied as 3D RT in 2 Gy/F without elective nodal irradiation. Cardiac toxicity is defined as myocardial infarction (MI), exudative pericarditis (ED), cardiac insufficiency (CI), pulmonary embolism (PE), found dead with unknown cause, non specific cardiac disease (CD), supra- or ventricular arrhythmia (SA, VA). The cardiac events (CE) were collected from patient files. All patients were followed to death. Median follow-up was 86 month, with 24 month as minimum.

Results: 38 pts had a CE: 7 MI, 3 EP, 5 CI, 4 PE, 2 found dead, 3 CD, 13 SA and 1 VA. Median survival was 17.2 month and overall survival for 1, 2 and 5 year was 64%, 35% and 14%, respectively. In a Cox regression analyses of time to CE, age > 65 year, + induction chemotherapy, smoking, high mean dose to left + right ventricles or whole heart was not a statistically significant factor, whereas low FEV-1, large GTV, low Hb, poor PS, high V20 to lunge, and gender did.

Discussion: We did not find a correlation between high mean dose to left + right ventricles or whole heart and having a CE. Having a CE was not related to worsen survival.

Factors in Model	Relative Hazard Ratio (95% CI)	p-Value
FEV-1 (	1.30 (1.00–1.68)	0.046
GTV (>150 ml)	2.02 (1.51–2.71)	<0.0001
Hb (	1.44 (1.12–1.86)	0.0046
Mean dose to ventricles (>20 Gy)	1.23 (0.92–1.67)	0.17
PS (>1)	1.64 (1.11–2.42)	0.014
Gender (male)	1.37 (1.06–1.77)	0.016
V20 (>35%)	1.85 (1.43–2.40)	<0.0001

Disclosure: All authors have declared no conflicts of interest.

200P

AMIFOSTINE AS A RADIOPROTECTOR IN THE MANAGEMENT OF ADVANCED NON-SMALL CELL LUNG CANCER - HISTOPATHOLOGICAL FEATURES

J. Stejskal[1], M. Kubecová[2], D. Dvořáková[3], V. Ulrych[1], I. Kolářová[1], M. Kheck[3], J. Vaňásek[1] *[1]Radiation Oncology, Regional Hospital Pardubice, Pardubice/CZECH REPUBLIC, [2]Radiation Oncology, University Hospital Prague, Praha/CZECH REPUBLIC, [3]Pathology, Regional Hospital Jihlava, Jihlava/CZECH REPUBLIC*

Purpose: Locally advanced non-small cell lung cancer (LA-NSCLC) represents a disease with poor prognosis. Radiochemotherapy (RT-CT) is an effective treatment for LA-NSCLC. This management can be limited by acute and late toxicities, especially acute esophagitis (AE) and radiation pneumonitis (RP). Amifostine could reduce the incidence of induced acute and late toxicities.

Methods: Between 2000 and 2007, a total of 36 patients with locally advanced NSCLC stage IIIA and IIIB were treated. All patients were randomized to treatment with neoadjuvant chemotherapy (4 cycles) followed by concomitant RT-CT (2 cycles) plus amifostine i.v. infusion 500 mg daily – group A (n=18) and without amifostine – group B (n=18). Chemotherapy consisted of paclitaxel 175 mg/m2 and cisplatin 75 mg/m2, i.v. infusion, both day 1, every 3 weeks. All patients were treated using 3D conformal radiotherapy (3D-CRT). All patients were assessed at each follow-up visit for signs and symptoms of AE and RP according to the CTC-version 2.0. Lung tissue had been sampled from two different sites. In both patient groups, the first sample came from the area of PTV 2 (Amax, Bmax) while the second sample was taken from the intact lung outside the PTV 1 (Aref, Bref). Hematoxylin and eosin-stained slides were reviewed with light microscopy.

Results: Median 3D-CRT dose was 67.4 Gy (63.8 - 72.8 Gy). Symptoms of AE grade 3/4 and RP grade 3/4 occurred in 3 and 4 patients in group A vs. 8 and 9 patients in group B. Differences were statistically significant (p=0.001). Median thickness of the alveolocapillary space was 8.6 μm

(range 2.1-11.2) and 3.2 μm (range 0.9-4.2) for the Amax and Aref samples compared to 49.5 μm (range 10.2-71.4) and 2.8 μm (range 1.1-3.8) for the Bmax and B ref samples, respectively. The difference between Amax and Bmax samples was statistically significant (p=0.0001).
Conclusions: The incidence of esophagitis and pneumonitis was lower for patients receiving amifostine than for patients receiving radiochemotherapy alone. Significant differences of the thickness of alveolocapillary space may represent the effect of amifostine as a radioprotector. Amifostine reduces the incidence of pneumonitis, lung fibrosis, and esophagitis.
Disclosure: All authors have declared no conflicts of interest.

ADVANCED NSCLC

201O

EGFR MUTATION TESTING IN NON-SMALL-CELL LUNG CANCER (NSCLC): CLINICAL RECOMMENDATIONS FROM THE EUROPEAN EGFR WORKSHOP GROUP

R. Pirker[1], F.J.F. Herth[2], K. Kerr[3], M. Filipits[4], D. Grunenwald[5], H. Popper[6], R. Rosell[7], E. Smit[8], F. Cappuzzo[9], R.A. Stahel[10] *[1]Department of Internal Medicine I, Medical University of Vienna, Wien/AUSTRIA, [2]Department of Internal Medicine, Pneumology and Critical Care Medicine, University of Heidelberg, Heidelberg/GERMANY, [3]Department of Pathology, Aberdeen Royal Infirmary, Aberdeen/UNITED KINGDOM, [4]Department of Medicine I, Medical University Vienna, Vienna/AUSTRIA, [5]Thoracic Surgery, University of Paris Hôpital Tenon, Paris/FRANCE, [6]Laboratories for Molecular Cytogenetics, Environmental and Pulmonary Pathology, Institute of Pathology, Medical University of Graz, Graz/AUSTRIA, [7]Medical Oncology Service, Catalan Institute of Oncology, Badalona/SPAIN, [8]Department of Pulmonary Diseases, Vrije Universiteit Medical Center, Amsterdam/NETHERLANDS, [9]Oncology, Livorno Hospital, Livorno/ITALY, [10]Klinik Und Poliklinik für Onkologie, Universitätsspital, Zürich/SWITZERLAND*

Purpose: The epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) gefitinib has received European approval for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of the EGFR-TKI. ASCO guidelines recommend EGFR mutation testing in NSCLC patients, whereas this procedure is less well established in European clinical practice.
Methods: Recommendations to facilitate the implementation of standardized EGFR mutation testing in clinical practice were developed at an IASLC-ETOP European multidisciplinary workshop of biologists, pathologists, surgeons, chest physicians, and medical oncologists. All aspects of the EGFR mutation testing process were discussed, such as biopsy and sampling, pathology and mutation testing.
Results: The decision to request EGFR mutation testing should be made by the treating physician. Results should be available within 7 working days. All patients with NSCLC may eventually be tested, but exceptions may be made when likelihood of mutation is low. No consensus agreement on pre-screening algorithms was achieved. Standardization of tumor sample handling is required. Numerous methods can be used to detect EGFR mutations including direct sequencing, Amplification Refractory Mutation System (ARMS), length analysis, and denaturing high performance liquid chromatography (dHPLC). Some tests only seek the most common activating mutations, others can detect all mutations. Ideally pathologists should report tumor histology and mutation status concurrently. Sample size/quality, tumor nuclei percentage, methodology used, exons tested, and mutation present/absent should be included in the final report. Close collaboration and co-ordination between the different specialists involved is considered to be essential for the success of EGFR mutation testing. Reference laboratories may also be helpful.
Conclusions: These recommendations from a multidisciplinary European workshop will help to optimize routine EGFR mutation testing in Europe.
Disclosure: R. Pirker: R Pirker has acted as a consultant or in an advisory role for, and has received honoraria from, AstraZeneca, Merck Serono, Roche, and Lilly. K. Kerr: KM Kerr has acted as a consultant or in an advisory role for AstraZeneca, Roche-Genentech-OSI, Lilly, and BI, and has received honoraria from AstraZeneca. M. Filipits: M Filipits has received honoraria from AstraZeneca, Merck and Co., and Lilly. H. Popper: HH Popper has acted as a consultant or in an advisory role for AstraZeneca and Lilly, and has received honoraria from AstraZeneca, Lilly, and Menarini. F. Cappuzzo: F Cappuzzo has acted as a consultant or in an advisory role for AstraZeneca, Boehringer Ingelheim, and Roche, and has received honoraria from AstraZeneca, Boehringer Ingelheim, Roche, and Lilly. R.A. Stahel: RA Stahel has acted as a consultant or in an advisory role for, and has received honoraria from, AstraZeneca and Roche. All other authors have declared no conflicts of interest.

202O

DIFFERENT KRAS MUTATIONS MAY PREDICT A DIFFERENT IMPACT ON DRUGS ACTIVITY IN LUNG (NSCLC) CANCER

M.C. Garassino[1], O. Martelli[2], M. Broggini[3], F. Bianchi[4], S. Veronese[5], I. Floriani[6], S. Marsoni[7], M. Marabese[8], G. Farina[9], A. Scanni[1] *[1]Oncology, Fatebenefratelli and Ophtalmic Hospital, Milano/ITALY, [2]Oncology, San Giovanni e Addolorata, Rome/ITALY, [3]Oncology, Istituto "Mario Negri", Milano/ITALY, [4]Oncology, Fatebenefratelli and Ophtalmic Hospital, Milan/ITALY, [5]Pathology, Ospedale Ca'granda Niguarda, Milan/ITALY, [6]Istituto Di Ricerche Farmacologiche "Mario Negri", Laboratorio di Clinical Trials, Milano/ITALY, [7]Oncology, SENDO Tech Srl, Milan/ITALY, [8]Oncology, Istituto" Mario Negri", Milan/ITALY, [9]Oncology, Ospedale Fatebenefratelli e Oftalmico, Milan/ITALY*

Background: The RAS/RAF/MEK/ERK pathway is a therapeutic target in both colorectal (CRC) and NSCLC cancer, but while mutated KRAS is a negative prognostic marker and a negative predictor for anti EGFR therapy in CRC, its role in lung cancer is quite ambiguous. KRAS is a pool of mutations mostly occurring in codons 12 and 13 but differing for the replaced basis and for the aminoacid substitution. In CRC the most expressed KRAS mutation is G12D. We hypothesized a different KRAS mutational status in NSCLC patients, bearing a potential different profile in the tumour response to treatment which we tested in vitro.
Methods: TAILOR (NCT00637910) is a multicenter Italian phase III trial powered to evaluate a differential effect of all biological markers in selecting patients for erlotinib and docetaxel as 2nd line. Consecutive patients are registered and molecularly profiled centrally. KRAS and EGFR mutations were detected by direct sequencing. Therefore, we identified all KRAS mutations types. The EGFR-wt NCI-H1299 lung cell line was transfected with expression plasmids encoding all different identified KRAS mutations and tested in vitro for the activity of cisplatin, taxanes, erlotinib and pemetrexed.
Results: To date, KRAS and EGFR mutational status is available on 161 of 256 patients registered into the trial. We found six types of KRAS mutation in 35 patients (20%): G12C (45.7%) G12D (20%) G12V (20%) G12A (5.7%) G13C (5.7%) G13D (2.8%). Preliminary data, in the NCI-H1299 transfected cell lines, indicate that specific KRAS mutations are associated to different sensitivity or resistance drug profiles.
Conclusions: Final results will be presented at the congress and clearly suggest that the specific mutational status of KRAS gene in NSCLC seems to differ from that reported for CRC. This clinical observation, with in vitro results suggesting different patterns of sensitivity/resistance to EGFR inhibition in transfected cell lines, might explain the ambiguous role of KRAS as a predictor to anti EGFR therapy in NSCLC. Final results of the randomized TAILOR study will definetely allow to verify this suggestive hypothesis.
Disclosure: All authors have declared no conflicts of interest.

203O

SERUM PROTEOMIC PREDICTION OF OUTCOMES IN ADVANCED NSCLC PATIENTS TREATED WITH ERLOTINIB/PLACEBO IN THE NCIC CLINICAL TRIALS GROUP BR.21 TRIAL

D.P. Carbone[1], L. Seymour[2], K. Ding[3], H. Roder[4], M. Tsao[5], F.A. Shepherd[6]
[1]Medicine and Cancer Biology, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville/USA, [2]Ncic Ctg, Queens University, Toronto/CANADA, [3]Community Health & Epidemiology, Queen's University, Ontario/CANADA, [4]Chief Scientific Officer, Biodesix, Inc., Broomfield/USA, [5]Oncology, Princess Margaret Hospital, Toronto/CANADA, [6]Medical Oncology, Princess Margaret Hospital, Toronto/CANADA

Background: BR21 demonstrated a survival benefit from erlotinib in previously treated patients with NSCLC. Serum proteomic profiling by MALDI MS has demonstrated the ability to predict PFS and OS outcomes in patients treated with EGFR-TKIs. These profiles, proteomic good and proteomic poor, have been found to be specific for EGFR-TKIs and not for chemotherapy treatments. The purpose of this study is to validate the ability of proteomic profiling to predict outcomes to EGFR-TKI treatment in samples derived from BR.21, a phase III randomized trial of erlotinib vs. placebo in second- or third-line advanced NSCLC.

Methods: Blinded baseline plasma samples were available from 441 patients from the BR.21 study of erlotinib 150 mg/day vs. placebo. Sample MALDI MS analysis was run in triplicate and analyzed by Biodesix, Inc. Colorado in their CLIA-approved facility. A clinical label (good, poor, undefined) together with spectral characteristics of the eight peaks in the proteomic classifier were recorded.

Results: Proteomic results were available from 441 patients 266 (60.3%) good proteomic profile, 170 (38.5%) poor profile and only 5 (1.1%) indeterminate. Analyses of response rates, overall and progression-free survival will be performed and correlated with other known prognostic factors, treatment arm (erlotinib or placebo) and signature. In addition, for the subset of patients with EGFR and KRAS biomarker data available, correlations will be made with proteomic profile and outcome. Final analysis will be available by the time of the meeting.

Disclosure: D.P. Carbone: Genentech advisory board, research support, Biodesix advisory board; H. Roder: Employed by Biodesix as Chief Scientific Officer; F.A. Shepherd: Consulting, Genentech. All other authors have declared no conflicts of interest.

204O

SURVIVAL BENEFIT WITH ERLOTINIB MAINTENANCE THERAPY RELATIVE TO PRIOR CHEMOTHERAPEUTIC RESPONSE: A SUBANALYSIS OF THE PHASE III SATURN STUDY IN NSCLC

B. Coudert[1], T. Ciuleanu[2], K. Park[3], Y. Wu[4], G. Giaccone[5], F. Cappuzzo[6]
[1]Medical Oncology, Centre Georges François Leclerc, Dijon/FRANCE, [2]Oncology, Institutul Oncologic Prof Dr I. Chiricuta, Cluj-Napoca/ROMANIA, [3]Division of Hematology/Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul/KOREA, [4]Department of Lung Cancer, Cancer Center & Lung Cancer Research Institute, Guangzhou/CHINA, [5]Chief Medical Oncology Branch, CCR, National Cancer Institute, NIH, Bethesda/USA, [6]Oncology, Livorno Hospital, Livorno/ITALY

Background: The phase III SATURN trial investigating erlotinib maintenance therapy vs placebo met its endpoints of improved progression-free survival (PFS) and overall survival (OS) with clinical and statistical significance. Numerous subgroup analyses were conducted to identify patients with particularly large clinical benefit. We present the trial outcomes according to response to initial chemotherapy: complete or partial response (CR/PR) vs stable disease (SD).

Methods: Patients with neither progression nor unacceptable toxicity following 4 cycles of platinum-based chemotherapy (CT) were randomised to receive either erlotinib 150mg/day or placebo until progression or unacceptable toxicity. Co-primary endpoints were PFS in all patients and PFS in EGFR immunohistochemistry-positive (IHC+) disease. Secondary endpoints included OS, response, safety and quality of life.

Results: 889 patients with CR, PR or SD after first-line CT received erlotinib (n=438) or placebo (n=451). PFS was significantly prolonged in patients with SD after first-line CT (HR=0.68 [0.56–0.83]; p<0.0001) and in those with CR/PR after first-line CT (HR=0.74 [0.60–0.92]; log-rank p=0.0059). However, OS was significantly prolonged only in those patients who had SD (HR=0.72 [0.59–0.89]; p=0.0019 vs HR=0.94 [0.74–1.20]; p=0.6181 in those with CR/PR). OS results for the EGFR wild-type population were similar to the overall population: HR=0.65 [0.48–0.87]; p=0.0041 for SD vs HR=0.97 [0.68–1.38]; p=0.8544 for CR/PR. Similar outcomes were seen in non-squamous (HR= 0.76 [0.59–1.00]; p=0.0457 for SD vs HR=0.85 [0.62–1.16]; p=0.3031 for CR/PR) and squamous-cell carcinoma (HR=0.67 [0.48–0.92]; p=0.0116 for SD vs HR=1.07 [0.73–1.56]; p=0.7309 for CR/PR).

Conclusions: Erlotinib maintenance therapy can increase PFS in all patients with SD or CR/PR after first-line platinum-based CT. Patients with SD gained a particularly large survival benefit. We hypothesise that differences in the proliferative capacities of the tumours may explain this difference. These results may help physicians to identify patients most likely to benefit from erlotinib maintenance therapy.

Disclosure: B. Coudert: I have financial interests to declare. Advisory boards for: Laboratoire Astra Zeneca Laboratoire LILLY Laboratoire ROCHE Laboratoire sanofi aventis Laboratoire Shering Plough K. Park: I have financial intersts to declare. I have been involved in Advisory Boards for: Pfizer, Roche, AstraZeneca, Eli Lilly, Merck Sereno; F. Cappuzzo: I have financial interests to declare. I have taken part in Advisory Boards for: Roche, Lilly, Boeringer, AstraZeneca, Glaxo, BMS. All other authors have declared no conflicts of interest.

205O

QUALITY OF LIFE (QOL) IN A RANDOMIZED PHASE III FIRST-LINE STUDY OF GEFITINIB (G) VS CARBOPLATIN/PACLITAXEL (CP) IN CLINICALLY SELECTED ASIAN PATIENTS (PTS) WITH ADVANCED NSCLC (IPASS)

S. Thongprasert[1], E. Duffield[2], Y. Wu[3], C. Yang[4], N. Saijo[5], D.T. Chu[6], V. Chan[7], T. Mok[8], P. Magill[9], M. Fukuoka[10]
[1]Medical Oncology Unit, Department of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai/THAILAND, [2]Research, AstraZeneca, Macclesfield/UNITED KINGDOM, [3]Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou/CHINA, [4]Department of Oncology, National Taiwan University Hospital, Taipei/TAIWAN, [5]Department of Medical Oncology, National Cancer Center Hospital East, Chiba/JAPAN, [6]Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing/CHINA, [7]Medical Oncology Section, Veteran's Memorial Medical Centre, Quezon City/PHILIPPINES, [8]Department of Clinical Oncology, The Chinese University of Hong Kong, Shatin, Hong Kong/CHINA, [9]AstraZeneca, Macclesfield/UNITED KINGDOM, [10]Department of Medical Oncology, Kinki Universty School of Medicine, Osaka/JAPAN

Purpose: QoL is important for cancer pts. Evaluation of symptom improvement and QoL were pre-planned secondary objectives for the overall popu-

lation and post-hoc analyses for EGFR mutation positive/negative (M+/-) populations in the IPASS study.

Methods: QoL was measured by the FACT-L questionnaire (total score, trial outcome index [TOI]) and, symptom improvement (SI) by the lung cancer subscale (LCS) of the FACT-L. Improvements were defined as increases from baseline of ≥6 (total FACT-L and TOI) or ≥2 (LCS) points maintained for ≥21 days. Treatments were compared by logistic regression, and improvement rates calculated as the percentage of pts with an overall improved response. Time to worsening (FACT-L, TOI, LCS; supplementary evaluation) was the interval from randomization to worsening.

Results: QoL was evaluable in 1151 (n= 590 [G]; n=561 [CP]) pts; compliance rates were 93.6% (G) and 85.3% (CP) for FACT-L (with similar compliance in M+/M-/M unknown subgroups). Significantly more pts receiving G than CP experienced total score and TOI improvements; LCS improvement was similar for both treatments. Significantly more EGFR M+ pts experienced improvements in total score, TOI and LCS with G vs CP; results significantly favoured CP for EGFR M- pts. In pts with tumours of unknown M status, QoL improvements were similar to the overall population. Time to worsening for FACT-L was longer with G vs CP (median 8.3 vs 2.5 months) overall and for EGFR M+ pts (15.6 vs 3.0 months). Results for G were similar to CP in EGFR M- patients (median 1.4 months for both arms).

Conclusions: Clinically important improvements in QoL were observed more frequently in pts treated with G than CP with marked differences in the M+ (favouring G) and M- (favouring CP) subgroups. SI was similar for G and CP overall, with results significantly favouring G and CP in the M+ and M- subgroups, respectively.

Disclosure: S. Thongprasert: Honoraria from AstraZeneca. Research Funding: AstraZeneca, Sanofi-Aventis; E. Duffield: Equity/stock holder: AstraZeneca. Employee of AstraZeneca; Y. Wu: Consultancy fees and paid advisory boards: AstraZeneca, Roche, Pfizer, Eli Lilly. Lecture fees from commercial sponsors: AstraZeneca, Roche, Eli Lilly; C. Yang: Consultancy fees and paid advisory boards: AstraZeneca. Lecture fees from commercial sponsors: AstraZeneca; N. Saijo: Equity/stock holder: Takeda. Research Funding: AstraZeneca, Taiho, Takeda, Chugai; D.T. Chu: Honoraria from AstraZeneca; V. Chan: Clinical trials: Roche Philippines, Glaxo and AMGEN. Advisory Board: Glaxo; T. Mok: Consultancy fees and paid advisory boards: AstraZeneca, Roche, Pfizer, Eli Lilly. Lecture fees from commercial sponsors: AstraZeneca, Roche, Eli Lilly. Research funding: AstraZeneca; P. Magill: Equity/stock holder: AstraZeneca. Employee of AstraZeneca. M. Fukuoka: Honoraria from AstraZeneca, Chugai and Boehringer Ingelheim.

		G		C/P		Odds ratio		
Population	QoL Measure	N	% Improved	N	% Improved	G:CP	95% CI	p-Value
Overall	FACT-L	590	48.0	561	40.8	1.34	1.06–1.69	0.0148
	TOI	590	46.4	561	32.8	1.78	1.40–2.26	<0.0001
	LCS	590	51.5	561	48.5	1.13	0.90–1.42	0.3037
EGFR M+	FACT-L	131	70.2	128	44.5	3.01	1.79–5.07	<0.0001
	TOI	131	70.2	128	38.3	3.96	2.33–6.71	<0.0001
	LCS	131	75.6	128	53.9	2.70	1.58–4.62	0.0003
EGFR M-	FACT-L	89	14.6	80	36.3	0.31	0.15–0.65	0.0021
	TOI	89	12.4	80	28.8	0.35	0.16–0.79	0.0111
	LCS	89	20.2	80	47.5	0.28	0.14–0.55	0.0002

206O

RANDOMIZED TRIAL OF CONCURRENT VERSUS SEQUENTIAL DOCETAXEL PLUS BORTEZOMIB (PS-341) IN PLATINUM-TREATED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS): A CALIFORNIA CANCER CONSORTIUM STUDY

P.N. Lara[1], J. Longmate[2], A. Argiris[3], B. Gitlitz[4], P.C. Mack[5], D. Lau[1], M. Koczywas[6], N.B. Leighl[7], D.R. Gandara[8] *[1]Medical Oncology, University of California, Davis Campus, Sacramento/USA, [2]Biostatistics, City of Hope, Duarte/USA, [3]Cancer Center, University of Pittsburgh, Pittsburgh/USA, [4]Medical Oncology, University of Southern California, Los Angeles/USA, [5]Department of Internal Medicine Hematology/oncology, University of California, Davis Campus, Sacramento/USA, [6]Medical Oncology and Therapeutics Research, City of Hope, Duarte/USA, [7]Medical Oncology, Princess Margaret Hospital, Toronto/CANADA, [8]Department of Internal Medicine Hematology/oncology, University of California Davis Cancer Center, Sacramento/USA*

Background: The proteasome inhibitor PS-341 sensitizes tumor cells to chemotherapy-induced apoptosis. In A549 & Calu1 NSCLC lines, the sequence of docetaxel (Doce) followed by PS-341 appears to optimally induce cell death by reducing levels of anti-apoptotic Bcl-2 & increasing levels of the tumor suppressor p27, as compared to the reverse sequence or simultaneous administration. To further explore these observations, we conducted a randomized phase II trial of concurrent vs. sequential Doce-PS-341 in NSCLC pts.

Methods: Platinum pre-treated metastatic NSCLC pts were randomized to either concurrent (Arm 1) or sequential (Arm 2) Doce 75 mg/m2 IV followed by PS-341. Arm 1 pts received PS-341 (1.6 mg/m2 IV) on days 1 and 8; Arm 2 pts received PS-341 starting on day 2. Prophylactic GCSF support was recommended. Cycle length was 3 weeks. Pts must have path-confirmed NSCLC, Zubrod performance status 0-1, and adequate end-organ function. Prior erlotinib was allowed (n=13) as were pts with treated/controlled brain metastasis. Primary endpoint was RECIST response rate (RR), while progression-free (PFS) and overall survival (OS) were secondary endpoints. With 40 pts per arm, there was 90% probability to correctly "pick the winner" if the RR on the 2 arms were 0.05 vs. 0.13, or 0.10 vs. 0.20, or 0.15 vs. 0.27.

Results: Eighty-one pts were randomized: 40 in Arm 1, 41 in Arm 2. Grade (Gr) 3+ toxicities were mostly due to myelosuppression (arm 1 vs. 2), leukopenia (6 vs. 11), lymphopenia (10 vs. 2), neutropenia (8 vs. 15), & thrombocytopenia (0 vs. 3). One pt each had gr4 sodium and syncope. One pt (Arm 2) died after gr4 heme toxicities, gr3 neuropathy and gr3 anorexia.

	Arm 1 (Concurrent)	Arm 2 (Sequential)	Overall
Male Sex	23 (57%)	20 (49%)	43 (53%)
Zubrod PS=0	17 (42%)	21 (51%)	38 (47%)
Median age, years	61	62	61
Partial response (PR)	4 (10%)	4 (10%)	8 (10%)
Disease control rate (PR+SD)	20 (50%)	20 (49%)	40 (49%)
6-month PFS	30%	17%	25%
OS, median in months	13.3 (7,17)	7.8 (6,18)	10.5 (7, 14)

Conclusion Docetaxel plus PS-341 concurrently given on day 1 has similar RR as sequential therapy, but results in OS that exceeds prior published OS estimates for either agent alone or in combination. (NO1 CM-62209).

Disclosure: All authors have declared no conflicts of interest.

207O

EFFICACY AND SAFETY OF DOUBLET COMPARED TO SINGLE AGENT IN ADVANCED NON SMALL CELL LUNG CANCER. A SYSTEMATIC REVIEW AND META-ANALYSIS

G. Des Guetz[1], B. Uzzan[1], P. Nicolas[1], J. Morere[2] *[1]Oncology, Hôpital Avicenne, Bobigny/FRANCE, [2]Medical Oncology, Hôpital Avicenne, Paris/France*

Background: In the elderly (age > 70) with advanced Non Small Cell Lung Cancer (NSCLC), the relative risk-to-benefit ratio of chemotherapy (CT) administered as single-agent or doublets (including the same single agent) is not established. We performed a meta-analysis (MA) of all published studies to clarify this issue.

Methods: PubMed query using the following keywords simultaneously Randomized Controlled Trial, Aged, Antineoplastic Combined Chemotherapy Protocols/therapeutic use, Carcinoma, NSCL.drug therapy. Articles were also obtained by cross-checking references; abstracts from ASCO and WCLC proceedings. The efficacy outcome was based on 1-year Overall Survival (OS). Hazard Ratios (HRs) were calculated from the recorded events. We used EasyMA software and fixed-effect model, due to absence of statistical heterogeneity between studies. By convention, HRs < 1 corresponded to a decreased survival among the single-agent compared with the doublet.

Results: Eight eligible studies included 1804 patients (mean age 73; 1362 men and 368 women; 461 stage IIIB and 1114 stage IV; 600 epidermoid cancers, 565 adenocarcinomas, 410 other pathological types). One-year OS was similar for single-agent and doublets (HR 0.98; 95% Confidence Interval or CI: 0.92–1.05), HRs for nausea/vomiting, neutropenia, thrombopenia and anaemia were significantly higher for doublets than for single agent (1.29, CI 1.13–1.46; 1.28, CI 1.17–1.41; 1.60, CI 1.26–2.02; 1.36, CI 1.19–1.55 respectively). HRs for diarrhea and stomatitis were close to 1. Concerning grade ¾ toxicity, only the HRs for the biological side effects were significantly higher for doublets: neutropenia (1.40; 1.15–1.71), thrombopenia (2.46; 1.60–3.78) and anaemia (1.61; 1.04–2.48). Alopecia, peripheral neuropathy, febrile neutropenia could not be analyzed precisely due to their low frequency.

Conclusion: Compared with single-agent CT, doublets not improved OS. Neutropenia, thrombopenia and anaemia were more frequent with doublets. Thus, the benefit-to-risk ratio of doublets in advanced NSCLC is not proved. Future elderly-specific studies should be needed to determine the best CT regimen.

Disclosure: All authors have declared no conflicts of interest.

208O

RISK FACTORS FOR EARLY COMPLICATIONS OF HIGH DOSE RATE ENDOBRONCHIAL BRACHYTHERAPY (HDR EBBT) IN THE PALLIATIVE TREATMENT OF LUNG CANCER

B. Zaric[1], B. Perin[1], A.N. Jovelic[2], N. Lalic[1], N. Secen[1], M.N. Antonic[3] *[1]Department for Interventional Pulmonology, Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Sremska Kamenica/SERBIA AND MONTENEGRO, [2]Clinic for Cardiology, Institute for Cardiovascular Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Sremska Kamenica/SERBIA AND MONTENEGRO, [3]Clinic for Pulmonary Oncology, Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Sremska Kamenica/SERBIA AND MONTENEGRO*

Introduction: The major aims of this study were to identify the complication rate and clinical risk factors for early complications of HDR-EBBT. Identification of these risk factors can result in a decrease or avoidance of complications.

Patients and methods: In this study we analyzed risk factors for complications in 761 patients with advanced stage lung cancer who were treated with HDR-EBBT as a part of the multi-modality therapy. We reviewed patient, radiology and bronchology charts for complications of HDR-EBBT. Complications were defined as severe hypoxemia, global respiratory failure, cardiac arrhythmia requiring additional treatment, haemoptysis, pneumothorax, pneumomediastinum, pulmonary oedema, TE fistulae and death. Risk factors were defined as: acute myocardial infarction≥6 months ago, hypertension, arrhythmia, chronic obstructive pulmonary disease (COPD), cardiomyopathy, previous external beam radiotherapy, chemotherapy and interventional pulmonology treatment. Age, gender, tumor histology and tumor localization were also analyzed for multivariate analysis.

Results: The rate of complications was 5.4%. Statistically significant (p=0.001) risk factors for complications of HDR-EBBT were hypertension, controlled chronic cardiac arrhythmias, COPD and cardiomyopathy. We found a significant correlation between the age and the number of risk factors, and occurrence of complications (p=0.001).

Conclusion: The results of this study suggest a closer monitoring of patients with identified risk factors is advisable. The closer monitoring of the patients should be performed prior to, and after the treatment in order to avoid complications.

Disclosure: All authors have declared no conflicts of interest.

209O

PEMETREXED-RELATED RENAL TOXICITY IN PATIENTS (PTS) WITH THORACIC MALIGNANCIES

P. Trenta[1], R. Iacovelli[2], A. Palazzo[2], D. Conte[2], F. Morano[3], G. Campenni[2], E. Risi[2], K. Truscelli[1], S. Mezi[2], E. Cortesi[2] *[1]Medical Oncology, Policlinico Umberto I, Rome/ITALY, [2]Experimental Medicine, Medical Oncology B, Sapienza University of Rome, Rome/ITALY, [3]Experimental Medicine, Medical Oncology, Sapienza University of Rome, Rome/ITALY*

Background: Pemetrexed is a multitargeted antifolate drug approved in treatment of pleural mesothelioma (PM) and lung adenocarcinoma (ADK). This agent is almost exclusively cleared by renal excretion. Pemetrexed-related renal toxicity is reported in clinical trials. We report our experience about variations of renal function in pts treated with pemetrexed.

Patients and methods: Since January 2006 to December 2009, a total of 39 pts (36 ADK and 3 PM), with glomerular filtration rate (GFR) ≥ 45 ml/m, received pemetrexed (500 mg/m2, d 1, every 3 wks) in combination with platinum compounds in first line setting or as single agent until tolerance or tumor progression in second line setting. Renal function was evaluated with GFR, calculated with Cockcrof-Gault formula. Laboratory data were collected at the start and at the end of therapy. Pts' baseline renal functions were divided according to chronic renal failure criteria.

Results: A median of 6.0 cycles (1 to 13) of pemetrexed was administered. 28 pts (71.7%) showed a GFR decrease. 19 pts (48.7%) showed grade (G) 1 to 3 of renal toxicity, with 12.8% of G3. In first line setting (16 ADK and 3 PM), 16 pts (84,2%) had a decrease of GFR. 4 pts with baseline GFR (b-GFR) ≥ 100 ml/m showed a 8.5% reduction of GFR, without renal toxicity. 12 pts with GFR < 100 ml/m showed a 36% median reduction of GFR, with 3 cases (25%) of GFR < 25 ml/m (G3 toxicity): one occurred in 1 pt with a b-GFR of 90 ml/m and 2 in pts with a b-GFR < 70 ml/m. In second line setting (20 ADK pts), 12 pts (60%) had a decrease of GFR. 3 pts with b-GFR ≥ 100 ml/m showed a 17% reduction of GFR, without renal toxicity. 9 pts with b-GFR < 100ml/m experienced a GFR median reduction of 28% with 2 cases (22%) of G3 toxicity. No relationship between percentage of GFR reduction and cycles number was observed. In both settings G3 toxicities occurred in women aged <65 yrs (median 62 yrs).

Conclusions: We observed that acute, high grade, no-dose cumulative renal toxicity is a common adverse event in pts treated with pemetrexed alone or

in association with platinum compounds. Moreover, toxicity is strictly related to baseline pts' renal function (b-GFR < 100 ml/m), female sex and age (< 65 yrs). These data seem to be relevant especially in planning maintenance strategy with pemetrexed.

Disclosure: All authors have declared no conflicts of interest.

210O

MO19390 (SAIL): FINAL SAFETY AND EFFICACY DATA FOR FIRST-LINE BEVACIZUMAB (BV)-BASED THERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

P. Garrido Lopez[1], C. Chouaid[2], R. Passalacqua[3], J. De Castro[4], J. Laskin[5] *[1]Medical Oncology, Hospital Ramon Y Cajal, Madrid/SPAIN, [2]Service De Pneumologie, Hôpital Saint Antoine, APHP, Paris/FRANCE, [3]Medicina 1 E Oncologia Medica, Azienda Istituti Ospitalieri di Cremona, Cremona/ITALY, [4]Servicio De Oncología Médica, Hospital Universitario La Paz, Madrid/SPAIN, [5]Medical Oncology, BC Cancer Agency, Vancouver/CANADA*

Background: SAiL is a large, international, multicentre, single-arm study that assessed the safety and efficacy of first-line Bv plus chemotherapy in advanced non-squamous NSCLC in a real-life clinical setting. Final data analysis reported an overall survival (OS) benefit of 14.6 months, further confirming the findings of the pivotal phase III clinical trials (E4599 and AVAiL).

Methods: The primary endpoint was safety, and secondary endpoints included time to disease progression (TTP) and OS. Pts with untreated locally advanced, metastatic or recurrent non-squamous NSCLC (ECOG PS 0–2) received Bv (7.5 or 15mg/kg) plus standard chemotherapy for up to 6 cycles, followed by Bv until disease progression.

Results: Final analysis was based on 2,172 pts (mean age 59 years). Pts were (%): male 60.1; stage IIIB/IV 19.6/80.4; adenocarcinoma/large cell/other 85.9/7.0/4.1; ECOG PS 0/1/2 37.4/56.3/6.3. Pts received a median of 7 Bv cycles and 5 chemotherapy cycles. 37.9% of pts experienced an SAE (any grade [G]), of which 26.2% were considered to be Bv-related. The results of SAiL confirm on a large scale that adverse events (AEs) of special interest for Bv are essentially G 1–2, with a low incidence of clinically significant events; bleeding events of any G (42.7% of pts) consisted mainly of G1–2 epistaxis (26.6% of pts). Other AEs of special interest with G ≥3 also had low incidence (% of pts): pulmonary haemorrhage (0.7%), proteinuria (3.1%) and thromboembolic events (7.9%). Bv was infrequently interrupted or discontinued due to bleeding (2.0% and 8.1% respectively) or hypertension events (6.8% and 3.9% respectively). No new safety signals were reported. Final efficacy outcomes are remarkable; for the overall population median TTP was 7.8 months, median OS was 14.6 months, overall response rate was 51.5% and 88.7% of pts had a best response of stable disease (37.2%) or better.

Conclusions: This final analysis of SAiL confirms the well-established and manageable safety profile of first-line Bv in combination with chemotherapy for advanced NSCLC. The efficacy outcomes in this real-life population are consistent with those seen in the pivotal trials of Bv in NSCLC (E4599 and AVAiL).

Disclosure: P. Garrido Lopez: Advisory Role for Roche, Lilly, Boehringer-Ingelheim and Astra-Zeneca. Honoraria for Roche and Lilly C. Chouaid: Christos Chouaid has received fees for speaking and consulting from Astra-Zeneca, Boehringer-Ingelheim, Roche, Amgen and Lilly; travel to the ASCO and/or IASLC congress was funded by Merck Serono and Roche. J. Laskin: I have received small honoraria for academic talks sponsored by: Roche Canada, Eli Lilly, and Astra Zeneca. My instituition receives research funding from Roche that is directed to my investigator initiated research projects. All other authors have declared no conflicts of interest.

211O

SAFETY OF BEVACIZUMAB (BV)-BASED THERAPY AS FIRST-LINE TREATMENT OF ELDERLY PATIENTS (PTS) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): MO19390 (SAIL)

M. Reck[1], J. Mazières[2], Z. Mark[3], W. Schuette[4], E. Dansin[5] *[1]Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf/GERMANY, [2]Department of Pneumology, Larrey Hospital, CHU Toulouse, Toulouse/FRANCE, [3]3th Pulmonology, Pest Megyei Tudogyogyintezet, Torokbalint/HUNGARY, [4]Klinik Fuer Innere Medizin Ii, Krankenhaus Martha-Maria Halle-Doelau GmbH, Halle/GERMANY, [5]Oncology, Centre Oscar Lambret, Lille/FRANCE*

Background: SAiL (MO19390) is an international, open-label, single-arm study of first-line Bv plus chemotherapy in pts (n=2,172) with advanced NSCLC. SAiL showed an overall survival (OS) benefit of 14.6 months for the overall population. Here, we present a final safety subanalysis of Bv plus chemotherapy in pts aged >65 years (yrs).

Methods: Eligible pts received up to 6 cycles of Bv (7.5 or 15mg/kg) plus chemotherapy. Non-progressors continued Bv as single-agent therapy until progression or unacceptable toxicity. Primary endpoint was safety; secondary endpoints included time to disease progression (TTP) and OS.

Results: 610 pts >65 yrs (median 70 yrs) and 1,562 pts ≤65 yrs (median 56 yrs) were evaluable for this final analysis. Pts >65 yrs were (%): male 62.8; ECOG PS 0/1/2 32/61/7; adenocarcinoma/large cell/other 83/9/4. Median cycles of Bv and chemotherapy were 6 and 4 for pts >65 yrs and 8 and 5 for pts ≤65 yrs. The incidence of grade (G) ≥3 SAEs considered to be related to Bv was overall in similar ranges (13.1% and 9.4% for pts >65 yrs and pts ≤65 yrs, respectively). Most Bv-related SAEs in pts >65 yrs (73%) and pts ≤65 yrs (75%) resolved or improved. Incidence of AEs of special interest (SI) was relatively low and comparable between groups (21.5% and 19.1%, for >65 yrs and ≤65 yrs respectively), which is interesting considering the higher baseline rate of comorbidities in the elderly pts subgroup. Rate of pulmonary haemorrhage was nearly the same for both groups (0.7% and 0.6%, for >65 yrs and ≤65 yrs respectively). Rate of G ≥3 congestive heart failure events was low at 0.8% for >65 yrs and 0.4% for ≤65 yrs. There were no G 5 hypertension events. Of all AEs of SI, 1.6% and 1.4% were G 5 for pts >65 yrs and ≤65 yrs respectively. The efficacy outcomes were also similar for both groups: median TTP for pts >65 yrs vs ≤65 yrs was 8.3 vs 7.6 months, respectively, and median OS was 14.6 months for both groups.

Conclusions: Pts >65 yrs are not at increased risk of experiencing AEs of SI when treated with first-line Bv-based therapy compared with pts ≤65 yrs. TTP and OS data from this final analysis of SAiL indicate that Bv-based therapy offers a similar level of clinical benefit, irrespective of age.

Disclosure: M. Reck: Honoraria: Hoffmann-La Roche, Lilly, Merck, Astra-Zeneca; Advisory Board: Hoffmann-La Roche, Lilly, Merck, Astra-Zeneca All other authors have declared no conflicts of interest.

212O

FINAL SAFETY DATA FOR CHINESE PATIENTS (PTS) WITH NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC) WHO RECEIVED FIRST-LINE BEVACIZUMAB (BV) PLUS CHEMOTHERAPY IN SAIL (MO10390)

Y. Wu[1], A.C. Cheng[2], J.S. Au[3], Y. Zhu[4], C. Tsai[5] *[1]Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou/CHINA, [2]Oncology, Princess Margaret Hospital, Hong Kong/HONG KONG, [3]Clinical Oncology, Queen Elizabeth Hospital, Hong Kong/HONG KONG, [4]Oncology, Beijing Chest Hospital, Beijing/CHINA, [5]Department of Chest, Taipei Veterans General Hospital, Taipei/TAIWAN*

Background: The large international SAiL study aimed to assess the safety profile of first-line Bv-based therapy in advanced NSCLC in a real-life clinical population. In the overall population there was an overall survival (OS) of 14.6 months. Here, we present the final results of a pre-planned analysis of Chinese pts enrolled in the trial.
Methods: To ensure comparability of the data from this pre-planned analysis and those from the E4599 trial, a specific protocol amendment was submitted to allow only Chinese pts with ECOG PS 0–1 and Bv at a dose of 15mg/kg plus carboplatin/paclitaxel for up to 6 cycles, followed by single-agent Bv until progression. Primary endpoint was safety; secondary endpoints included time to disease progression (TTP) and OS.
Results: The intent-to-treat population (n=198) was from 9 centres in mainland China: male 55%; mean age 55 years; past or active smokers 46%, stage IV disease 70%. Median number of Bv cycles was 10, with 71.2% of pts receiving ≥7 Bv cycles. Incidence of clinically significant adverse events (AEs) was low. The most common AEs of special interest were grade [g] 1–2 proteinuria (36.9%) and epistaxis (38.9%). Only 13.1% of pts had any [g] ≥3 AE of special interest; proteinuria (8.6%), hypertension (3.0%), epistaxis (1.5%), haemoptysis (0.5%) and thromboembolism (0.5%). No CNS bleeding was reported, including in the 26 pts who developed CNS metastases during therapy. No [g] ≥3 wound-healing complications or congestive heart failures were reported and only 8 serious AEs were deemed to be Bv-related. Bv was interrupted for only 3.1% of AEs and discontinued for 1.3% of AEs. Only 2 [g] 5 events were reported. Efficacy outcomes were remarkable: overall response rate 68.7%; disease control rate 96.4%; median TTP 8.8 months; median OS 18.5 months.
Conclusions: The SAiL study confirms the safety and remarkable efficacy of first-line Bv in combination with carboplatin/paclitaxel in Chinese pts with advanced non-squamous NSCLC. These findings are consistent with those for the global SAiL population and the overall population in E4599, the pivotal phase III trial. No new safety signals were identified in this analysis.
Disclosure: Y. Wu: I have honoraria from Roche, AstraZeneca, Eli Lilly, Pfizer to disclose. All other authors have declared no conflicts of interest.

213O

RISK OF SEVERE PULMONARY HEMORRHAGE (SPH) ASSOCIATED WITH DEVELOPMENT OF CAVITATION WHILE ON BEVACIZUMAB (BV) THERAPY IN PATIENTS (PTS) WITH NON SMALL CELL LUNG CANCER (NSCLC): RESULTS FROM ARIES, A BV TREATMENT OBSERVATIONAL COHORT STUDY (OCS)

D.R. Spigel[1], J.R. Brahmer[2], N.A. Fischbach[3], P. Kumar[4], M. Kosty[5], A.J. Wozniak[6], S.L. Teng[7], E.D. Flick[8], A.P. Sing[9], T.J. Lynch[10] *[1]Oncology, Sarah Cannon Research Institute, Nashville/USA, [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore/USA, [3]Oncology, Oncology Associates of Bridgeport PC, Fairfield/USA, [4]Hematology, Oncology, & Transplantation, University of Minnesota, Minneapolis/USA, [5]Hematology/Oncology, Scripps Clinic, La Jolla/USA, [6]Karmanos Cancer Institute, Wayne State University, Detroit/USA, [7]Biostatistics, Genentech, Inc, South San Francisco/USA, [8]Epidemiology, Genentech, Inc, South San Francisco/USA, [9]Biooncology, Genentech, Inc, South San Francisco/USA, [10]Oncology, Yale Cancer Center, New Haven/USA*

Background: BV (Avastin®) prolongs progression free and overall survival (OS) in advanced NSCLC pts. sPH (>grade 3) is a rare but often fatal event that has been associated with BV-based therapy in phase 3 trials (rate, 2–4%). Potential risk factors include squamous histology, history of hemoptysis, and tumor cavitation. Rates of baseline (BL) cavitation in NSCLC pts and development of cavitation on BV therapy are unknown. ARIES is an OCS of 1970 pts with NSCLC that has assessed BL scans for presence of tumor cavitation. A substudy collected follow-up (F/U) scans to examine the potential association of developing cavitation on BV therapy and risk of sPH. In addition, any pt that develops sPH is assessed for tumor cavitation.
Methods: Pts at specified ARIES sites submitted BL and on-study CT scans to an independent review facility. Substudy evaluable pts had at least 1 measurable (meas) tumor at BL and at least 1 post-BL scan. Correlations between cavitation (pre-existing or developing), clinical, tumor and treatment characteristics were evaluated by chi-square test or t-test. Incidence of sPH based on cavitation status was assessed by Fisher's exact test. OS is estimated by Kaplan Meier.
Results: As of 12/14/09, 1494 pts had meas tumors at BL. Of these, 199 have a post-BL scan. For the 1494 pt cohort: median F/U is 9.6 mo. BL characteristics for the substudy (n=199) and overall cohort with meas tumor at BL (n=1494), respectively, include: 30% vs 33% ≥70 yrs; 68% vs 70% adenocarcinoma; 4.5% vs 4.4% therapeutic anticoagulation; 43% vs 49% central tumor; 13% vs 15% cavitation. 60 (30.2%) substudy evaluable pts developed cavities while on BV, none of whom had sPH. There was 1 sPH event (0.5%) reported from the 218 pts with BL cavitation in their meas tumor. Preliminary median OS (95% CI) for substudy pts developing cavitation and the entire ARIES cohort are similar at 13.9 mo (10.0, 20.5) and 13.7 mo (12.6, 14.9), respectively.
Conclusions: sPH is a rare, potentially fatal event in pts with NSCLC receiving BV. The findings of this substudy suggest that cavitation alone is not a risk factor for sPH.
Disclosure: D.R. Spigel: Advisor to Genentech (not financially compensated); J.R. Brahmer: Advisor to Genentech (financially compensated); P. Kumar: Advisor to Genentech (financially compensated) and have received honoraria from Genentech; M. Kosty: Have received honoraria and research funding from Genentech; A.J. Wozniak: Genentech advisory board (financially compensated) and research funding from Genentech; S.L. Teng: Employee of Genentech, Inc and stockholder in Roche; E.D. Flick: Employee of Genentech and stockholder of Roche; A.P. Sing: Employee of Genentech and stockholder of Roche T.J. Lynch: Board of Directors member and stockholder: Infinity Pharma Consultant: Genentech, Merck, Boehringer-Ingelheim (BIPI), Astra-Zeneca. All other authors have declared no conflicts of interest.

214O

SYNCHRONOUS BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER: TIME FOR REAPPRAISAL OF EXTRACRANIAL TREATMENT OPTIONS?

J.S.W. Lind[1], F.J. Lagerwaard[2], E.F. Smit[3], P.E. Postmus[4], B.J. Slotman[5], S. Senan[2] *[1]Pulmonary Diseases, VUMC, Amsterdam/NETHERLANDS, [2]Radiation Oncology, VU University Medical Center, Amsterdam/NETHERLANDS, [3]Pulmonary Diseases, VU University Medical Center, Amsterdam/NETHERLANDS, [4]Pulmonary Diseases 4a50, VU University Medical Center, Amsterdam/NETHERLANDS*

Purpose: The optimal treatment of the primary tumour in patients with brain metastases (BM) from newly diagnosed non-small cell lung cancer (NSCLC) remains unclear. Our aim was to identify patient groups with synchronous BM for whom radical treatment of the primary site may be appropriate.
Methods: The medical records of 167 patients treated at our centre between November 2000-June 2009 for newly diagnosed NSCLC and synchronous BM were reviewed. All patients underwent surgery/radio-surgery (n=86) or whole-brain radiotherapy (WBRT; n=81) of their BM. Univariate and multivariate analysis were performed to assess prognostic factors significant for overall survival (OS).
Results: The median OS of patients undergoing surgery/radio-surgery for BM was 12.1 months. Those undergoing 'radical' thoracic treatment (n=24)

had a longer median OS (28.4 months) than those undergoing chemotherapy (n=74; 12.1 months) or supportive therapy (n=69; 5.6 months), p<0.01. Patients with stage I thoracic disease (n=23) had a longer median OS (18.5 months) than those with stage III (n=43; 9.4 months) or with intra/extra-thoracic metastases other than BM (stage IV; n=20; 2.7 months), p<0.01. The median OS of the WBRT patients was 3.7 months. One patient underwent radical thoracic treatment. Patients undergoing chemotherapy (n=42) had a longer median OS (5.7 months) than patients undergoing supportive therapy only (n=38; 1.6 months), p<0.01. Patients with performance status (PS) 0-1 (n=53) had a median OS of 5.0 months; OS was 1.8 months for PS 2-3 (n=27), p<0.01.

Conclusions: Radical thoracic treatments may be justified in patients eligible to undergo surgery/radio-surgery for synchronous BM from NSCLC, even when stage III thoracic disease is present. The role of chemotherapy in selected patients with a good PS undergoing WBRT warrants further evaluation.

Disclosure: All authors have declared no conflicts of interest.

215O

AN ANALYSIS OF PATIENTS WITH BRAIN METASTASES FROM NON SMALL CELL LUNG CANCER TREATED WITH SHORT COURSE ACCELERATED RADIOTHERAPY (SCAR)

A. Munshi[1], J.P. Agarwal[1], T. Wadasadawala[1], R. Apsani[1], M. Upasani[1], S.G. Laskar[1], C.S. Pramesh[1], N. Jambhekar[1], H. Menon[1], K. Prabhash[2]
[1]Radiation Oncology, Tata Memorial Hospital, Mumbai/INDIA, [2]Medical Oncology, Tata Memorial Hospital, Mumbai/INDIA

Aims: Study various prognostic factors affecting outcome and validate Radiation Therapy Oncology Group-Recursive Partitioning Analysis (RTOG-RPA) class in non small cell lung cancer (NSCLC) with brain metastases treated with short course accelerated radiotherapy (SCAR).

Material and methods: Case records of 100 patients of NSCLC consecutively treated at Tata Memorial Hospital from August 2006 to August 2009 were studied for various patient, tumor and treatment related prognostic factors. Patients received whole brain radiotherapy to a dose of 20Gy/5# over one week (n=90) or 30Gy/10# over two weeks (n=10). Univariate and multivariate analysis was conducted using SPSS v15.

Results: Overall survival (OS) for the entire cohort was 7 months (1-61 months) whereas median post metastases survival (PMS) was 4.0 months (0.5-30.0 months). Of the various prognostic factors, RPA class (II vs. III, p value=0.003), Karnofsky Performance Score (KPS <70 vs. ≥70, p value=0.005), primary disease status (controlled vs. uncontrolled, p value=0.031), time of detection of brain metastases (synchronous vs. metachronous, p value=0.000), use of systemic therapy (yes vs. no, p value=0.00) and metastases free interval (MFI <6 months vs. > 6 months, p value=0.000) emerged significant on univariate analysis. On multivariate analysis, use of systemic therapy (p value=0.000) and length of MFI of at least 6 months strongly predicted OS. There was a strong correlation between median OS and MFI (p value=0.000), it was stronger for RPA class II as compared to RPA class III (r=0.665 vs. 0.557).

Conclusion: SCAR regime is an effective and resource sparing palliative strategy for brain metastases in NSCLC. Patients with long MFI have significant survival advantage especially if they belong to RPA class II. Thus, short MFI and synchronous presentation indicate aggressive tumor biology. Use of systemic therapy significantly improves survival. However, validation of these findings in future prospective trials is required.

Disclosure: All authors have declared no conflicts of interest.

216O

PULMONARY NEUROENDOCRINE TUMOURS: PREVALENCE IN 1,000 RESECTED PATIENTS AND ANALYSES OF PATIENT CHARACTERISTICS, SMOKING HABITS AND TUMOUR STAGE

W. Engel-Riedel, J. Zimmermann, C. Ludwig, E. Stoelben *Lung Departure, Kliniken der Stadt Köln gGmbH, Cologne/GERMANY*

Objective: Neuroendocrine tumours of the lung can be divided in typical carcinoid (TC), atypical carcinoid (AT), large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC). Apart from SCLC which accounts for 20-25% of pulmonary tumors, carcinoids and LCNEC are rare tumors with a reported prevalence of approximately 3% among surgically resected lung cancers. Generally speaking there is only little information on the prevalence of neuroendocrine tumors in resected patients so that we would like to present the data collected our institution.

Patients and method: Retrospective analysis of 1,000 surgically resected lung cancer patients in our institution between January 2007 and March 2009. For patients with a diagnosis of TC, AT and LCNEC we compared the data in terms of age, sex, smoking habits and tumor stage.

Results: Among the resected patients 17 (1.7%) were diagnosed with TC, 6 with AT (0.6%) and 25 patients with LCNEC (2.5%). A mixed histology of LCNEC and SCLC was found in 8 out the 25 patients with a LCNEC. LCNEC highly correlated with smoking (all were smokers) and the patients were diagnosed at a later stage compared to those with carcinoids. Patients with TC and AT happened more likely to be women, never-smokers and were mainly diagnosed in Stage I. There was no significant difference in age between these groups.

Conclusions: Neuroendocrine tumours of the lung are rare. Retrospective analysis of this data allows us to differentiate between these patients in terms of prognosis. The importance of clinical trials is underlined especially for patients with LCNEC as they have a poor prognosis.

Disclosure: All authors have declared no conflicts of interest.

217PD

PHASE I STUDY OF THE IGF-IR INHIBITOR FIGITUMUMAB (CP-751,871) IN COMBINATION WITH CISPLATIN (C) AND GEMCITABINE (G) OR C AND PEMETREXED (P) IN TREATMENT-NAïVE PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

J. Corral[1], J.M. Sanchez-Torres[2], K. O'Byrne[3], L. Iglesias[2], D. Li[4], M. Atienza[5], J. Canon[6], M. Carpentieri[7], A. Gualberto[4], L. Paz-Ares[1] *[1]Oncology, Hospital Universitario Virgen del Rocio, Seville/SPAIN, [2]Oncology, Hospital Universitario 12 De Octubre, Madrid/SPAIN, [3]Oncology, St James Hospital, Dublin/IRELAND, [4]Oncology Business Unit, Pfizer Inc, New London/USA, [5]Oncology, Hosptial Universitario Virgen del Rocio, Seville/SPAIN, [6]Oncology, Grand Hopital de Charleroi, Charleroi/BELGIUM, [7]Oncology Business Unit, Pfizer Inc, Milan/ITALY*

Background: Figitumumab (F) is a potent and selective fully human IgG2 monoclonal antibody against IGF-IR. Preclinical data indicate that F increases the antitumor activity of chemotherapy in cancer xenograft models. We evaluated the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of F in combination with C and G or C and P in pts with treatment-naïve advanced NSCLC.

Methods: This open-label, dose-escalation study investigated F 6–20 mg/kg given in 2.5-hr infusions on day 1 of 3-wk cycles in combination with C (80 mg/m^2, day 1) and G (1,250 mg/m^2, days 1 & 8) for ≤6 cycles. The tolerability of 1-hr F infusion was also investigated in expansion cohorts (C 80 mg/m^2 + G 1,250 mg/m^2, or C 75 mg/m^2 + P 500 mg/m^2). Pts could receive additional cycles of single-agent F upon chemotherapy discontinua-

tion. The primary objective was the identification of the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of F in combination with chemotherapy.

Results: 45 pts were enrolled (median age 59 yrs, range 44–74); 44% had adenocarcinoma and 16% had squamous cell carcinoma. The only dose-limiting toxicity (DLT) was grade 4 neutropenia that lasted 8 days in 1/6 pts treated with CG + F at 20 mg/kg. No dose escalation above 20 mg/kg was planned. No pts required dose reduction. Safety and preliminary efficacy results are shown in the table. Two responding pts underwent surgery; no residual tumor was found (pathologic CRs). Median TTP was 5.7 mos (3 pts still on follow up). Analyses of PK and PD endpoints are ongoing.

Conclusions: F was well tolerated in combination with CG for the first-line treatment of pts with NSCLC. In addition, no safety concerns were observed with CP + F at 20 mg/kg. Based on the favorable safety profile, the 1-hr infusion of F (20 mg/kg every 3 wks) was selected as the RP2D. Preliminary efficacy results are encouraging.

	CG+F (6mg/kg)	CG+F (10mg/kg)	CG+F (20mg/kg)	CP+F (20mg/kg)
Patients, n	6	3	23	13
Cycles, median (range)		3 (1–5)		4 (2–6)
Objective Response Rate, n (%)		13 (40.6)		3 (23.1)
CR		2 (6.3)		0
PR		11 (34.4)		3 (23.1)
SD		7 (21.9)		3 (23.1)
Grade 3/4 toxicity (treatment related, >8%), n (%)				
Hyperglycemia		6 (18.8)		1 (7.7)
Asthenia		4 (12.5)		1 (7.7)
Neutropenia		12 (37.5)		5 (38.5)
Anemia		3 (9.4)		1 (7.7)
Thrombocytopenia		9 (28.1)		3 (23.1)

Disclosure: K. O'Byrne: I have received grants to support a PhD studentship for 4 years (supplied by Pfizer Ireland), honoraria for participation in advisory boards, and participated on asteering committee for ADVIGO program (Pfizer Inc). D. Li: I hereby declare that I have no conflict of interest in stock ownership, membership of any advisory board and other substantive relationships. I am Pfizer employee. J. Canon: I have received funding for data management from Pfizer Inc. M. Carpentieri: I am employed by Pfizer Inc. and hold Stock in Pfizer Inc. A. Gualberto: I am employed by Pfizer Inc. and hold Stock in Pfizer Inc. L. Paz-Ares: I have acted as an advisory consultant for Pfizer Inc. All other authors have declared no conflicts of interest.

218PD

CLINICAL OUTCOMES IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER TREATED IN PHASE I CLINICAL TRIALS

F. Janku, J. Gong, I. Garrido-Laguna, H.A. Parsons, C. Vaklavas, R. Kurzrock *Investigational Cancer Therapeutics, UT MD Anderson Cancer Center, Houston/USA*

Background: Lung cancer is the most frequent cause of cancer-related death in the US. The outcomes of patients with advanced non-small-cell lung cancer (NSCLC) treated on phase I clinical trials have not been systematically analyzed.

Methods: We reviewed the records of consecutive patients with advanced/metastatic NSCLC who were referred to the Phase I Clinical Trials Program from August 2004 to May 2009. Best response was assessed by Response Evaluation Criteria in Solid Tumors 1.0.

Results: Eighty-five patients (54 men and 31 women) were identified. The median age was 62 years (range: 30–85). Of 72 patients evaluable for response, 10 (14%) had a partial response (PR), and 30 (49%) had stable disease (SD) for ≥12 weeks. The median progression-free survival (PFS) was 2.8 months (95% CI; 2.2-3.4), similar to the 3.4 months (95% CI; 2.5-4.3) PFS observed in the 2nd line treatment within the same population (Table). The median overall survival (OS) was 10.6 months. The 1-year survival rate was 25%. In univariate analysis, factors predicting shorter survival were hemoglobin < 12 g/dL (p=0.0035), > 2 organ systems involved (p=0.021), ECOG > 1 (p<0.0001), smoking history (p=0.005), and male gender (p=0.038). PS > 1, smoking history and male gender were associated with worse survival in the multivariate analysis.

Conclusion: Patients with advanced NSCLC treated on phase I clinical trials had a PFS comparable to 2nd line treatment, and OS of 10.6 months. Poor PS, smoking history, and male gender were significant factors associated with shorter OS in the multivariate analysis. Table: PFS and OS on 1st line, 2nd line, and Phase I treament.

	1st Line Treatment	2nd Line Treatment	Phase I Treatment
PFS months	6.1	3.4	2.8
OS years	3.5	2.9	0.9 (10.6 months)

Disclosure: All authors have declared no conflicts of interest.

219PD

RANDOMISED PHASE II TRIAL OF 4 DOSE LEVELS OF SINGLE AGENT DOCETAXEL IN PERFORMANCE STATUS (PS) 2 PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC): DOC PS2 TRIAL

R. Califano[1], R. Griffiths[2], P. Lorigan[3], L.F. Ashcroft[4], P. Burt[5], M. Harris[5], P. Taylor[6], C. Faivre-Finn[7], N. Thatcher[8], F. Blackhall[9] *[1]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester/UNITED KINGDOM, [2]Medical Oncology, The Christie NHS Foundation Trust, Manchester/UNITED KINGDOM, [3]Department of Medical Oncology, Christie Hospital, Manchester/UNITED KINGDOM, [4]Department of Biostatistics, Christie Hospital, Manchester/UNITED KINGDOM, [5]Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester/UNITED KINGDOM, [6]Northwest Lung Centre, South Manchester University Hospital, Manchester/UNITED KINGDOM, [7]Department of Clinical Oncology, Christie Hospital NHS Trust, Withington, Manchester/UNITED KINGDOM, [8]Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester/UNITED KINGDOM, [9]Department of Medical Oncology, Christie Hospital NHS Trust, Manchester/UNITED KINGDOM*

Background: The role of chemotherapy for advanced NSCLC patients and poor PS (Karnofsky score 50-60) remains controversial. We evaluated 4 doses of docetaxel with the aim of identifying a less toxic, clinically effective dose.

Methods: Seventy-two patients with stage III (22%) (unsuitable for radiotherapy) and IV (78%) NSCLC were randomized to receive 4 doses of 3-weekly docetaxel, for 4 cycles: Arm A) 40 mg/m2 (n=17), Arm B) 50 mg/m2 (n=17), Arm C) 60 mg/m2 (n=19), Arm D) 50 mg/m2 escalated by 10 mg/m2 to a maximum of 70 mg/m2 if no dose-limiting toxicities occurred (n=19). Primary endpoints: Maximum tolerated dose,

RR, duration of response, symptom improvement, toxicity and QoL. Secondary endpoint: overall survival (OS). Patients and disease characteristics were well balanced. Median age was 67 (range 45-81), M/F=31/41, Histology subtype: Squamous/Adenocarcinoma/Mixed/NOS= 42%/49%/4%/5%.

Results: Seven patients did not receive any treatment because of deterioration in PS or death. 50% of patients in arm D, who received more than one cycle, received dose escalation. There was no statistical difference in the number of cycles administered: arms A, B and D median two cycles and arm C three cycles and no difference in RR: Arm A= 6%, Arm B=6%, Arm C=10%, and Arm D=0%. Incidence of G3-G4 leucopenia was higher in arm C (p=0.01) and G3-G4 neutropenia was higher in Arm D (p=0.03). Most common G3 non-haematological toxicity was infection, with no difference between the groups; there were no G4 toxicities. We found no difference in administration of intravenous (iv) antibiotics or hospitalization between the arms. QoL: no difference in total scores between baseline and cycles 1, 2, 3 and 4. Amalgamating scores for specific symptoms, looking at baseline to pre-cycle 2, there was a significant decrease in pain scores (p=0.025). We found no difference in OS (p=0.992). Median survival was 86, 86, 88 and 82 days and 6-month survival was 32%, 29%, 21% and 21% for arms A, B C, and D, respectively.

Conclusions: In this poor prognosis group of patients responses to docetaxel were seen at all dose levels including 40mg/m2. Higher dose levels are not associated with increased toxicities, use of iv antibiotics or hospitalization rates. However, these data do not support further evaluation of single agent docetaxel in the chemonaive PS2 population.

Disclosure: All authors have declared no conflicts of interest.

220PD

DOCETAXEL (D) VERSUS DOCETAXEL/GEMCITABINE (D&G) IN THE TREATMENT OF OLDER PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): AN ALPE ADRIA THORACIC ONCOLOGY MULTIDISCIPLINARY GROUP RANDOMIZED PHASE II TRIAL (ATOM 017)

E. Rijavec[1], O. Belvedere[2], M. Aita[3], C. Rossetto[3], A. Follador[3], C. Sacco[4], T. Ceschia[5], C. Genova[1], G. Fasola[3], F. Grossi[1] *[1]Medical Oncology, National Institute for Cancer Research, Genoa/ITALY, [2]Leeds Institute of Molecular Medicine, University of Leeds, Leeds/UNITED KINGDOM, [3]Dipartimento di Oncologia, Azienda Ospedaliera Universitaria, Udine/ITALY, [4]U.O. Oncologia, Azienda Ospedaliera S. Maria della Misericordia, Udine/ITALY, [5]Radiotherapy, Azienda Ospedaliera S. Maria della Misericordia, Udine/ITALY*

Optimal chemotherapy for older patients with advanced NSCLC is still undetermined. Both single agent D and the combination of D&G are active and well-tolerated. The aim of this study was to compare the efficacy of single-agent weekly D with weekly D&G in elderly patients with advanced NSCLC. This multicenter, one-stage, randomized phase II trial aimed to identify the most promising of the two regimens; 49 patients per arm were planned, with ≥ 8 objective responses required for the "winner" to warrant further study. Chemotherapy-naive patients with stage wet-IIIB/IV NSCLC aged ≥ 70 years, with ECOG performance status ≤ 2 were randomized to receive D (35 mg/m2) on days 1, 8, and 15 (arm A) or D (35 mg/m2) plus G (800 mg/m2) on days 1, 8, and 15 (arm B). In both arms, treatment was repeated every 4 weeks for a maximum of 4 cycles. The primary end point was response rate (RECIST); secondary endpoints were: toxicity, time-to-progression (TTP), survival. Between July 2002 and November 2009, 75 patients were randomized; 69 were evaluable (intention to treat). Enrollment was closed early due to slow accrual. Median age was 75 years (range 70-82). There was 1 (3%) CR in arm B, with 5 (14%) and 10 (28%) PRs in arms A and B, respectively. Disease control (CR+PR+SD) was achieved in 56% and 73% of patients in arms A and B, respectively. Median survival was 7.2 months in arm A and 7.9 months in arm B (p=.58; HR=1.15, 95% CI 0.69-1.9). Median TTP was longer in arm B (7.4 months and 3.9 months; p=.099, HR=1.57, 95% CI 0.91-2.7). Grade 3-4 neutropenia was more common with D&G than D (3% and 25%, respectively; p=.013), as was anemia (3% and 9%, respectively). No case of neutropenic fever was observed. Non-hematological toxicity was mild with all grades fatigue occurring in 58% and 78% of patients receiving D and D&G, respectively. Treatment with D&G resulted in higher response rate and modest improvement in TTP but not survival when compared with single-agent D. The combination of D&G has met the statistical endpoint of ≥ 8 responses and is worthy of further investigation.

Disclosure: M. Aita: Honoraria: Sanofi-Aventis; G. Fasola: Honoraria: sanofi-Aventis and Eli-Lilly; F. Grossi: Honoraria: Sanofi-Aventis and Eli-Lilly Research funding: Eli-Lilly; All other authors have declared no conflicts of interest.

221PD

CLINICAL OUTCOMES OF 2ND LINE ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS RECEIVING MONOTHERAPY IN THE OUTPATIENT COMMUNITY SETTING

S.K. Gruschkus[1], C. Reyes[2], M.T. Forsyth[1], E.S. Nadler[3] *[1]Healthcare Informatics, US Oncology, The Woodlands/USA, [2]Health Outcomes & Payer Support, Genentech, Inc, South San Francisco/USA, [3]Texas Oncology, US Oncology, Dallas/USA*

Background: 2nd line monotherapy options for advanced NSCLC include erlotinib (E), docetaxel (D), or pemetrexed (P). The purpose of this retrospective study was to describe clinical outcomes among patients (pts) receiving 2nd line monotherapy in a large network of outpatient community clinics in the United States.

Methods: This retrospective study used data from US Oncology's iKnowMed EMR system. Advanced NSCLC patients who received 2nd line monotherapy from 7/1/2006 – 6/30/2008 were identified. Patients were followed through 7/1/2009 to estimate treatment duration, progression-free (PFS), and overall survival (OS). Disease progression was defined as escalation in line of therapy. The Kaplan Meier method and Cox proportional hazards regression analysis were used to estimate and compare PFS and OS across treatment cohorts.

Results: We identified 610 pts – 73 (12%) received E, 87 (14%) received D, and 450 (74%) received P. Overall median age of pts was 67 years (range 31 – 91) and 55% were male. No significant differences in stage at diagnosis, baseline performance status, hemoglobin level, or body mass index were observed by treatment. Mean therapy duration was 88 days (95% CI:72-103) for patients treated with D; 103 days for P (95% CI=93-113); and 116 days for E (95% CI=78-154). Overall median OS was 197 days (192 days for D; 211 days for P; and 229 days for E; log-rank p=0.13). Overall median PFS was 133 days (132 days for D; 132 days for P; and 155 days for E; log-rank p=0.39). In Cox regression analyses using a backwards elimination approach, we found no significant association between treatment and OS (p=0.36) or PFS (p=0.26) after considering age, gender, stage at diagnosis, performance status, and hemoglobin level as potential covariates.

Conclusions: In this observational study within the outpatient community setting, we observed no significant differences in OS/PFS among patients receiving 2nd line P vs. E vs. D. Given this observed parity in objective clinical outcomes, other factors such as costs, convenience, and tolerability may become increasingly important factors in determining the most appropriate 2nd line therapy for NSCLC.

Disclosure: C. Reyes: Employment and stock ownership in Genentech E.S. Nadler: Speaker's bureau for Genentech All other authors have declared no conflicts of interest.

222PD

USEFULNESS OF MONITORING SERUM CARCINOEMBRYONIC ANTIGEN (CEA) TO DEFINE RESPONSE TO CHEMOTHERAPY AND ITS CORRELATION WITH SURVIVAL IN PATIENTS WITH NON SMALL-CELL LUNG CANCER WITH ABNORMAL BASELINE CEA LEVELS

M. Morales[1], O. Peña[1], A. Astorga[1], J. De la Garza[2], L. Martinez-Barrera[3], O. Arrieta[1] *[1]Department of Medical Oncology, Instituto Nacional de Cancerología, Mexico City/MEXICO, [2]Medical Oncology, Instituto Nacional de Cancerologia, Mexico City/MEXICO, [3]Department of Medical Oncology, Instituto Nacional de Enfermedades Respiratoria, Mexico City/MEXICO*

Background: Carcinoembryonic antigen (CEA, CEACAM5) is an oncofetal protein that functions as a cell-adhesion molecule. It is usually over-expressed in a variety of neoplasms; moreover, high serum CEA levels are an independent prognostic factor for recurrence and survival in patients with non small-cell lung cancer (NSCLC). To date, there are no markers that satisfactorily predict objective response to chemotherapy in NSCLC.

Purpose: The aim of the study was to evaluate the relationship between serum CEA with response rate to chemotherapy, progression free-survival (PFS) and overall survival (OS) in patients with NSCLC.

Methods: NSCLC patients were evaluated for the serum CEA levels at baseline and after 2 cycles of chemotherapy. Serum CEA levels were correlated with objective response rate, PFS and OS.

Results: 182 (67.4%) of 270 patients had a baseline CEA serum level >5ng/ml (range 5-7,440). 169 patients (92.9%) received a platinum-based chemotherapy and 13 patients (7.1%) a tyrosine kinase inhibitor-based chemotherapy. The median follow-up was 12.6 months. Objective global response was found in 29.7% and ≤25% CEA reduction was found in 32.4% of the patients. 100% of patients with complete response had a ≤25% CEA reduction value, 60% for partial response, 24.7% for stable disease and 9.3% for progressive disease (Pearson's ×2 value 38.49, $p<0.0001$). Sensitivity, specificity, positive predictive value and negative predictive value were 80%, 62%, 57% and 83% respectively. PFS was longer in patients with a 25% reduction in CEA (11.3 months [CI 95% 9.5-13.1] vs 8.7 months [CI 95% 7.5-9.8], $p=0.04$) and OS showed a tendency for longer survival 19.9 months [CI 95%12.3-27.5] vs 14.7 months [CI 95% 13.2-16.1]; $p=0.09$).

Conclusions: A 25% reduction from baseline CEA is associated with objective response and PFS. CEA is a noninvasive, accurate and specific predictor of objective response to treatment in locally advanced and advanced NSCLC.

Disclosure: All authors have declared no conflicts of interest.

223PD

SERUM CARCINOEMBRYONIC ANTIGEN (CEA) LEVELS ARE ASSOCIATED WITH WORSE PROGNOSIS IN ADVANCED NON- SMALL CELL LUNG CANCER (NSCLC)

S. Cedrés, I. Nuñez, M. Longo, P.N. Martínez, E. Rodriguez Checa, M. Cazorla, E. Felip *Medical Oncology, Vall d'Hebron University Hospital, Barcelona/SPAIN*

Background: The usefulness of tumor markers in NSCLC is not well defined. High levels of CEA are considered a negative prognostic factor in early-stages NSCLC but its role in advanced disease is yet to be defined. The aim of our study is to analyze the prognostic value of basal level of CEA in advanced NSCLC patients.

Methods and patients: Two hundred and seventy five patients diagnosed in our institution between April 2004 and March 2009 were retrospectively reviewed. Baseline prognostic factors analyzed were gender, histology and brain metastases. Overall survival (OS) and progression free survival (DPFS) were calculated by the Kaplan-Meier method. The cutoff value of serum CEA level was 5 ng/ml.

Results: Baseline patients characteristics: median age 63 (30–81 years), males 84.4%,stage III: 38.3% and IV: 61.7%; squamous carcinoma 22.4%, adenocarcinoma 38.6%, large cell carcinoma 21.7% and undifferentiated carcinoma 17.3%. High levels of CEA were detected in 163 (58.8%) patients. Significant higher levels of CEA at baseline were present in adenocarcinoma ($p=0.03$) but not difference according sex or brain metastases were detected. After a median follow-up of 9.1 months, 229 patients relapsed and 185 patients had died. The PFS was 5.3 months in patients with CEA>5 ng/ml and 7.4 months in patients with normal CEA ($p<0.011$). The OS was 10.0 months vs 14.0 months in patients with normal CEA ($p=0.085$). In the multivariate analysis only high levels of CEA and histology were significant correlated with worse prognostic.

Conclusion: In our analysis, high levels of CEA at baseline are correlated with worse survival in stage III-IV NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

224PD

ERLOTINIB IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC): RESULTS ON 973 PATIENTS FROM TARCEVA REGISTER OF CZECH REPUBLIC

J. Skřičková[1], M. Pešek[2], P. Zatloukal[3], V. Kolek[4], L. Koubková[5], F. Salajka[6], M. Tomíšková[7], J. Krejčí[8], M. Štícha[9], B. Kadlec[10] *[1]Department of TB and Respiratory Disease, University Hospital Brno, Brno/CZECH REPUBLIC, [2]Department of Tuberculosis and Respiratory Diseases, University Hospital Plzeň, Plzeň-Bory/CZECH REPUBLIC, [3]Department of TB and Respiratory Disease, University Hospital Bulovka, Praha/CZECH REPUBLIC, [4]Department of Pneumology, University Hospital Olomouc, Czech Republic, Olomouc/CZECH REPUBLIC, [5]Department of Pulmonology, University Hospital Motol, Prague/CZECH REPUBLIC, [6]Department of Pulmonology, University Hospital Hradec Králové, Hradec Králové/CZECH REPUBLIC, [7]Department of Respiratory Diseases and TB, University Hospital Brno, Brno/CZECH REPUBLIC, [8]Department of TB and Respiratory Disease, University Hospital Plzen, Plzen/CZECH REPUBLIC, [9]Institut of Biostatistics and Analyses, Masaryk University Brno, Brno/CZECH REPUBLIC, [10]Department of Respiratory Diseases and TB, University Hospital Brno, Brno/CZECH REPUBLIC*

Background: Our study evaluates the data from Czech Tarceva Register, which is the common project of the Czech Pneumological Society, Czech Society for Oncology and Institute of Biostatistics and Analyses of Masaryk University Brno. We evaluated the efficacy and toxicity of the 973 patients with advanced NSCLC treated with erlotinib between 12/2005 and 10/2009 in 10 institutions in the Czech Republic.

Patients and methods: In 973 patients was erlotinib administered orally 150mg/day until disease progression or unacceptable toxicity. Female were 329 (33,8 %) and male 644 (66,2%), non-smokers were 220 (22,6%), stop-smokers 393 (40,4%) and current smokers 360 (37,0%) patients. Median age was 65 years.

Results: Erlotinib was used as 1st line therapy in 12,8%, as 2nd line in 44,2% and as 3rd line in 43,0% patients. At the time of indication for erlotinib was ECOG PS 0 in 68 patients, PS 1 in 538, PS 2 in 341 and PS 3 in 26 patients. Adenocarcinoma was confirmed in 449 (46,2%), squamous-cell carcinoma in 380 (39,7%), large–cell carcinoma in 25 (2,6%) and non specified carcinoma in 109 (12,6%) patients. Complete response (CR) was confirmed in 8 (0,8%), PR (partial response) in 77 (7,9%) patients, SD (stable disease) in 425 (43,7%), 269 (43,7%) patients progressed and 194 patients was not evaluated. Major toxicities were skin toxicity in 413 (42,4,3%) and diarrhoea in 189 (19,4 %). but the therapy was finished due to toxicity grade 3-4 only in 38 (5,3%) patients. Median survival (95% CI) was 6,8 month (6,0; 7,5). Probability of 3-month survival was 72,3% (69,3;75,3), probability of 6-month survival was 52,9% (49,3; 56,5) and probability of one-year survival was 30,9 (26,9; 34,9). Progression free survival (PFS) (95% CI) was 2,9 months. Statistically significant ($p < 0,001$) were the differences between groups of patients according to PS (0+1 vs. 2+3) and according skin toxicity. The best median survival (13,3 month) was in patients with PS 0. We don't find the differences between groups of patients according smoking ($p=0,006$), according morphology ($p=0,046$) and according sex ($p=0,377$).
Conclusions: Erlotinib was well tolerated with evidence of antitumour efficacy in 1st, 2nd and 3rd line of treatment.
Disclosure: All authors have declared no conflicts of interest.

225PD

TEN-YEAR RETROSPECTIVE ANALYSIS OF 494 CONSECUTIVE METASTATIC NSCLC PATIENTS TREATED WITH FIRST LINE CHEMOTHERAPY: A SINGLE INSTITUTION EXPERIENCE

F. Oniga, O. Nascimben, R. Biason, C. Mastromauro, M. Medici, P. D'Amanzo, M.G. Ghi, R. Carnuccio, G. Crivellari, A. Paccagnella *Oncology, Ospedale dell' Angelo di Mestre (VE), Zelarino (VE)/ITALY*

Purpose: Clinical outcome is a major question in oncology. The aim of the study was to assess an instrument to measure the real clinical outcome of non selected patients (pts).
Methods: From Jan 1998 to Jan 2009 essential clinical data from all consecutive pts of our center were recorded and constantly updated in an electronic database. We considered 9 items in non selected NSCLC: histology, stage (IV), sex, age, PS (ECOG 0 or 1), 1st line chemotherapy schedule with date of start, date of last follow up and status (dead or alive). We analysed the clinical outcome of 3rd generation chemotherapy employed at our center: mono chemotherapy (vinorelbine (V), gemcitabine (G)), doublets (carboplatin (C)-G, C-paclitaxel (P), CV) and triplet (CPG). Pts treated with target therapy were excluded. We tested univariate and multivariate statistical analysis to understand if different outcome of pts was related to the different chemotherapy combinations or to pts' prognostic factor.
Results: A total of 494 metastatic NSCLC pts were analysed and 424 underwent 3rd generation chemotherapy. Pts characteristics were: median age 68 y (33-85), sex M/F 78%/22%, ECOG PS 0/1 48%/52%, Histology Adeno/Squamo/LC/Other 45%/32%/1%/22%, chemotherapy schedule mono/doublets/triplet 19%/60%/21%. Median survival for all pts was 8.3 months. Median survival was respectively 6 months for monochemotherapy, 8.1 for doublets and 11.1 for triplet group. At univariate analysis, only PS and chemotherapy were statistically significant for overall survival. At multivariate analysis, after correcting for prognostic factor , the only significant independent variable of better outcome were PS (0 vs. 1, $p=0.0000$) and triplet chemotherapy treatment (triplet vs. doublet vs. mono, $p=0.0022$).
Conclusion: With the limits of a retrospective analysis, this methodical seems a simple powerful instrument to evaluate clinical outcome of oncologic treatments. The results suggest a survival advantage for the triplet (CPG), independent from prognostic factors. This analysis seems to confirm, in single center clinical practice, the data from multicenter randomised trial comparing CPG to CP (J Clin Oncol 24:681-7, 2006).
Disclosure: All authors have declared no conflicts of interest.

226PD

TO ANALYSE THE ROLE OF QUALITY OF LIFE IN GUIDING MANAGEMENT DECISIONS IN ADVANCED NSCLC

U. Batra[1], D.C. Doval[2], S. Goyal[2] *[1]Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore/INDIA, [2]Department of Medical Oncology, Rajiv Gandhi Cancer Institute & Research Center, Delhi/INDIA*

Background: The therapeutic options for patients with advanced non-small-cell lung cancer (NSCLC) are essentially palliative. Survival and Quality of Life improvements are two major goals in treating advanced NSCLC. Lung cancer is not just associated with a high mortality but a high morbidity as well, with a significant proportion of patients severely incapacitated by disease-related symptoms such as chest pain, cough, hemoptysis, and dyspnea. In such scenario, the evaluation and improvement of quality of life (QOL) assumes great importance in the overall management of these patients.
Aim: This study was designed to evaluate the impact of chemotherapy on Quality of Life and symptoms for all patients and to evaluate correlation between Quality of Life and Response rates.
Materials and methods: 50 patients with stage IIIB or IV NSCLC undergoing palliative chemotherapy were evaluated. Patients received Gemcitabine/ Pemetrexed based Platinum based doublet chemotherapy. Quality of life was measured using EORTC QLQ-C30 questionnaire. Patients were evaluated after every 3 cycles.
Results: 42 men and 8 women were evaluated. The most common histology was squamous cell carcinoma (55%) followed by adenocarcinoma (38%).The overall response rate was as follows: Partial response: 38% Complete response: 5% Stable disease: 30% Progressive disease: 27% Quality of life score was better in patients who achieved any response rates to chemotherapy. Even in patients who achieved stable disease, QOL was better than in patients with Progressive disease.In the SD category, patients who had higher QOL fared better than patients with low QOL index.
Conclusion: An improvement in Quality of life is associated with higher response rates and better prognosis for patients. Quality of life indices are an important tool in guiding management decisions in lung cancer and should be used more frequently in making treatment decisions.
Disclosure: All authors have declared no conflicts of interest.

227P

EGFR GENOTYPE DOES NOT AFFECT CLINICAL OUTCOMES OF THE KOREAN PATIENTS WITH ADVANCED PULMONARY ADENOCARCINOMA IN THE FIRST-LINE CYTOTOXIC CHEMOTHERAPY

K.Y. Lee[1], H.J. Kim[1], W. Kim[2], K. Lee[3] *[1]Internal Medicine, Konkuk University Hospital, Seoul/KOREA, [2]Pathology, Konkuk University Hospital, Seoul/KOREA, [3]Internal Medicine, Yeungnam University Hospital, Daegu/KOREA*

Introduction: EGFR mutation is the most important predictive marker for EGFR-TKI, and tailored therapy based on EGFR genotyping in the front-line treatment of advanced NSCLC patients becomes increasingly important.

EGFR mutations are more frequent in female, non-smokers, adenocarcinoma and Asian people. However, few clinical studies have addressed whether EGFR genotyping before the initiation of treatment affect clinical outcomes of the first-line cytotoxic chemotherapy and the subsequent EGFR-TKI treatment. This study was undertaken to investigate the effects of EGFR mutations on treatment response to the first-line chemotherapy in the Korean patients with advanced pulmonary adenocarcinoma.

Methods: One hundred and forty-four stage III or IV pulmonary adenocarcinoma patients were included at two centers in Korea. DNA from biopsy or cytology specimen was determined for EGFR mutation by pyrosequence-based typing in the initial staging period. All patients received at least two cycles of the first-line platinum-based doublet chemotherapy. EGFR-TKI was used as second or third-line treatment in patients after failure to cytotoxic chemotherapy. We evaluated objective response rate (ORR) and progression-free survival to the first-line chemotherapy and 1-year survival rate between the groups with EGFR-mutant and EGFR wild-type.

Results: EGFR mutations were presented in 47 patients (32.6%): exon 19 deletion mutations 66.0 %, exon 21 L858R point mutation 23.4 %, and others 10.6 %. There was no significant statistical difference in objective response rate (ORR) (40.4%, 95% CI [26.4-54.5] vs. 37.1%, 95% CI [27.5-46.7] , p=0.70) and disease control rate (DCR) (83.0%, 95% CI [76.9-89.1] vs. 78.4%, 95% CI [71.2-84.8], p=0.52) and median progression-free survival (PFS) (6.6 months, range 2.0-15.3 vs. 4.8 months, range 1.7-15.4) between patients with EGFR-mutant and wild-type. However, the patients with EGFR mutations showed better 1-yr survival rate (YSR) (85.7%, 95% CI [74.1-97.3] vs. 54.2%, 95% CI [41.5-67.0], p=0.002) and longer median PFS (7.7 ± 5.6 months vs. 4.1 ± 3.9, p=0.007) to EGFR-TKI than those patients with EGFR wild-type.

Conclusions: First-line platinum-based combination chemotherapy administered in advanced pulmonary adenocarcinoma showed similar ORR, DCR and PFS regardless of EGFR mutation status. However, patients with EGFR mutation who received cytotoxic chemotherapy had superior 1-YSR and longer PFS to EGFR-TKI than those with wild-type EGFR. These results suggest that EGFR genotype does not affect clinical outcomes of the first-line cytotoxic chemotherapy before the subsequent EGFR-TKI treatment.

Disclosure: All authors have declared no conflicts of interest.

228P

COMPARISON OF EGFR-TKIS AND PEMETREXED FOR KOREAN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

J.H. Lee, Y.J. Ryu, E.M. Chun, J.H. Chang *Internal Medicine, Ewha Womans University School of Medicine, Seoul/KOREA*

Background: Recently the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and pemetrexed became standard palliative chemotherapy for advanced non-small cell lung cancer (NSCLC). We compared the efficacy of EGFR-TKIs and pemetrexed in Korean patients with advanced NSCLC.

Methods: We collected the clinical information of advanced NSCLC patients treated with EGFR-TKIs or pemetrexed for more than two weeks at a University Hospital between July 2003 and December 2009. Median survivals were calculated using the Kaplan-Meier method.

Results: One-hundred thirty-six patients (108 EGFR-TKIs vs. 28 pemetrexed) were enrolled. Their median age was 64 years and 86 (63%) were male. Fifty-five patients (40%) were non-smokers and 94 (69%) had non-squamous cell carcinoma (NSQ). There were 37% at stage IIIb. Out of 136 patients, 2 achieved a complete remission (CR), 48 achieved a partial remission (PR), and 15 experienced stable disease (SD) while 59 experienced progressive disease (PD), resulting in a response rate of 37% and a disease control rate of 48%. After a median follow-up of 494 days, the median progression-free and overall survival time was 69 and 210 days, respectively. There were no differences in median survival time (EGFR-TKIs 301 days vs. pemetrexed 155 days, p=0.058), and time to progression (93 days vs. 64 days, p=0.333). Although the overall response rate is higher in EGFR-TKIs-treated patients (EGFR-TKIs 42% vs. pemetrexed 18%, p=0.02), pemetrexed was more frequently chosen for more than third line chemotherapy because of its late introduction (EGFR-TKIs 5% vs. pemetrexed 24%, p=0.002). In patients with NSQ, there was no difference in the response rate (EGFR-TKIs 47% vs. pemetrexed 24%, p=0.08). Multivariate analysis using Cox regression model identified NSQ as an independent predictor of survival (p=0.001; relative risk [RR], 0.397; 95% confidence interval [CI], 0.233-0.678). Among patients with NSQ, non-smoker and stage IIIB were associated with longer survival (p=0.038; RR, 0.489; 95% CI, 0.249-0.961) (p=0.046; RR, 0.413; 95% CI, 0.173-0.984).

Conclusions: In advanced NSCLC, both EGFR-TKIs and pemetrexed had similar efficacy in the overall survival and time to progression.

Disclosure: All authors have declared no conflicts of interest.

229P

CLINICAL ACTIVITY OF BIBW 2992, AN IRREVERSIBLE INHIBITOR OF EGFR/HER1 AND HER2 IN ADENOCARCINOMA OF THE LUNG WITH MUTATIONS IN THE KINASE DOMAIN OF HER2NEU

J. De Grève[1], L. Decoster[1], J. De Mey[2], P. In 't Veld[1], C. Geers[1], M. Taton[3], M. Shahidi[4], D. Galdermans[5], E. Teugels[6], D. Schallier[6] *[1]Medical Oncology, Oncologisch Centrum, UZ Brussel, Brussels/BELGIUM, [2]Medical Oncology, Oncologisch Centrum, UZ Brussels, Brussels/BELGIUM, [3]Reasearch and Development, Boehringer Ingelheim, Brussels/BELGIUM, [4]Boehringer Ingelheim, Uk, Bracknell, Berks/UNITED KINGDOM, [5]Medical Oncology, ZNA Middleheim Hospital, Antwerp/BELGIUM, [6]Medical Oncology, UZ Brussel, Brussels/BELGIUM*

Background: 2–4% of lung adenocarcinomas harbour HER2neu mutations and, similarly to EGFR mutations, are more common in females, non-smokers and patients of Asian background. BIBW 2992 is a potent, irreversible inhibitor of EGFR/HER1 and HER2 (IC_{50} 0.5 and 14 nM, respectively) with preclinical and clinical activity in EGFR mutated NSCLC. This exploratory Phase II study is investigating the use of BIBW 2992 in demographically and genetically selected patients with NSCLC.

Methods: The studies primary endpoint is objective response rate. Stage IIIB/IV lung adenocarcinoma patients who are never or light ex-smokers with EGFR or HER2 mutation positive tumours (current report) or are EGFR FISH+ are eligible. BIBW 2992 is administered at 50 mg qd until disease progression. Tumour assessments are performed every 8 weeks. Any patients who progress may continue treatment with BIBW 2992 and weekly paclitaxel (80 mg/m^2 weekly, 3/4 weeks).

Results: To date, five patients with lung adenocarcinoma and HER2 mutations in exon 20 have been included. All patients are female, non-smokers with Stage III/IV adenocarcinoma of the lung and had failed prior chemotherapy. Preliminary analysis shows significant improvement of patients' symptoms and performance status as well as reduction in tumor size, amounting to a partial response in three patients. One patient has remained on treatment >12 months. Diarrhoea and skin rash were the predominant adverse events and led to early discontinuation of BIBW 2992 in one patient. Updated information on all patients will be provided at the meeting.

Conclusions: The presence of HER2 mutations characterizes a subgroup of NSCLC that is dependent on the HER2 pathway for survival. In pre-treated

patients with adenocarcinoma and activating HER2 mutations, BIBW 2992 can provide a significant benefit. This clinical observation closely mimics recent results obtained with BIBW 2992 in a HER2-driven lung cancer in a transgenic animal model. Further investigation of BIBW 2992, an irreversible EGFR/HER2 inhibitor, as a potential new treatment option for these patients is warranted.

Disclosure: J. De Grève: Unrestricted research grant from Boehringer Ingelheim; M. Taton: Boehringer Ingelheim employee; M. Shahidi: Boehringer Ingelheim employee. All other authors have declared no conflicts of interest.

230P

PHASE I OPEN-LABEL TRIAL OF CONTINUOUS DOSE OF BIBW 2992 IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER FAILING CHEMOTHERAPY AND/OR ERLOTINIB AND/OR GEFITINIB (LUX-LUNG 4)

N. Yamamoto[1], T. Tamura[2], T. Takahashi[3], H. Murakami[1], H. Nokihara[4], T. Naito[1], K. Nishio[5], Y. Seki[6], A. Sarashina[7], M. Shahidi[8] *[1]Department of Thoracic Oncology, Shizuoka Cancer Centre, Shizuoka/JAPAN, [2]Medical Oncology, National Cancer Center Hospital, Tokyo/JAPAN, [3]Department of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka/JAPAN, [4]Department of Thoracic Oncology, National Cancer Center, Tokyo/JAPAN, [5]Department of Oncology, Kinki University of Medicine, Osaka/JAPAN, [6]Research & Development, Nippon Boehringer Ingelheim, Tokyo/JAPAN, [7]Research and Development, Nippon Boehringer Ingelheim, Kobe/JAPAN, [8]Boehringer Ingelheim, Uk, Bracknell, Berks/UNITED KINGDOM*

Background: BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2, has preclinical activity in lung cancer models harbouring activating and resistant EGFR mutations. A Phase I study of BIBW 2992 in pts advanced with NSCLC was conducted to evaluate the safety, tolerability, PK, tumour response and recommended dose for Phase II.

Methods: In this study, pts with NSCLC (stage IIIB/IV; ECOG 0–1), who had either failed standard chemotherapy and/or treatment with gefitinib or erlotinib, or those with no other appropriate therapy available, were eligible. Oral BIBW 2992 started at 20 mg qd; doses were increased to 50 mg qd until 33.3% or more Grade >2 toxicity occurred. PK sampling was performed on Days 1–2 and at steady state of the initial treatment course. Tumour response was assessed by RECIST. EGFR mutation analysis in serum and tumour specimens was performed where possible.

Results: 12 evaluable pts have been treated (doses of 20–50 mg; 5 male, 7 female; median age 62.5 years [range 39–67]). One DLT was seen in Course 1; 1 pt developed Grade 3 mucositis at 50 mg, which subsided following dose reduction. Most AEs were mild (Grade 1 or 2) and included diarrhoea, dry skin, stomatitis, rash, paronychia, and anorexia. Peak plasma concentrations of BIBW 2992 were reached 3-4 hrs after administration; the half life was 30–40 hrs. 6/12 pts had tumour size reductions, with three achieving prolonged SD (table). EGFR mutation status was wild-type for 4 pts and EGFR exon 19 deletion and T790M for 2 pts.

Age	Sex	Histology	Dose (daily)	Months on Study**	Previous Treatment	EGFR Mutation Status
64*	F	Adeno	20 mg	11	1. cisplatin + TS-1 2. gefitinib 3. erlotinib 4. gefitinib	Exon 19 del T790M
57*	F	Adeno	40 mg	19+	1. cisplatin + gemcitabine 2. nimotuzumab	WT (serum)
65*	M	Adeno	40 mg	13+	1. cisplatin + docetaxel 2. docetaxel 3. gefitinib 4. gefitinib + gemcitabine 5. gefitinib	WT (serum)

*never-smoker; **as of the date of 10th Jan 2010.

Conclusion: The safety and PK profile of BIBW 2992 in Japanese pts were similar to non-Japanese pts. Continuous oral BIBW 2992 at a starting dose of 50 mg once daily was well tolerated with acceptable safety profile. The recommended starting dose for Phase II has been defined as 50 mg in Japanese pts.

Disclosure: Y. Seki: Boehringer Ingelheim employee; A. Sarashina: Boehringer Ingelheim employee; M. Shahidi: Boehringer Ingelheim employee. All other authors have declared no conflicts of interest.

231P

PLINABULIN (NPI-2358), A NOVEL VASCULAR DISRUPTING AGENT (VDA), IN NON-SMALL CELL LUNG CANCER (NSCLC)

O. Aren[1], L. Matamala[1], M. Reyes[1], A. Santini[1], K. McArthur[2], G.K. Lloyd[3], M.A. Spear[4] *[1]Medical Oncology Service, Instituto Nacional Del Cancer, Santiago/CHILE, [2]Clinical, Nereus Pharmacueticals, Inc, San Diego/USA, [3]Research and Development, Nereus Pharmaceuticals, San Diego/USA, [4]Clinical, Nereus Pharmaceuticals, San Diego/USA*

Plinabulin is a vascular disrupting agent (VDA) that destabilizes the endothelial cytoskeletal structure, leading to selective collapse of established tumor vasculature. VDAs are a new class of oncology agents that have utility in attacking tumor vasculature through a mechanism different from the VEGF targeted agents, thus they have different efficacy and toxicity profiles from these agents as well as cytotoxic agents. Recently, data has indicated significant potential in the treatment of NSCLC. A large increase in survival was seen by adding DMXAA (another VDA) to carboplatin / paclitaxel in a randomized Phase 2 trial in patients with NSCLC, with subset analysis indicating favorable outcomes in squamous cell carcinoma. The first-in-human study of plinabulin was a dynamic accelerated dose titration (DADT) with encouraging pharmacokinetic, pharmacodynamics (decreases in tumor blood flow) and safety results. In murine models plinabulin was markedly synergistic with cytotoxic chemotherapy agents, particularly docetaxel in NSCLC models, with improvements in both toxicity and efficacy seen. This led to a Phase 1/2 clinical trial of the combination with docetaxel in NSCLC. The Phase 1 portion of the study indicated favorable safety, pharmacokinetic and efficacy profiles for the combination. This led to the initiation of the Phase 2 portion in which patients with advanced NSCLC that received prior chemotherapy were enrolled. 110 patients were randomized to receive 75 mg/m^2 docetaxel +/− 30 mg/m^2 plinabulin, and subsequently an additional 57 patients are being randomized to receive docetaxel +/− 20 mg/m^2 plinabulin. Interim response data for the 30 mg/m^2 combination arm was encouraging with 26% (5/19) of then evaluable patients having a ≥30% decrease in tumor measurements compared with 3% (1/30) in the docetaxel arm. Safety and efficacy data will continue to be compared between plinabulin dosing groups to determine which dose to assess in a Phase 3 study. Given the differences in safety and efficacy with currently available therapies, and potential for use in underserved patient subsets, this data continues to suggest VDAs may translate into new treatment paradigms for NSCLC and other malignancies.

Disclosure: K. McArthur: Katherine McArthur is an employee of Nereus Pharmaceuticals and has options in company stock. G.K. Lloyd: Dr. Lloyd is an employee of Nereus Pharmaceuticals and has options in company stock.M.A.

Spear: Dr. Spear is an employee of Nereus Pharmaceuticals and has options in company stock. All other authors have declared no conflicts of interest.

232P

HIGH RESPONSE OF SECOND-LINE CHEMOTHERAPY WITH PEMETREXED OR GEMCITABINE COMBINED WITH CARBOPLATIN IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER EXPERIENCING PROGRESSION FOLLOWING 6 -MONTHS AFTER CONCLUDING PLATINUM-BASED CHEMOTHERAPY

O. Arrieta[1], C. Villarreal-Garza[1], M. Morales[1], D. Pachuca[1], R.M. Michel[1], L. Martinez-Barrera[2], A. Astorga[1] *[1]Department of Medical Oncology, Instituto Nacional de Cancerología, Mexico City/MEXICO, [2]Department of Medical Oncology, Instituto Nacional de Enfermedades Respiratoria, Mexico City/MEXICO*

Background: Because of improved therapeutic results after first-line platinum-based chemotherapy in patients with stage IV non-small-cell lung cancer (NSCLC), second-line chemotherapy may be considered for a growing number of patients. Approximately 10% of patients have an interval time after concluding first-line platinum-based chemotherapy greater than six months. These patients may achieve high tumor responses when platinum is again used in second-line treatment.

Patients and methods: Twenty-three patients experiencing progression following 6-months after concluding platinum-based chemotherapy were managed with second-line treatment with carboplatin combined with gemcitabine or pemetrexed. Overall response, progression-free survival (PFS), and overall survival (OS) after initiation of second-line treatment were calculated for all patients.

Results: Median PFS after first-line treatment was 12.6 months (95% CI, 10.4–14.7 months). Partial response was achieved in 7 of 23 patients, resulting in an overall response of 30.4% (95% confidence interval [95% CI], 11.6–49.0). Following initiation of second-line chemotherapy, median PFS was 5.9 months (95% CI, 1–10.9 months) and median OS was 12.5 months (95% CI, 3.5-21.5 months). The 1-year survival rate for all patients was 61.0% (95% CI, 29.5–82.0). Adding these results to those of the previously 10 published trials, 75 of 326 patients, 23%, (95% CI, 18.7-27.3) presented an overall response with the use of second-line platinum-based chemotherapy.

Conclusion: The use of platinum combinations as second-line chemotherapy seems to have a place in the management of patients with advanced NSCLC, especially those with an interval time to progression greater than 6 months.

Disclosure: All authors have declared no conflicts of interest.

233P

DORSET CANCER CENTRE EXPERIENCE OF FIRST- AND SUBSEQUENT LINE SYSTEMIC THERAPY IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

K.L. Bradley[1], M.T. Lwin[1], B.K. Eccles[2], V.M. Laurence[1], T.R. Geldart[3] *[1]Clinical Oncology, Dorset Cancer Centre, Poole, Dorset/UNITED KINGDOM, [2]Oncology, Royal Bournemouth Hospital, Bournemouth/UNITED KINGDOM, [3]Clinical Oncology, Dorset Cancer Centre, Bournemouth/UNITED KINGDOM*

Purpose: Systemic therapy has a key role in the treatment of non-small cell lung cancer, both in the primary setting, and at relapse or progression. We present our outcomes and compare these with published data.

Methods: We carried out a retrospective review of consecutive patients treated with systemic therapy at our centre during a two-year period, January 2007 to December 2008. In analysis of outcomes following first-line therapy, we included patients with stage IIIb or IV disease whose primary treatment was palliative systemic therapy. Second-, third- and fourth-line data also include patients previously treated radically with surgery, radiotherapy or chemoradiotherapy. We report response-rates, overall survival and time-to-progression in each setting.

Results: 176 systemic treatment episodes were identified during the study period. Following 1st line therapy, 1 year survival was 37% and 2 year survival, 11%.

Line of Therapy	Number Treated	Response Rates (%) CR	PR	SD	PD	Overall Survival Median/ (Range) (months)
1	113	0	48 (42%)	17 (15%)	48 (42%)	9 (1–32)
2	48	0	7 (14%)	7 (14%)	34 (71%)	16 (5–60)
3	12	0	4 (33%)	3 (25%)	5 (42%)	31 (14–44)
4	3	0	0	0	3 (100%)	40 (19–60)

From the second-line of systemic therapy, patients were a heterogeneous group. Outcomes varied with previous treatment received.

Conclusion: Following first line systemic therapy for advanced non-small cell lung cancer, response rates are reported around 19% with median survival 7.9 months, 1 year survival of 33% and 2 year survival of 11% [1]. Our audit of our own data shows that even within a district general hospital setting, outcomes from lung cancer can be as good as or better than trial outcomes by adopting a tailored approach to treatment.

References

Schiller, JH et al. Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2002;346:92–98.

Previous Treatment	Number Treated	Overall Survival (months)
Radical treatment (stage I-IIIa)	4	19 (15–60)
Palliative treatment (stage IIIb/IV)	44	15 (5–45)
Total number of patients treated with 2nd line chemotherapy	48	16 (5–60)

Disclosure: All authors have declared no conflicts of interest.

234P

SALVAGE CHEMOTHERAPY WITH PEMETREXED (PEM) FOR NON SMALL CELL LUNG CANCER (NSCLC): AN IMPLEMENTATION STUDY

T. Berghmans[1], C. Jungels[2], A.P. Meert[3], J.J. Lafitte[4], J. Sculier[5] *[1]Medicine, Institut Jules Bordet, Brussels/BELGIUM, [2]Intensive Care Unit and Thoracic Oncology, Institut Jules Bordet, Brussels/BELGIUM, [3]Soins Intensifs et Cancerologie Pulmonaire, Institut Jules Bordet, Brussels/BELGIUM, [4]Pneumology, CHRU Lille, Lille/FRANCE, [5]Soins Intensifs et Oncologie Thoracique, Institut Jules Bordet, Bruxelles/BELGIUM*

Purpose: Salvage treatment with PEM in NSCLC has been reported in the context of phase II-III trials, only dealing with selected patients. The aim of this retrospective study is to assess the generalizability of these results in an

unselected population, in terms of response rate, survival, progression-free survival and toxicity.

Patients and methods: All consecutive NSCLC patients progressing after at least 1 previous chemotherapy regimen and receiving PEM (500mg/m^2/21 days with folate and vitB12 supplementation) at the Bordet Institute were eligible. Response was assessed according to WHO criteria and toxicity using CTC criteria. Overall and progression-free (PFS) survival times were the periods from the first day of PEM until death (or last date known to be alive) and first date of progression, respectively.

Results: From 07/07 until 09/09, 33 patients with relapsed stage IV NSCLC were treated with PEM. Their principal characteristics were: male/female 22/11, median age 59 years, adenocarcinoma/squamous/other histology 23/6/4. PEM was administered as 2^d, 3rd or >3rd line in 15/10/8 patients. Patients received a median of 3 cycles of PEM (range 1–11), with the following results:

	Present Study	Literature Data (phase II-III trials)
Response rate	12.9% (95% CI 1.1%–24.7%)*	6.0–18.5%
Stabilisation rate (response plus no change)	42% (95% CI 25%–59%)	36–68%
Median PFS	2.5 months	2–3 months
Median survival time	6.4 months	5.7–16.0 months

*all observed in non-squamous histologies. Grade 3 and 4 neutrophil and platelet toxicity were observed in 7 (including 1 toxic death) and 2 patients, respectively. PEM was stopped in two patients for excessive toxicity.

Conclusions: Salvage PEM for relapsing NSCLC after previous chemotherapy showed, in unselected heavily pre-treated population, a similar activity to prospective studies despite significant toxicity. Further inclusion of patients from another institution is planned.

Disclosure: All authors have declared no conflicts of interest.

235P

A RETROSPECTIVE STUDY OF PEMETREXED COMBINED WITH OXALIPLATIN AS THE SECOND LINE TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER: COMPARABLE TOXICITY, BETTER OUTCOME

J. Zhu, X.X. Zhang, M.J. Huang, L. Zhou *Department of Thoracic Oncology, West China Hospital, Chengdu/CHINA*

Background: Outcome of the single agent regimen as the second-line or post second-line chemotherapy for metastatic NSCLC is poor. Pemetrexed combined with oxaliplatin was reported to be well-tolerated and active for the chemotherapy-naïve NSCLC. Current retrospective study was designed to evaluate the feasibility and the therapeutic effect of pemetrexed plus oxaliplatin regimen for pretreated NSCLC.

Patients and methods: Medical records of consecutive patients with metastatic NSCLC failed to the prior chemotherapy between January 2007 and January 2009 were reviewed for treatment, toxicity and outcome. A total of 79 patients were administered pemetrexed included regimen whose records could be exactly traced. 34 of them were treated with the regimen PO (pemetrexed 500mg/m^2 day1 plus oxaliplatin 125mg/m^2 day1, repeated every 21 days). Another 45 patients were administered pemetrexed only. Chi-Square test was used to compare the response rates between groups. Kaplan-Meier curve and Log-Rank test was used to analyze the survival.

Results: Treatment of the two groups were well-tolerated, no therapy related death happened. The most common toxicity was neutropenia. Comparable response rate (15.2% vs. 11.1%, P=0.743) and tumor control rate (63.6% vs. 47.5%, P=0.168) were observed in the two groups. Median time to progression and overall survival in the PO group were 18 weeks (95% CI: 13.72~22.28 weeks) and 31 weeks (95% CI: 15.56~46.44 weeks), respectively. It was significantly longer than pemetrexed group (P=0.002 and 0.006, respectively).

Conclusions: Pemetrexed combined with oxaliplatin as the second line treatment for advanced NSCLC showed comparable safety and response as single pemetrexed regimen. The survival was impressively improved in the doublet agents group in current study. A prospective study is supported.

Disclosure: All authors have declared no conflicts of interest.

236P

PEMETREXED: 3RD LINE PALLIATIVE CHEMOTHERAPY AND BEYOND IN METASTATIC NON SMALL CELL LUNG CANCER (NSCLC): SINGLE INSTITUTION CASE SERIES

H. Charalambous, M.P. Decatris *Department of Medical Oncology, Bank of Cyprus Oncology Centre, Nicosia/CYPRUS*

Introduction: Pemetrexed (Pem) is indicated only for first and second line treatment of non squamous NSCLC. There are currently no data for its use as third line or beyond third line treatment. Due to funding restrictions in Cyprus (no reimbursement for Pem), Pem was used in selected patients when all other therapeutic options had been used (ie post first line gemcitabine platinum doublet, second line docetaxel and third line erlotinib).

Methods: Six patients are included in this retrospective study. One patient received Pem as 3rd line, four patients as 4th line (previous treatments as above) and one as 5th line (previous treatments as above and also vinorelbine). Two patients are still on treatment, whilst three patients are still alive. All patients received Pem 500mg/m^2 with folic acid and B12 supplementation. Patients had regular Chest X-rays and CT scans (every 2–3 cycles) and formal assessment of their toxicity with CTC criteria every 3 weeks. PFS and OS were calculated with the Kaplan-Meier Method.

Results: 5 males and 1 female patients, median age 55 years (range 49-68), 2 never and 3 ex smokers, WHO performance status PS1 n=4 and WHO PS2 n=2, histology adenocarcinoma n=3, mixed adenocarcinoma / BAC n=2 and pure BAC n=1. They received a median 11 cycles of Pem (range 2-16). Toxicity: grade 1-2 (g1–2) malaise n=6, g1 constipation n=3, g1 stomatitis n=2, g 1 taste disturbance n=1, g1 neurosensory changes n=1, g1 diarhoea n=1, g1 nausea n=1 and g1 anorexia n=1. Five of the six patients had symptomatic improvement. Radiological response 1 patient had a partial response, 3 patients minor response, 1 patient stable disease and 1 patient progressive disease. Median PFS was 196 days (95% Confidence intervals CI 0–426 days). Median survival from the date of starting Pem chemotherapy was 457 days (95% CI 36-878), whilst median overall survival from the initiation of first line therapy was 31.3 months (951 days, range 892–1175).

Conclusions: In well selected patients with well preserved performance status, lack of significant other comorbidity and non squamous NSCLC, Pem as 3rd line chemotherapy and beyond can result in very meaningful palliation of symptoms and prolongation in survival.

Disclosure: All authors have declared no conflicts of interest.

237P

CIS-PLATINUM, PEMETREXED AND BEVACIZUMAB (CPBEV) AS FIRST-LINE THERAPY FOR LOCALLY ADVANCED OR METASTATIC ADENOCARCINOMA OF THE LUNG: PRELIMINARY DATA OF SAFETY AND EFFICACY OF A PHASE II STUDY

R. Bordonaro[1], H. Soto-Parra[1], A. Nacci[2], F. Latteri[1], P. Rizzo[2], S. Cordio[1], P. Salice[1], D. Sambataro[1], E. Potenza[1], S. Cinieri[2] *[1]Oncology, ARNAS Garibaldi, Catania/ITALY, [2]Oncology, Perrino Hospital, Brindisi/ITALY*

The paradigms of advanced non-small cell lung cancer therapy are rapidly changing; data from two large randomized trials showed that Pemetrexed and Bevacizumab, when administered separately with platinum compounds, prolong survival of patients with non-squamous histologies. On these basis, we started a phase II trial to test safety and activity of a three-drugs-regimen containing cis-platinum, pemetrexed and bevacizumab (CPBev). Eligible criteria are: chemonaive patients with proven histology of non-squamous non-small cell lung cancer, PS-ECOG-WHO $\leq$ 2, adequate hematological, liver and renal functions, no previous history of hemoptysis, stage IIIB - IV without cerebral metastases, at least one measurable lesion, absence of uncontrolled hypertension or other severe comorbidities, non anamnestic episodes of venous thromboembolism. In the baseline assessment a CT-scan of the brain, of the thorax and of the abdomen and a Bone scan were mandatory. We adopt the two-stage of Simon model as statistical design of the study. Administered doses were 75 and 500 mg/p.s.m for cis-platinum and pemetrexed respectively and 7.5 mg./kg for Bevacizumab, for 3 – 6 cycles. G-CSF were administered only after the first cycle of therapy, whereas vitamin supplementation started from day 1 of the first cycle. Since now, 13 patients have been enrolled. Patients characteristics are: male/female 11/2, median age (years) 60 (r. 36 – 77), ECOG-WHO/PS 0/1: 8/2. At a preliminary evaluation of safety data, no grade 3-4 extra-hematological adverse events were registered. Administration of the CPBev regimen seems feasible and safe. To date, 11 of the 13 pts. enrolled completed six cycles of therapy; we registered 5 PR, 4 SD and 2 PD. If another clinical response will be register among the next 4 pts., enrollment will proceed to the second step of the study design.

Disclosure: All authors have declared no conflicts of interest.

238P

PEMETREXED-INDUCED FLUID RETENTION

A. Katz, D.A. Bastos, A. Calabrich, A. Shimada *Medical Oncology, Hospital Sirio Libanês, Sao Paulo/BRAZIL*

Despite the favorable toxicity and safety profiles of pemetrexed, several adverse events have been reported, including blood and lymphatic system disorders, gastrointestinal and general disorders. We describe a case series consisting of eight patients who developed clinically significant fluid retention, an uncommon adverse effect associated with the use of pemetrexed. All patients have received vitamin supplementation and were pretreated with corticosteroids as indicated in the package insert. Other causes of edema were excluded and all patients had normal echocardiogram, normal levels of B-type natriuretic peptide and albumin, normal renal, hepatic and thyroid function tests and no significant proteinuria. Most patients presented with mild to moderate edema, mainly in periorbital area, while 4 developed pleural effusions. One of these patients required a bilateral thoracocentesis was necessary for symptom relief and the pleural effusion analysis was consistent with an exsudate with no malignant cells and negative cultures. There was complete disappearance of generalized edema and bilateral pleural effusion after discontinuation of pemetrexed treatment. Other patients also had complete resolution of the fluid retention (including pleural effusion) after pemetrexed was discontinued due to disease progression. All other cases were managed with observation only or salt restriction and diuretics, with limited control of this side effect. Pemetrexed-associated peripheral and eyelid edema has been rarely reported, with an estimated incidence of 1% in clinical trails. To our knowledge there were no severe cases reported with need for treatment discontinuation until now. The mechanism involved in the development of fluid retention and consequent edema is unknown but may be due to capillary leakage syndrome. Now that pemetrexed has demonstrated efficacy in the first line setting and is an option as maintenance or early second line therapy, more patients will be exposed to this agent and therefore more individuals will potentially develop this treatment related adverse effect. Therefore, we believe it is important to report this unusual adverse event and to understand its pathophysiology in order to attempt to develop strategies to avoid and manage this side effect.

Disclosure: All authors have declared no conflicts of interest.

239P

RISK OF FATAL ADVERSE EVENTS WITH BEVACIZUMAB IN LUNG CANCER PATIENTS TREATED WITH CHEMOTHERAPY: A META-ANALYSIS

V. Ranpura[1], S. Hapani[1], S. Wu[2] *[1]Department of Medicine, Suny Stony Brook University Medical Center, Stony Brook/USA, [2]Department of Medical Oncology and Hematology, Suny Stony Brook University Medical Center, Stony Brook/USA*

Background: Bevacizumab is approved for the treatment of metastatic non-squamous non-small cell lung cancer (NSQ-NSCLC) in combination with chemotherapy. However, its use has been associated with fatal adverse events (AE), particularly in squamous NSCLC. In order to assess the risk of fatal AE with bevacizumab in NSCLC, particularly NSQ-NSCLC, we performed a systematic review and meta-analysis of published randomized control trials (RCT).

Methods: We searched the databases of PubMed, Web of Science, and American Society of Clinical Oncology conferences until August, 2009 to identify relevant clinical trials. Eligible studies included prospective RCTs in which bevacizumab was compared to a control concurrently with standard anti-neoplastic therapy in lung cancer. Summary incidence rates, relative risks (RRs), and 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models based on the heterogeneity of the included studies.

Results: A total of 2,072 patients with NSCLC from 4 RCTs were included for analysis. The incidences of fatal AE in NSCLC and NSQ-NSCLC were 4.2% (95% CI: 1.5-10.9%) and 2.7% (95% CI: 1.2-6.0%) respectively. When compared to controls, bevacizumab significantly increased the risk of fatal AE in NSCLC and NSQ-NSCLC with RRs of 3.54 (95 % CI: 1.48-8.51, p=0.005) and 3.39 (95% CI: 1.28-8.95) respectively. The risk was increased significantly for bevacizumab at 5mg/kg/wk (RR, 4.20; 95 % CI 1.72-10.21, p=0.002), but not at 2.5mg/kg/week (RR, 2.19, 95 % CI 0.56-0.84, p=0.26). The most common cause of fatal AE was pulmonary hemorrhage (51.4%), followed by neutropenia (17.1%).

Conclusion: Bevacizumab significantly increased the risk of fatal AE in patients with NSQ-NSCLC receiving chemotherapy. Further studies are strongly recommended to optimize the treatment.

Disclosure: S. Wu: Dr. Wu receives Honararia from Onyx, Novartis and Wyeth Pharmaceuticals and speaker for Onyx, Novartis and Pfizer pharmaceuticals All other authors have declared no conflicts of interest.

240P

METASTATIC ADENOCARCINOMA OF THE LUNG IN ELDERLY PATIENTS RESPONSIVE TO ERLOTINIB, REPORT OF 3 CASES AND LITERATURE REVIEW

G. Shoja e Razavi, A. Goharian *Internal Medicine, Golestan University of Medicine, Gorgan/IRAN*

Introduction: Advanced lung cancers generally show aggressive behaviour and their prognosis are usually unfavorable specially in elderly patients ,be cause the age and underlying diseases not only delay the diagnosis but also complicates the outcome and management of the patients.Among different pathologic subtypes of lung cancer,adenocarcinoma shows different natural history specially when erlotinib is added to its theraputic regimen.We report 3 cases of elderly patients with metastatic adenocarcinoma of the lung which responded to Erlotinib in combination with Navelbine and Cisplatin and followed with Erlotinib as single agent.

Materials and method: 3 cases (one male and two females) were selected from the patients referred to Medical Oncology Clinic at 5th Azar University Hospital. All the cases have had Coronary Artery Bypass Graft due to IHD and the tumor was found during thoracotomy for CABG in one case and 2 to 3 months after surgery in another case. The third case was first presented with abnormal gait, dizziness and mild abnormal unilateral muscle weakness and a right cerebellar mass detected on brain MRI with past history of CABG 2 years ego. Further investigation for the latter showed a lung mass without any other distant metastases and metastatic work up for the first two cases showed asymptomatic metastases in left frontal area.Cardiologic consult and echocardiogram showed borderline LVEF and Taxanes were omitted from chemotherapy schedule for the patients. Single cerebellar metastasis was removed surgically in patient with symptomatic cerebellar mass lesion perior to reference to our clinic.

Results: Median age of the patients was 73 ranging from 70 to 76 years. skeletal metastases were present in patient with cerebellar lesion but not in other cases and no visceral mets. were found in none of the cases.All of the patients were planned to receive navelbine 25mg/m2 D1 and8 with Cisplatin 75mg/m2 on D1 every 21 days with Erlotinib 150 mg per Day continously.The case with metastatic bone disease receives monthly Zometa 4 mg infusions as well. Whole brain RT was done perior to chemotherapy for the case with resected cerebellar metastasis and following 4 courses of chemotherapy for 2 cases with asymptomatic brain lesions.Re evaluation showed tumor disappearance in 1 case and 50% reduction in tumor size in 2 other cases, chemotherapy was held and erlotinib continued at the same dose (150 mg daily).

Conclusions: The patients were followed for median of 9 months. One case died due to Acute Coronary Syndrome which was unrelated to underlying malignancy and the 2 cases are alive and symptom free with stable disease after 9 months of follow up. No side effect was found and no neutropenic fever episode was reported as well.We found the combination of Navelbin, Cis platin and Erlotinib feasible without significant side effects but positive effects on metastatic friable elderly patients with Adenocarcinoma of Lung.

Disclosure: All authors have declared no conflicts of interest.

241P

TARGETED THERAPY FOR NSCLC: A CASE FOR CHANGE

B.K. Eccles[1], M.T. Lwin[2], K.L. Bradley[2], V.M. Laurence[2], T. Geldart[3] *[1]Oncology, Royal Bournemouth Hospital, Bournemouth/UNITED KINGDOM, [2]Clinical Oncology, Dorset Cancer Centre, Poole, Dorset/UNITED KINGDOM, [3]Department of Oncology and Haematology, Royal Bournemouth Hospital, Bournemouth/UNITED KINGDOM*

Histology directed therapy is a hot topic in treatment of NSCLC. Recent data suggests that response to first line tyrosine kinase inhibitors is strongly correlated with EGFR mutational status. Recent data also suggests a differential response to chemotherapy based on histological subtype. Within the UK, historically NSCLC has not been routinely sub-classified by all histopathologists and at present mutational testing is not routinely available. NHS funding for TKI therapy is only available for patients receiving 2nd line therapy for advanced disease.

Methods: We present recent retrospective data on use of erlotinib in 2 UK district general hospitals for patients with advanced (stageIIIb/IV) NSCLC over a 3 year period from Jan 2007 - Jan 2010 looking at smoking history, number of previous therapies, duration of treatment, response-rate, overall survival, and grade of rash, classification of histological subtype, method of histological diagnosis and sample quality / size.

Results: 43 patients were identified during the study period. 1 patient received gefitinib, the rest erlotinib. 2 patients were treated in the 1st line setting (4.7%), 38 (88%) 2nd line, 2 (4.7%) 3rd line and 1 patient 4th line (2.3%). Clinical benefit (Partial response, PR and stable disease, SD) was seen in 35%; with no complete responders, 14% PR (n=6), 21% SD (n=9). 55 % progressive disease (n=23) and unknown response in 11% (n=5). Overall survival from date of diagnosis ranged from 2-44 months with 13 patients still alive, 3 of which are still receiving treatment. Median overall survival was 14 months, broken down into 20.8 months in those with clinical benefit and 11.8 months in those who progressed or whose response could not be evaluated. Histology was squamous subtype in 21%, non-squamous in 49% and not otherwise specified in 28%. Histology was obtained by biopsy in (49%) or brushings (33%); but only 46% of histology was of a sufficient sample for mutational testing.

Conclusion: Our data show good overall survival but many patients fail to benefit from an unselected treatment approach. Close multidisciplinary working with chest physicians and histopathologists will be required to maximise histological information and facilitate histology directed therapy.

Disclosure: All authors have declared no conflicts of interest.

242P

RADIOTHERAPY FOR LOCOREGIONAL RECURRENT NON-SMALL CELL LUNG CANCER

J. Kim[1], M. Kim[2], N. Jang[1], J. Lee[3] *[1]Radiation Oncology, Seoul National University Bundang Hospital, Seongnam-si/KOREA, [2]Radiation Oncology, Seoul National University Hospital, Seoul/KOREA, [3]Medical Oncology, Seoul National University Bundang Hospital, Seongnam-si/KOREA*

Purpose: To evaluate outcome and complication of curative radiotherapy for locoregionally recurrent non-small cell lung cancer (NSCLC).

Methods and materials: From 2004 to 2008, 21 patients received curative radiotherapy for locoregionally recurrent NSCLC without systemic metastasis after surgery at Seoul National University Bundang Hospital. At the time of recurrence, median age was 70 years (range 49-81), and 19 patients were male. Majority of patients (N= 17) was ECOG 0 or 1 performance status. The interval between the date of initial surgery and the date of recurrence diagnosis (disease free interval) was median 15 months. Distribution of recurrence sites were as follows; 10 patients in mediastinal lymph node area, 4 in ipsilateral hilar area, 4 in ipsilateral lung parenchyma, 2 in bronchial stump and 1 in ipsilateral supraclavicular area. Radiotherapy was administered with median 66 Gy (range 59.4-70 Gy) by 3D conformal technique. Thirteen patients received chemotherapy concurrently during radiotherapy. Pulmonary function test (PFT) was also analyzed to detect the lung function change after radiation.

Results: The median survival, 1- and 2-year survival rates were 17 months, 68% and 34%, respectively. In multivariate analysis, good performance status, longer disease free interval and radiation dose more than 66 Gy increased in survival significantly (p=0.043, 0.019, and 0.028, respectively).

Concurrent chemotherapy did not affect survival significantly (p= 0.1836). DLCO of lung after radiotherapy decreased significantly compared with pre-radiotherapy status (p=0.033), but not FEV1 (p=0.312). Radiation pneumonitis of any grade was seen in 11 patients. Three patients died of acute respiratory distress syndrome; 1 patient due to combined bacterial pneumonia, 1 due to exacerbation of underlying interstitial pulmonary fibrosis, 1 due to radiation pneumonitis.

Conclusion: Our retrospective study showed that curative radiotherapy for locoregionally recurrent NSCLC resulted in median survival of 17 months and 2-year survival rate 34%, comparable to other studies. Patients suitable for curative radiotherapy for recurrent NSCLC could be treated aggressively, such as high dose radiation. However, post-radiotherapy lung function should be carefully evaluated to avoid serious lung damage after treatment, considering poor lung function of post-resection patients.

Disclosure: All authors have declared no conflicts of interest.

243P

CEREBRAL METASTASES IN PATIENTS WITH LUNG CARCINOMA AT THE CLINIC FOR LUNG DISEASES CLINICAL CENTRE BANJA LUKA FOR THE PERIOD AUGUST 1, 2008 - AUGUST 1, 2009

S. Mijatović[1], M. Stanetić[2], L. Novaković Lacković[2] *[1]Clinic of Oncology, Clinical Centre Banja Luka, Banja Luka/BOSNIA AND HERZEGOVINA, [2]Clinic for Lung Diseases, Clinical Centre Banja Luka, Banja Luka/BOSNIA AND HERZEGOVINA*

Lung carcinoma is the most frequent source of brain metastases. Although the brain is not the most common metastatic site, brain metastases often causes greater morbidity and mortality than other metastatic sites. The aim of this work is to analyse time to development of cerebral metastases, their number and recommended treatment in lung cancer patients, according to tumor type and previous therapy. In retrospective analysis medical records of 54 patients with diagnosed cerebral metastases from lung carcinoma treated at the Clinic for Lung Diseases Clinical Centre Banja Luka in the period August 1, 2008 - August 1, 2009 were analyzed; 43 males and 11 females, with age mean of 56.4. 24 patients developed brain metastases following the lung cancer diagnosis (median time to development of cerebral metastases was 8.7 months). 10 of those patients had a complete primary tumor resection; in 3 (30%) of those patients solitary metastasis was diagnosed 1 month after the resection, all of them with verified NSCLC. 15 patients had cerebral metastases diagnosed at the same time as the primary tumor. In 10 patients cerebral lesions were diagnosed first, all of them with diagnosed NSCLC. Single metastatic lesions were found in 24 (44.4%) patients (23 with NSCLC, 1 with SCLC), while 30 (55.6%) patients (21 NSCLC, 9 SCLC) had multiple brain metastases. 19 patients were treated only with first-line chemotherapy; most commonly used protocol was PE. 5 patients received second-line chemotherapy, while one patient was treated with third-line chemotherapy. 2 patients with verified SCLC received profilactic endocranial radiation; one of them developed brain metastases 2 months, the other one 7 months after radiation. Four patients among 24 cases of solitary lesions were operated before the primary tumor diagnosis; in 20 other patients 14 (70%) had an operable solitary lesion. Sugested treatment for one patient was combined resection of the primary tumor and the solitary lesion. For 25 (46.3%) patients palliative radiotherapy was recommended. At first for 29 patients recommended treatment was chemotherapy and for 9 patients symptomatic therapy.

Disclosure: All authors have declared no conflicts of interest.

244P

WHOLE-BRAIN RADIOTHERAPY VERSUS STEREOTACTIC RADIOSURGERY IN CEREBRAL LUNG CANCER METASTASES

C.M. Sagerup, B.H. Høvik, Å. Helland, O.T. Brustugun *Insitute of Clinical Medicine, Radiumhospitalet, University of Oslo, Oslo/NORWAY*

Objective: Lung cancer is the most common cause of brain metastases, and up to 50% develop CNS manifestations. In our institution, stereotactic radiosurgery (SRS) is offered to patients with 3 or less brain metastases (≤ 40mm in dm). The purpose of this report is to present our results comparing overall survival in lung cancer patients treated with SRS and whole brain radiation therapy (WBRT).

Patients and methods: We performed a retrospective analysis of 33 patients treated with SRS (+/- WBRT) in the period 2007-2009 and 52 patients treated with WBRT (30 Gy's in 3 Gy fractions) alone in the period 2004-2006. Cerebral magnetic resonance imaging was performed in all patients, and number of cerebral metastases did not exceed 3 in either treatment group. The Kaplan-Meier method was used and univariate comparison with log-rank test was performed.

Results: In the SRS group, 23 (70%) patients had a solitary metastasis and 10 patients (30%) extracranial metastases. 26 patients (79%) had deceased and 7 were alive at time of analysis. Median follow up of survivors was 6 months (mean 10, range 4.5- 20.3). 16 patients (47%) received SRS as their only radiation treatment. Doses ranged from 14 to 26 Gy (median 18 Gy). 17 patients received WBRT previous to (n=6), or in combination with (n=11) SRS. Doses ranged from 10 to 25 Gy (median 18 Gy). In the WBRT group, 17 patients (33%) had a solitary metastasis and 17 patients (33%) had extracranial metastases. 1 patient was alive at time of analysis. A significant survival benefit was seen when SRS was used as a boost in addition to WBRT vs. WBRT alone (10 months vs. 3 months, p =0.0489). Compared to WBRT alone, a survival benefit was present in patients with 1 metastasis who received SRS for a new or recurrent lesion previously treated with WBRT (p =0.0398) as well as in patients who received SRS as a boost in addition to WBRT (p =0.0466). When comparing patients treated with SRS only to patients who received WBRT, no significant difference in survival was evident (p = 0.413).

Conclusion: No statistically significant difference in survival between the treatment modalities was found when not used in combination. A survival benefit in patients that receive SRS in addition to WBRT versus WBRT alone is suggested.

Disclosure: All authors have declared no conflicts of interest.

245P

MULTIDISCIPLINARY MANAGEMENT OF BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER: A RETROSPECTIVE STUDY

Y. Xu, S. Ma, X. Yu, Y. Yu, Y. Ji, X. Sun *Department of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou/CHINA*

Objective: The incidence of brain metastases (BM) from non-small cell lung cancer (NSCLC) is increasing, and the management of this complication at a single institution is reported.

Methods: The records of all patients with BM from December 2003 to January 2007 were reviewed, and 251 patients with BM from NSCLC were identified. Associations between patient and tumor characteristics, treatment modality, and survival were assessed.

Results: 198 patients (79%) had other systemic disease. Twenty-five patients (10%) underwent surgery, 183 patients (73%) underwent whole-brain radiotherapy (WBRT) during their management, and 135 patients (54%) received sys-

temic chemotherapy. Twenty-five patients (10%) treated with Gefitinib. 133 patients (53%) who were treated radically with chemotherapy, radiation and possibly surgery developed brain failure. The overall 1-, 2- and 3-year survival rates were 34.1%, 13.7% and 8.7% with a median survival time of 9.0 months (95% CI 8.04–9.97 months). On multivariate analysis, recursive partitioning analysis (RPA) grouping, weight loss, LDH in blood serum and treatment were independent prognostic factors. The median survival time of chemotherapy alone, WBRT alone, surgery alone, WBRT with chemotherapy, surgery with chemoradiation, WBRT with Gefitinib and others was 6.0, 9.0, 12.0, 9.0, 22.0, 13.0 and 4.0 months, respectively, which were significantly different (X2=43.104, P=0.000). In 95 patients who were treated radically with chemotherapy, radiation and possibly surgery developed brain failure, a longer (≥9 months) interval from diagnosis of NSCLC to diagnosis of BM was associated significantly with longer survival (X^2=4.606, P=0.032). The stratify analysis indicated the median OS of patients received concurrent WBRT/chemotherapy (13.0 months) was longer than it of patients received sequential WBRT/chemotherapy (9.0 months) (X^2=3.89ï¼ŒP=0.049).

Conclusion: The main prognostic factors are RAP grouping, weight loss, LDH in blood serum and treatment. The effect of combined treatment of multidisciplinary is favorable, but the choice of the patient is important.

Disclosure: All authors have declared no conflicts of interest.

246P

LOW INCIDENCE OF GRADE ≥3 BLEEDING EVENTS AND LOW DISCONTINUATION RATES IN SAIL (MO19390): FIRST-LINE BEVACIZUMAB (BV) IN PATIENTS (PTS) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER NSCLC

L. Crinò[1], C. Steppert[2], S. Cinieri[3], N. Thatcher[4] *[1]Medical Oncology, S. Maria della Misericordia Hospital, Perugia/ITALY, [2]Thoraxclinic, BK Obermain, Ebensfeld/GERMANY, [3]Medical Oncology Division, Senatore Antonio Perrino Hospital, Brindisi/ITALY, [4]Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester/UNITED KINGDOM*

Background: SAiL is a large, international, open-label study of first-line Bv in combination with chemotherapy, and has reported an overall survival (OS) of 14.6 months. Final safety data focusing on the incidence of serious bleeding events, including pulmonary haemorrhage, are reported here.

Methods: Eligible pts had no history of grade [G] >2 haemoptysis (up to 3 months prior to enrolment) and received Bv (7.5 or 15mg/kg) in combination with chemotherapy for up to 6 cycles followed by Bv until disease progression or unacceptable toxicity. Primary endpoint was safety; secondary endpoints included time to disease progression (TTP) and OS.

Results: Final data are available for 2,172 pts. Baseline characteristics were (%): male 60.1; stage IIIB/IV 19.6/80.4; adenocarcinoma 85.9; ECOG PS 0/1/2 37.4/56.3/6.3. Mean age was 59 years. 37.9% of pts experienced a serious adverse event (SAEs) of any G; approximately 3/4 of these events were considered to be non-Bv-related (mostly related to chemotherapy). Bleeding events of any cause and any G were reported in 42.7% of pts, with the most common event being G 1-2 epistaxis (26.6%) and G ≥3 bleeding events occurring in only 3.6% of pts. G ≥3 pulmonary haemorrhage (PH) was reported in 0.7% of pts, G ≥3 central nervous system (CNS) bleeding in 0.1% of pts and G ≥3 gastrointestinal bleeding in 0.4% of pts. Bv was temporarily interrupted for 2.0% and permanently discontinued for 8.1% of bleeding events.

Conclusions: Bv-treated pts in SAiL were at low risk of experiencing G ≥3 bleeding events, with G ≥3 PH occurring in only 0.7% of pts in this large study. Furthermore, the rate of discontinuation or interruption of Bv for bleeding events was low, reflecting the manageability of Bv in NSCLC pts in normal clinical practice.

Disclosure: N. Thatcher: Nick Thatcher has received honoraria and research funding rom Roche. He has also been compensated by Roche for acting as an advisor and providing expert testimony. All other authors have declared no conflicts of interest.

247P

EFFECTIVENESS AND TOLERANCE OF MAINTENANCE THERAPY IN PATIENTS WITH NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

E.S. Santos, A. Belalcazar, A. Vazquez, J.E. Gomez, L.E. Raez *Oncology, University of Miami, Miami/USA*

Background: Prior studies have established the role of pemetrexed (Pem) or bevacizumab (B) as maintenance chemotherapy (MCX) after first-line chemotherapy (FCX) with platinum-base doublet for patients (pts) diagnosed with advanced non-squamous non-small cell lung cancer (NSCLC). However, there is not enough data about the combination or the role of single agent Pem as MCX after FCX with Pem. Moreover, the best MCX (by efficacy and cost) is not yet defined. Thus, the objectives of this study were to evaluate the efficacy of Pem single agent or in combination as MCX for NSCLC pts who have received Pem as FCX.

Methods: A retrospective review from January 2008 to January 2010 focused on stage IIIB/IV NSCLC pts who have received or are planned to receive MCX with single agent Pem or in combination (as part of FCX or second-line); those whose MCX is part of FCX must also have Pem as FCX.

Results: Nineteen subjects were identified; median age: 60 years (range, 34-77), 10 males, 11 Hispanic, 6 White, 2 African-American, 17 had adenocarcinoma, 15 had received at least 1 cycle of MCX (median number of MCX cycles: 5; range: 1-18). All chemotherapy regimens were frontline unless otherwise specified: 16 Carboplatin/Pem/B (1 pt received it as second line), 1 Cisplatin/Pem/B, 1 Carboplatin/Pem, and 1 Pem/B (as second line). The best response after completion of FCX (n=18) was: 2 PR, 14 SD, and 2 PD. Thirteen of 15 pts on MCX also received Pem as FCX; 14 of these pt. received Pem/B combination and 1 Pem alone as MCX regimen. Two pts on MCX developed grade 3-4 adverse events: fatigue, anemia and thrombocytopenia. One of them died with pneumonia during Pem MCX without disease progression. After a median follow up of 7 months (range: 4-14), 4 pts have progressed (2 after completion of FCX and 2 on MCX after 9 and 18 cycles of MCX, respectively).

Conclusions: Carboplatin/Pem/B is becoming a common regimen used as FCX followed by MCX Pem/B in eligible patients with non-squamous NSCLC. As MCX, Pem/B is well tolerated with most AEs being grade 1-2. A longer follow up will take place and updated data in term of efficacy and long-term side effects will be presented.

Disclosure: E.S. Santos: Genentech- Speaker Bureau Lilly- Speaker Bureau; J.E. Gomez: Genentech- Speaker Bureau Lilly- Speaker Bureau; L.E. Raez: Genentech- Speaker Bureau Lilly- Speaker Bureau All other authors have declared no conflicts of interest.

248P

A PHASE II TRIAL OF IRINOTECAN MONOTHERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS WITH ECOG PERFORMANCE STATUS (PS) 2: RESULTS OF KOREAN CANCER STUDY GROUP LU05-05

B.S. Kim[1], Y.M. Ahn[1], H.K. Kim[2], J.H. Kim[3], K.H. Lee[4], E.K. Cho[5], S.H. Bae[6], S.J. Gong[7], H.W. Lee[8], J.H. Choi[9] *[1]Department of Internal Medicine, Seoul Veterans Hospital, Seoul/KOREA, [2]Department of Internal Medicine, St Vincent's Hospital, Seoul/KOREA, [3]Department of Internal Medicine, Yonsei Cancer Center, Seoul/KOREA, [4]Hemato-Oncology, Yeungnam uni-*

versity hospital, Daegu/KOREA, [5]Hematology-oncology, Medicine, Gachon University Gil Medical Center, Incheon/KOREA, [6]Oncology/Hematology, Daegu Catholic University Hospital, Daegu/KOREA, [7]Department of Internal Medicine, Seoul Eulji Hospital, Seoul/KOREA, [8]Hematology-Oncology, Ajou University School of Medicine, Suwon/KOREA, [9]Hematology-Oncology, Ajou University Hospital, Suwon/KOREA

Background: For advanced non-small cell lung cancer (NSCLC) patients (pts) with ECOG PS 2, single agent chemotherapy with 3rd generation agent has been recommended as a preferable option. This study evaluated the efficacy and safety of single agent irinotecan for advanced NSCLC pts with ECOG PS2.

Methods: This was an open-label, single-arm, multicenter phase II trial, designed to detect a response rate of 16%. Chemonaive NSCLC pts with stage IV or stage IIIB with malignant effusion received irinotecan 80 mg/m^2 on days 1 and 8 every 21 days for 4 cycles. The primary end point was response rate. Secondary end points included overall survival (OS), progression-free survival (PFS), and safety.

Results: Forty pts (planned: 56 pts) were enrolled with a median age of 68 (42-74), 30 males, and 35 pts with stage IV. Median cycle of irinotecan chemotherapy was 2 (1-6). As an intention to treat analysis, 7 pts (18%) had partial response, and 14 pts (35%) had stable disease. Median PFS was 2.6 months, while 1-year and median OS were 23% and 4.6 months, respectively. NCI CTCAE grade 3 or higher toxic effects were as follows: anemia (10%), neutropenia (10%), thrombocytopenia (10%), pneumonia (10%), diarrhea (8%), and general weakness (8%). Eight pts (20%) died during or just after treatment period (aspiration or infectious pneumonia: 2, pneumonia with sepsis: 1. pneumonia with myocardial infarction: 1, septic shock: 1, disease progression:1, unknown: 2).

Conclusions: Irinotecan monotherapy for advanced NSCLC pts with ECOG PS2 demonstrated modest activity in terms of response rate and comparable OS with previous trials. However, a relatively high rate of deaths during treatment suggests careful selection of pts and monitoring throughout chemotherapy period.

Disclosure: All authors have declared no conflicts of interest.

249P

THE PRIMARY TREATMENT OF PATIENT WITH ADVANCED NON-SMALL CELL LUNG CANCER PRESENTING WITH BRAIN METASTASIS AT DIAGNOSIS

M. Calis[1], V. Calis[2], O. Incekara[1] *[1]Radiation Oncology, Şişli Etfal Reserch and Training Hospital, Istanbul/TURKEY, [2]Neurosurgery, Istinye State Hospital, Istanbul/TURKEY*

A lot of trials evaluating platinum-based chemotherapy (CT) have recently challenged the standart option of radiotherapy (WBRT) in the treatment of NSCLC patients presenting with brain metastasis. The common approach including WBRT followed by CT could not represent the tretment of choice when brain metastases symptoms are absent or controlled by supportive therapy. A subset of 71 pts fulfilling the following criteria: patholojic proof of NSCLC, stage IV with BM at first diagnosis, age <70 yrs, ECOG PS<2, median age 56 yrs (33–69), median PS 1. The first treatment was surgery in 43 pts. platinum-based CT included etoposide in 71 pts. All of pts were performed WBRT. Regardless of treatment the overal BM response was 40% (36% vs 49% for Ct and local treatment subgroups, respectively). For the general population the overal response PFS and MST were 37%, 10 and 13 months, respectively. The optimal treatment choice for pts presenting with brain metastasis should deserve prospective evaluation.

Disclosure: All authors have declared no conflicts of interest.

250P

SURGICAL RESECTION OF ISOLATED ADRENAL METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER. A SINGLE INSTITUTION EXPERIENCE

S. Bastian, T. Clerici, T. Cerny, M. Früh *Oncology/Hematology, Cantonal Hospital of St. Gallen, St. Gallen/SWITZERLAND*

Introduction: The role of surgical resection of solitary adrenal metastases in patients with non-small cell lung cancer (NSCLC) is controversial. Proper selection of patients who are likely to benefit from adrenalectomy remains unclear.

Methods: We retrospectively reviewed clinico-pathological factors and outcomes in all NSCLC patients treated with adrenalectomy at our centre between 1997 and 2009.

Results: Pathological staging of the four patients showed pT1pN0, pT2pN0, pT2pN0 and ypT1ypN0 (after neoadjuvant chemotherapy for cT3cN2). There were three adeno- and one squamous cell carcinoma. All had a performance status of 0. Median age was 56 years (range: 53-58), including one female and three males. All were current or ex-smokers. None received adjuvant chemotherapy after resection of the primary. One received adjuvant radiotherapy due to close margins. Adrenal metastases were detected by Computed Tomography in one and Positron Emission Tomography in three patients. Three patients had metachronous adrenal metastases. Median time from lobectomy to occurrence of the adrenal metastases was 12.3 months (11–14 months). Two received laparoscopic and two open adrenalectomy. Peri-operative mortality was zero. No additive chemotherapy after adrenalectomy was given. Three patients recurred systemically after adrenalectomy. Median time to recurrence in these patients was four months (2-5 months). First- line chemotherapy regimen administered in progressing patients included carboplatin and gemcitabine, carboplatin and paclitaxel and gemcitabine monotherapy. Two patients died due to systemic progression six and 15 months after adrenalectomy. One patient who had an interval between resection of the primary and the adrenal metastasis of 14 months and remains in remission after more than 39 months following adrenalectomy.

Conclusion: Adrenalectomy in NSCLC patients with isolated adrenal metastases is feasible. However, despite careful patient selection, long term survival is rare due to often rapid systemic progression. Prolonged interval between resection of the primary tumor and adrenalectomy may indicate a more favourable outcome with surgery.

Disclosure: All authors have declared no conflicts of interest.

251P

INTUSSUSCEPTION ILEO-ILEUM AS A SYMPTOM OF NSCLC METASTASIS TO THE SMALL INTESTINE

A.L. Zygulska[1], A. Wojcik[2], P. Richter[3], R. Tomaszewska[4] *[1]Oncological, University Hospital, Krakow/POLAND, [2]Surgical, Narutowicz Hospital, Krakow/POLAND, [3]IIIrd Department of General Surgery, Jagiellonian University School of Medicine, Krakow/POLAND, [4]Department of Pathomorphology, Jagiellonian University School of Medicine, Krakow/POLAND*

Purpose: The case of 55-year old male patient who had intussusception ileo-ileum because of non-small cell lung cancer metastasis to the small intestine is presented. Background: Cases of metastases to the intestine from non-small cell lung cancer are casuistry.

Material and methods: The patient with non-small cell lung cancer and the initial clinical stage III A after 1 cycle of chemotherapy with cisplatine plus vinorelbine had resections superior lobe and 6 th segment of inferior lobe of the left lung on January 30 th · 2009. Diagnosis of squamous cell carcinoma with low grading was confirmed. Metastasis in 1 out of 5 lymph nodes of pulmonary hilus was diagnosed. After surgical operation the next 3 cycles of chemotherapy with cisplatine plus vinorelbine were given. The patient with

suspicion of occlusion was admitted to Surgical Ward during emergency service on May 13 th, 2009. He suffered from vomiting after every meal, coprostasis and malaise lasting 4 days. Radiogram of the alimentary tract suggested the presence of an obstacle in distal section of jejunum. Intussusception ileo-ileum with retraction of mesentery vessels was diagnosed with CT scans of the abdomen and the pelvis.

Results: Surgical operation was performed on May 28 th, 2009, during which intussusception of the small intestine in 1/3 proximal of bowel in stretch of 20 centimeters was diagnosed. After disinvagination a tumor of small intestine was revealed. Segmental resection of jejunum in macroscopic margins of normal tissue was done. Histopathological examination confirmed the same malignant lesion as in pulmonary tissue resectioned earlier. Postoperative course was uneventful.

Conclusions: 1. Resection of metastasis to the intestine from malignant neoplasms with primary localization apart from alimentary tract is the only effective treatment. 2. In spite of described single cases of long-term survival, prognosis is poor.

Disclosure: All authors have declared no conflicts of interest.

252P

QUALITY OF LIFE (QOL) AND SYMPTOM MANAGEMENT BARRIERS IN LUNG CANCER

M. Koczywas[1], M. Cristea[1], T. Borneman[2], B. Piper[3], G. Uman[4], B. Ferrell[2]
[1]Medical Oncology and Therapeutics Research, City of Hope, Duarte/USA, [2]Nursing Research and Education, City of Hope, Duarte/USA, [3]Nursing Research, Scottsdale Healthcare/University of Arizona, Scottsdale/USA, [4]Vital Research, Vital Research, Los Angeles/USA

QOL and symptom concerns are of great importance to patients with lung cancer. However, the quality of symptom management continues to be suboptimal. This project is a prospective, longitudinal study that assessed barriers to pain and fatigue management in cancer patients. This abstract reports baseline descriptive data for the lung cancer patients (n=72) in the study. Patients with moderate to severe pain and/or fatigue were accrued. Outcomes were obtained using the COH QOL tool, Barriers to Pain and Fatigue tools, Piper Fatigue Scale (PFS), and Patient Knowledge tools for pain and fatigue. Subjects' mean age was 60, and included 28% ethnic minorities. The majority (58%) had Stage IV disease, and 73% were receiving treatment. QOL concerns were identified for the following: fatigue, appetite changes, pain, sleep changes (physical well-being); loss of control, feeling useful, changes to appearance, high levels of distress from initial diagnosis and treatments, fear of recurrence (psychological well-being); family distress, interference with employment and daily activities (social well-being); and high levels of uncertainty (spiritual well-being). Subjects reported high levels of distress from fatigue that interfered with daily functions. Pain-related misconceptions included the inevitability of addiction with pain medications, difficulties in controlling medication-related side effects, and tolerance to pain medications. Fatigue-related misconceptions included the belief that there are no effective treatments for fatigue, and that fatigue is not as important as treating cancer. Overall, patient knowledge of pain and fatigue was high (0.82-0.91), but lack of knowledge persisted with items related to the cause of pain and fatigue, common side effects of pain medications, the proper use of pain medications, and avoiding exercise in order to conserve energy. The study results suggest that lung cancer patients have high QOL and symptom concerns, and barriers to pain and fatigue management are common. Findings will aid in the development of effective palliative care interventions to improve and maintain QOL and symptom management for this cancer population.

Disclosure: M. Koczywas: Speaker bureau for Genentech and Eli Lilly All other authors have declared no conflicts of interest.

253P

USE OF ZOLEDRONIC ACID IN LUNG CANCER

R.G. Calderone[1], K. Nimako[2], A.N. Leary[3], S. Popat[4], E. Kipps[2], M.N. O'Brien[5] *[1]Head and Neck, Istituto Nazionale dei Tumori, Milano/ITALY, [2]Lung, Royal Marsden Hospital, London/UNITED KINGDOM, [3]Breast Unit, Royal Marsden Hospital, London/UNITED KINGDOM, [4]Department of Medicine, Royal Marsden Hospital, London/UNITED KINGDOM, [5]Lung Unit, The Royal Marsden NHS Foundation Trust, London/UNITED KINGDOM*

Background: The skeleton is the preferred site of metastasis for many solid tumours. Patient with lung cancer have a prevalence of metastatic bone disease (MBD) of around 40%. Zometa, a 3rd generation bisphosphonates (BPs), is used to treat MBD in many cancers. There have been reports of increased survival in patients receiving BPs particularly in breast cancer. There has been a recent observation of an increased response rate when used with chemotherapy e.g. Doxorubicin and Zometa in a mouse model. We examined the rates of Zometa administration in lung cancer patients with MBD, and compared overall survival (OS) between patients who had Zometa from diagnosis to those who did not. In general Zometa was given for symptomatic MBD but there was no formal policy.

Material and method: This was a retrospective audit approved by the local audit committee with a plan to obtain at least 50 patients with MBD treated with Zometa and 50 without to have an 80% chance of seeing a HR of 2 corresponding to a survival difference of 25-30%. We identified 398 stage IV NSCLC patients, diagnosed between July 2004 and July 2009. Among them 168 presented with MBD (42%). We collected the data of 114 random patients to get 49 pts who received Zometa and this gave 75 who did not. Treatment consisted of platinum-based chemotherapy with or without Zometa.

Results: There were 29% (49/168) of patients diagnosed with MBD who received Zometa. Patients on Zometa had better (OS), with a median of 34 weeks, compared to those did not, who had a median of 19 weeks (p=0.01). After adjusting for prognostic factors, Zometa patients maintained better OS (p=0.06) 34 versus 21 weeks.

	Zometa (%)	No Zometa (%)
Patients	43	71
Gender		
Male : female	18/25 (42/58)	40/31(56/44)
Age		
Median (range)	61 (28–82)	63 (39–86)
Ethnicity		
Caucasian Black Other & not known	37 (32) 0 6	62 (53) 3 7
Histology		
Adenocarcinoma + BAC Squamous Other/not specified	28 (65) 5 10	36 (51) 15 20
PS		
0/1/2/3	3/28 (65) /8/4	8/46 (65) / 15/2
Chemotherapy		
Platinum + Navelbine Platinum + Gemcitabine Platinum + Taxane Other platinum comb. Single agent	18 4 5 0 16 (42)	32 19 3 3 14 (45)
Metastases		
Liver CNS	12 (28) 7	16 (23) 12
No sites (other than bone) None 1 site 2+ sites	10 11 22 (51)	16 20 35 (49)

Conclusions: Patients with MBD are common in advanced NSCLC, but the percentage of patients treated with BPS is still low. The addition of Zometa

increase OS in NSCLC patients with MBD in this audit. This may be a treatment worthy of further consideration even in asymptomatic patients and more formal policies on the treatment of MBD in NSCLC patients need to be put in place.
Disclosure: All authors have declared no conflicts of interest.

254P
OUR EXPERIENCE WITH ENDOBROCNCHIAL BRACHYTHERAPY AS PALLIATIVE TREATMENT IN ADVANCED NSCLC

R. Anghel[1], L.N. Minea[1], X. Bacinschi[1], I. Isacu[1], A. Tarlea[1], D. Ples[2]
[1]Radiochemotherapy, Institute of Oncology Bucharest, Bucharest/ROMANIA, [2]Oncology, Clinical hospital Constanta, Constanta/ROMANIA

Background: Patients with inoperable non-small cell lung cancer previously treated by external beam radiation therapy have a poor prognosis if endobronchial obstruction persists or relapses. The therapeutic options are limited to controlling symptoms (dyspnea, cough, hemoptysia) and maintaining their quality of life. We intended to evaluate if HDR endobronchial brachytherapy is tolerable and efficient as palliative treatment for these patients.
Methods: The study group was 48 patients with stage IIIB NSCLC treated in the Radiation Therapy Department of the Oncological Institute of Bucharest, Romania, between June 2005 and December 2008. All the patients previously underwent external beam radiation therapy. 37 patients had no or partial tumor response and 11 patients relapsed after initial complete response to external irradiation. These patients, which experienced obstructive symptoms and hemoptysia, were referred to brachytherapy. Endobronchial irradiation consisted in 2 fractions of 7.5 Gy Day 1 and 8 and was delivered using remote HDR afterloading brachytherapy with Iridium-192. The patients were evaluated prior to therapy, at the end of radiation, and every 2 months thereafter. The evaluation consisted in complete clinical examination, bronchoscopy and quality of life QLQ-C30 questionare, adverse events and survival follow-up.
Results: Bronchial obstruction and consequently dyspnea was significantly improved in 32 patients (66.67%) hemoptysis diminished in 43 cases (89.58%). Quality of life was improved in 39 cases (81.25%). Symptoms improvement lasted for at least 3 months in 21 cases and at least 6 months in 8 cases. The median actuarial survival for the entire group was 5 months from the beginning of therapy. Acute toxicities were mucositis, and mild hemoptisia. Grade 3-4 complications occurred in 5 patients (10.42%); one of them experienced fatal hemoptysia.
Conclusions: Endobronchial brachytherapy effectively palliates most symptoms caused by endobronchial obstruction with few complications but no overall survival benefit.
Disclosure: All authors have declared no conflicts of interest.

255P
CLINICAL OUTCOMES (CO) FOR SPECIAL POPULATIONS OF PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): RESULTS FROM ARIES, A BEVACIZUMAB (BV) OBSERVATIONAL COHORT STUDY (OCS)

A.J. Wozniak[1], J. Garst[2], M. Jahanzeb[3], M. Kosty[4], R. Vidaver[5], S. Beatty[6], S.L. Teng[6], E.D. Flick[7], A.P. Sing[8], T.J. Lynch[9] *[1]Karmanos Cancer Institute, Wayne State University, Detroit/USA, [2]Oncology, Regional Cancer Care, Durham/USA, [3]Hematology and Oncology, University of Tennessee Cancer Institute, Memphis/USA, [4]Hematology/Oncology, Scripps Clinic, La Jolla/USA, [5]Oncology, National Lung Cancer Partnership, Madison/USA, [6]Biostatistics, Genentech, Inc, South San Francisco/USA, [7]Epidemiology, Genentech, Inc, South San Francisco/USA, [8]Biooncology, Genentech, Inc, South San Francisco/USA, [9]Oncology, Yale Cancer Center, New Haven/USA*

Background: BV (Avastin®) prolongs progression-free (PFS) and overall survival (OS) in advanced NSCLC. ARIES, a prospective OCS evaluating BV in a real world setting, includes pts underrepresented in randomized controlled trials (RCTs), i.e. pts ≥70y, with poor performance status (PS), or with CNS metastases (mets). Preliminary COs (effectiveness and safety) in ARIES subpopulations are presented.
Methods: Pts with locally advanced non-squamous NSCLC on 1st line chemotherapy (CT) and BV enrolled. No prespecified treatments, doses or assessments. Data are collected electronically at baseline (BL) and quarterly (QU), including BV-targeted adverse events (AEs) and serious AEs (SAEs). Descriptive safety analyses were conducted for all pts and for subgroups. Median (med) PFS and OS are Kaplan-Meier estimates.
Results: ARIES enrolled 1970 NSCLC pts. Med follow-up at the 09/2009 data cut was 9.6 mo; 98% have ≥1 QU follow-up. Med PFS is 6.7 mo and OS is 13.6 mo for the entire cohort and were similar across subgroups except pts with PS≥2. The most common 1st line CT is carboplatin/paclitaxel (CP). Pts ≥70y and pts with PS≥2 or CNS mets at BL generally used more nonplatin-containing CT and pemetrexed. AE rates across subgroups were similar to the overall cohort except for increased arterial thromboembolic events (ATE) in pts ≥70y and with PS≥2. No CNS bleeding events occurred in pts with CNS mets at BL.
Conclusion: The COs (safety/effectiveness) of BV in pts ≥70y, or with PS≥2 or CNS mets are consistent with the known BV efficacy and safety profile. Pts with PS≥2 received less CP and had worse COs but not more AEs/SAEs. Pts ≥70y had COs similar to the overall cohort despite less doublet CT, suggesting that advanced age, poor PS or CNS mets should not necessarily exclude pts from receiving BV therapy.

	All NSCLC Pts (n = 1970)	Age ≥70 (n=650)	PS ≥2 (n=182)	CNS Mets (n=150)
Med PFS (mo)	6.7	6.8	5.8	6.0
Med OS (mo)	13.6	12.6	8.1	11.7
CP 1st-line CT, n (%)	1215 (62)	382 (59)	107 (59)	82 (55)
Severe pulmonary hemorrhage (PH), n (%)	15 (0.8)	2 (0.3)	2 (1)	—
Gr 3-5 bleeding excluding PH, n (%)	52 (3)	20 (3)	7 (4)	—
ATEs, n (%)	35 (2)	20 (3)	6 (3)	—
Gr 3-5 CNS bleed, n (%)	2 (0.1)	0	1 (0.5)	0

Disclosure: A.J. Wozniak: Consultant on advisory board at Genentech (financially compensated), and have received research funding from Genentech; J. Garst: Consultant on advisory board for Genentech (financially compensated) and has received Speaker's Bureau honoraria and research funding from Genentech M. Jahanzeb: Has received honoraria from and is a consultant (financially compensated) for Genentech, Aventis, Glaxo-Smith-Kline, and Eli Lilly; M. Kosty: Have received honoraria and research funding from Genentech; R. Vidaver: Genentech pays consulting fees and honoraria directly to National Lung Cancer Partnership (not to Dr. Vidaver personally); S. Beatty: Contract employee at Genentech; S.L. Teng: Employee at Genentech and stockholder of Roche; E.D. Flick: Employee at Genentech and stockholder of Roche; A.P. Sing: Employee at Genentech and stockholder of Roche; T.J. Lynch: On Board of Directors of and stockholder of Infinity

Pharma. Consultant (financially compensated) for Genentech, Merck, BIPI, Astra Zeneca

256P

OUTCOME OF METASTATIC NON-SMALL CELL LUNG CARCINOMA PATIENTS RECEIVING SYSTEMIC TREATMENT: A SINGLE LATINAMERICAN INSTITUTION EXPERIENCE

O. Aren[1], L. Matamala[1], M. Fica[2], A. Santini[1], H. Harbst[3], M. Carcamo[4], H. Cerda[1] *[1]Medical Oncology Service, Instituto Nacional del Cancer, Santiago/CHILE, [2]Servicio de Cirugia, Instituto Nacional del Torax, Santiago/CHILE, [3]Radiation Oncology Service, Instituto Nacional del Cancer, Santiago/CHILE, [4]Biostatistics Service, Instituto Nacional del Cancer, Santiago/CHILE*

Introduction: Non-Small Cell Lung Cancer (NSCLC) is one of the leading causes of cancer death in Chile. Palliative chemotherapy has shown clear benefit over best supportive care. We analized all patients that received systemic treatment for Stage IV NSCLC at our institution (Instituto Nacional del Cancer, Santiago, Chile), from January 2004 to April 2009.

Patients and methods: We analyzed 68 consecutive patients with metastatic NSCLC at presentation, who met the following inclusion criteria: no previous chemotherapy, performance status (PS) 0-2, adequate bone marrow reserve, normal hepatic and renal function, and no exclusion criteria: history of treatment for other cancers, treatment at other institutions, or lack of data on file. The database was obtained from the chemotherapy database at our institution, from January 2004 to April 2009. All patients met inclusion criteria, no patients met exclusion criteria. Survival was calculated (using Kaplan-Meier) from the date of histolgical diagnosis until death (obtained from death certificates) or last available control on file (for living patients).

Results: Median age was 60 years (range 20–87). 48 (59%) patients were male. The most frequent histology was adenocarcinoma (67%). Median number of cycles was 3 (range 1–6). First line chemotherapy was Platin (cisplatin or carboplatin) plus Etoposide in 56% of patients, paclitaxel-carboplatin in 29%, other combinations 15%. Only 29% of our patients received second line therapy, most frequently docetaxel, followed by TKI. Median overall survival (OS) time was 11.3 months (range 1.1–61.8; 95% CI: 11.19–15.68). One-year OS was 63.6%, two-year OS was 31.7%. OS at 36 months was 10,6%.

Conclusion: Despite methodological limitations, this patient sample had a remarkable good outcome in comparison previously reported results. The favorable results could be explained by the fact than treatments are conducted by a multidisciplinary experienced team dedicated exclusively to thoracic oncology.

Disclosure: All authors have declared no conflicts of interest.

257P

PRIMARY MUCINOUS ADENOCARCINOMA (SIGNET-RING TYPE) OF THE LUNG

N. Valizadeh *Hematology/Medical Oncology, Internal Medicine, Urmia University of Medical Sciences, Urmia/IRAN*

Background: Primary mucinous adenocarcinoma of the lung (Signet-ring type) is a very rare type of lung adenocarcinoma. It accounts for approximately 0.25% of all lung tumors.

Case report: A 50 year old man with a non-smoking history was presented with chronic productive cough. He did not report anorexia and weight loss, and physical examination revealed coarse rales in both lungs. A chest CT-scan showed a defined consolidation in the left lung with multiple hetrogenous density in both lungs. Bronchoscopy was performed and the biopsy result confirmed lung mucinous adenocarcinoma (signet-ring type). Upper GI-endoscopy was normal. Abdomino-pelvic CT was reported with normal findings, except for a small calcification in the prostate. Total and free PSA were in a normal range and further performed IHC was negative for PSA. We started treatment by Taxotere and cisplatin in 21 days interval.

Result: In this man with a non-smoking history, a diagnosis of primary lung mucinous adenocarcinoma with multiple metastasis in both lungs was established.

Conclusion: Primary lung mucinous adenocarcinoma is a rare pathologic subtype of lung cancer. It may be seen in non-smokers and may be metastatic at initial presentation. Primary mucinous adenocarcima of the lung has similar pathologic findings as extrapulmonary mucinous adenocarcinoma of other sites (gastrointestinal, stomach, ovary, breast, pancreas). When diagnosis of the extrapulmonary mucinous adenocarcinoma with lung metastasis is suspected, further evaluation by IHC is mandatory.

Disclosure: The author has declared no conflicts of interest.

258P

ADVANCED NON SMALL CELL LUNG CANCER

S.V.N. Krishnamurthy *Surgical Oncology, Kidwai Memorial Institute of Oncology, Bangalore/INDIA*

Introduction: Chemotherapy prolongs survival in advanced non-small cell cancer and shows an improved survival in patients receiving chemotherapy compared with those receiving best supportive care at acceptable treatment costs (JCO vol 6:1998 & Vol 8:1990). In our Institute, 90% of patients with lung cancer present in an advanced or a metastatic stage requiring immediate attention. The clinician is left with the option of providing the best palliation at the least available time for investigation. We are analyzing the time of presentation of these patients to the cancer centre as critical and that prompted us to analyse the mode of presentation, the age at presentation, the performance status of patients, the time to diagnosis, survival of patients and quality of life of patient with the available treatment over a 2 year period (2006–2007).

Method: 95 patients with suspected lung cancer were registered between January 2006 to December 2007; 15 of these patients died even before the establishment of diagnosis. Of the remaining 80 patients in whom diagnosis was confirmed, 4 patients were found to have stage II and were offered surgery and 40 patients refused treatment for various reasons. We analyzed 36 patients who received treatment during this period. The presentation of patients was quite variable. It ranged from cough with expectoration (5), hemoptysis (2), dyspnea (20), chest pain (6), hoarseness (2), swelling neck (6), and subcutaneous swelling (2). The youngest patient in this series was 46 years old and the oldest was 82. A total of 29 patients (80%) in this study were in the age group of >60 years. The Karnofsky performance status in majority (23 patients) were <50% which made time as an important factor in deciding about the treatment. We obtained a cytological confirmation of diagnosis by ultrasound (18) or CAT guidance (6), nodal/subcutaneous nodules (8), pleural fluid cytology (4). Six patients who presented with pleural effusion underwent immediate intercostal drainage. Chemotherapy was initiated within 7 days of attending the outpatient department. The standard therapy offered was a combination of gemcitabine and cisplatin. Gemcitabine was given in a dose of 1000mg/m2 on day 1, 8 and 15 and cisplatin 75mg/m2 in divided doses on day 1 and day 2. The cycles were repeated every 28th days. Only haemogram was repeated on the day of giving gemcitabine. We recorded that 10 patients had a fall in platelet counts to 1 lakh but only 3 patients who were symptomatic were given platelet transfusion and the delay in continuing chemotherapy in these patients ranged between 3-5 days. All the 36 patients completed a minimum of 3 cycles and 8 of these patients continued chemotherapy for a period of 6 months. Five patients received palliative radiotherapy to ipsilateral lung and 6 patients received radiation to brain successfully. Radiation was also offered to 3 patients who had symptomatic bone metastasis. In 6 patients who

underwent intercostal drainage before initiation of chemotherapy, we noticed disappearance of the pleural fluid and the intercostal tube was removed after the 1st cycle of chemotherapy.

Results: Of the 36 patients who successfully completed 3 cycles of chemotherapy, 24 patients (66.6%) had a survival of 5 months and 12 patients (33.3%) continued chemotherapy for 6 months with an interception of 15 days for those patient who received radiotherapy of lung, brain or bone. The symptom control in all 36 patients was excellent. As far as age is concerned, we did not see any major difference in the tolerability to chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

259P

PLEOMORPHIC CARCINOMA OF THE LUNG – PATIENT CHARACTERICTICS, THERAPY AND OUTCOME: A MONOCENTRIC RETROSPECTIVE ANALYSIS

C. Grohe[1], O. Zaba[1], H. Lüders[1], D. Holbe[1], G. Leschber[2] [1]*Pulmonary Division, ELK, Berlin/GERMANY,* [2]*Thoracic Surgery Division, ELK, Berlin/GERMANY*

Background: Pleomorphic carcinoma of the lung (PC) is an uncommon pulmonary tumour entity, which is not well characterized due to low patient numbers. In general these patients tend to show poorer prognosis than other histological subgroups of pulmonary malignancies. This is a retrospective study that included the data of 47 patients with PC at every stage (collected 2004-2009) particularly with regard to epidemiology, morbidity, therapy and outcome with a 5-year follow up.

Results: Characteristics of 47 pts: 33 male, 14 female; median age 66,7 years. 38,3% current smokers, 12,8 % former smokers, no documented never smokers but 48,9% with no documented smoking status. Stage IA: 12,7%; IB: 10,6%; IIA: 2,1%; IIB: 10,6%; IIIA: 6,4%; IIIB: 12,7%; IV: 44,7%. Surgical treatment was conducted in 42,6%, mainly simple lobectomy (70%) furthermore advanced lobectomy (25%) and pneumonectomy (5%). Chemotherapy was documented in 19 cases; Regimens: cisplatin/vinorelbine (n=12) , carboplatin/vinorelbine (n=2) , cisplatin/etoposide (n=2), cisplatin/gemcitabine (n=1) and gemcitabine mono (n=1). Metastasis were mainly located in the lung (n=10), brain (n=9), liver and suprarenal gland (each n=8). Median OS (all stages): 1,29 years. Only 35,2% reached 5-year survival and all of them had stages I or II. OS dependent on stage, I: 4,5 y, II: 3,4 y, III: 0,76 y , IV: 0,31 y. In patients with advanced disease (IIIB–IV) palliative chemotherapy showed different median OS, cisplatin/vinorelbine: 15,6 months , carboplatin/vinorelbine : 4,08 months, cisplatin/etoposide : 21,84 months, cisplatin/gemcitabine 6,96 months and gemcitabine mono 4,2 months. Median PFS at stage IV was 2,04 months only.

Discussion: Our analysis shows that male sex, ages 60-70 years and an active or former smoking history seem to be the main epidemiological characteristics in patients with PC. Concerning palliative chemotherapeutic treatment it appears to be hard to recommend a specific regimen due to low patient numbers although cisplatin based doublets with either vinorelbin or etoposide showed the best results in our collective. More multicenter studies with greater patient numbers are definitively necessary.

Disclosure: All authors have declared no conflicts of interest.

260P

CLINICAL SIGNIFICANCE OF CAVITATED LUNG MASS AMONG LUNG CANCER PATIENTS RECEIVING FIRST LINE CHEMOTHERAPY AT A TERTIARY CARE INSTITUTE IN NORTH INDIA

V.K. Mootha[1], N.N. Singh[2], A.N. Aggarwal[2], D. Behara[1] [1]*Pulmonary and Critical Care Medicine, PGIMER, chandigarh/INDIA,* [2]*Pulmonary Medicine, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh/INDIA*

Background: the clinical significance of the cavitated lung mass (CLM) on chest radiographs (CXR) prior to and during first line chemotherapy (CTx) of lung cancer (LC) is unclear. An evaluation of the incidence and prognostic value of CLM among LC patients (pts) receiving first line CTx was undertaken.

Methods: In a retrospective analysis, data about demographic and baseline characteristics, CTx administration and findings of serial CXRs was collected for consecutive newly diagnosed LC pts who received CTx/targeted therapy over a 18 month period. Outcome variables assessed were objective response rate (ORR) and overall survival (OS). Patients who received >3 cycles of CTx were included in analysis of ORR and new onset CLM. Numerical and categorical data were compared among pts with and without CLM using students t-test and chi-square test respectively.

Results: Out of 295 patients enrolled during study period, 30 pts who received gefitinib as first line therapy and 5 patients who had non bronchogenic tumors were excluded. Base line characteristics of 260 pts who received CTx are shown in Table. Twenty pts (7.7%) had CLM at baseline. The most commonly used CTx regimens were irinotecan-cisplatin in 92.5% of small cell LC pts and taxane-platinum in 90% of non-small cell LC pts respectively. Of the 260 pts, 187 received >3 cycles of CTx and were included for ORR analysis. Squamous cell histology was the only characteristic that is significantly associated with presence of baseline or new onset CLM.Distribution of ORR was as follows: CR+PR - 56.7%, SD-23.5% and PD- 19.8% and did not differ significantly between pts with and without CLM. New onset CLM was seen in 22 pts. Pateints with or without CLM at baseline or during CTx had same OS.

Conclusions: Squamous cell histology is the only characteristic that is associated with presence of CLM at diagnosis or after first line CTx. Presence of CLM has no effect on ORR or OS.

Table

Characteristic	All Patients (n=260)	Patients with Cavitated Lung Mass (n=20)	Patients Without Cavitated Lung Mass (n=240)	p Value
Age in years (mean[SD])	57.76 [10.9]	57.63 [10.94]	59.3 [10.75]	0.498
Gender (male)	217 (83.5%)	16 (80%)	197 (82.3%)	0.69
Tobacco smokers	197 (75.5%)	13 (65%)	184 (76.6%)	0.14
Histology	Squamous-98(37.7%) Adenocarcinoma- 61(23.5%) Undifferentiated-47 (18.1%) Small cell-54 (20.8%)	Squamous-16 (80%) Adenocarcinoma- 3(15%) Undifferentiated-0% Small cell-1 (5%)	Squamous-82(34.1%) Adenocarcinoma- 58(24.1%) Undifferentiated-47 (19.6%) Small cell-53 (22%)	0.002
Stage of NSCLC	Stage I- 2(1%) Stage II- 9(4.4%) Stage IIIA- 26(12.7%) Stage IIIB- 93(45.1%) Stage IV- 76(37.1%)	Stage I- 0% Stage II- 1(5%) Stage IIIA- 1(5%) Stage IIIB- 10 (50%) Stage IV- 7(35%)	Stage I- 2(1%) Stage II- 8(4.2%) Stage IIIA- 25 (13.6%) Stage IIIB-83 (44.6%) Stage IV- 69(36.5%)	0.903
Stage of SCLC	Limited- 25(46.3%) Extensive-29 (53.3%)	Limited-0(0%) Extensive-1(100%)	Limited-25 (46.2%) Extensive-28 (53.8%)	0.547
Bronchoscopic abnormality	Normal-60(23%) Abnormal-121 (46.5%) Not done-79 (30.3%)	Normal- 4(20%) Abnormal-12 (60%) Not done-4(20%)	Normal-56(23.3%) Abnormal- 109(45.4%) Not done- 75 (31.2%)	0.474
Extra thoracic disease	57 (22%)	3 (15%)	54 (22.5%)	0.579
Karnofsky performance status	100-166 (63.8%) 90-75 (28.8%) 80-18 (6.9%) <70-1 (0.4%)	100-10 (50%) 90-10 (50%) 80-0% <70-0%	100-156 (23.3%) 90-65 (27.3%) 80-18 (7.5%) <70-1 (0.4%)	0.146
Number of cycles received (mean[SD])	3.9 [1.75]	3.4 [1.5]	3.94 [1.77]	0.148
Survival in days (median)	178.5	194	148	0.145

Disclosure: All authors have declared no conflicts of interest.

MESOTHELIOMA AND SCLC

261O

IS THERE A ROLE FOR HIGH DOSE HEMITHORACIC RADIOTHERAPY IN UNPNEUMONECTOMISED MESOTHELIOMA PATIENTS?

M. Feigen *Radiation Oncology Centre, Austin Health, Heidelberg/AUSTRALIA*

Background: Malignant pleural mesothelioma is a disease with few cures where the majority of patients die of overwhelming tumor masses that spread over the involved hemithorax to adjacent organs. Even in cases selected for radical surgery, local recurrence rates are high and cannot be controlled long-term by intrapleural or systemic therapies. Radiotherapy has long been regarded as ineffective and hazardous.

Methods: We have since 2003 been offering high dose radiotherapy to selected patients who have residual local disease following incomplete surgical resection for mesothelioma, using technologically advanced methods including intensity-modulated radiotherapy, and utilising PET scans to precisely target active disease and assess locoregional control rates.

Results: We have found no major acute or late toxicities after radiation doses of 45 to 60 Gy to large volumes of the hemithorax in thirty patients, and total glycolytic volume analysis has found long-term reductions of 60% following radiotherapy. Benefits include tumor reduction, durable palliation and improved survival. There were no radiation-related deaths after a median followup of eighteen months. A phase II trial is being planned.

Conclusions: Our results demonstrate that high dose modern radiotherapy is an effective modality to control the locoregional progression of pleural mesothelioma. It should be considered in all patients who have had extrapleural pneumonectomies as well as in those undergoing less radical resections.

Disclosure: The author has declared no conflicts of interest.

262O

INTENSITY MODULATED RADIOTHERAPY AS PART OF THE TRIMODALITY CONCEPT IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

P. Dimmerling, D.R. Zwahlen, J. Krayenbühl, C. Glanzmann, G. Studer, I.F. Ciernik, O. Riesterer *Radiation Oncology, University Hospital Zurich, Zurich/SWITZERLAND*

Objectives: The impact of radiation therapy (RT) and the optimal techniques in the trimodal treatment concepts of malignant pleural mesothelioma (MPM) are subject of current investigations. We review the clinical outcome with IMRT after extrapleural pneumonectomy (EPP) at the University Hospital Zurich.

Materials and methods: From 2005 to 2009 12 patients with stage 1 or 2 MPM received IMRT after induction chemotherapy and EPP. 10 patients received postoperative, adjuvant IMRT and 2 patients were irradiated with curative intent for local recurrence. The target volume encompassed the hemi-thorax and a boost was given to the high risk area either as simultaneously integrated boost (SIB, 10 patients) or in a second phase (2 patients). IMRT was applied using 5 coplanar beams to a total median dose of 56 Gy (54-60). For plan comparison 9 IMRT plans were replanned for 3D conformal RT.

Results: The median age at diagnosis was 61 years (46-72) and median follow-up was 21 months (9-56). Two out of 10 adjuvantly treated patients experienced in-field local relapse and the local thoracic control rate was 80%. Median time to local progression and distant metastasis after radiotherapy were 6.5 (4-9) and 12 months (3.5-39.5), respectively. Median overall survival for all patients was 23.4 months (9-56). The 2 patients who were irradiated for local recurrence died 3 and 16 weeks after RT, respectively. IMRT was superior to 3-D conformal RT in respect of dose coverage and homogeneity ($p<0.01$), except for the remaining lung (mean lung dose with IMRT: 7.8 Gy, $p<0.01$). One patient experienced grade 4 pneumonitis. Replanning of the respective IMRT plan showed room for plan optimization if novel lung constraints were considered. This and recently published data led us to adapt our lung constraints for subsequent patients (mean lung dose below 7.0 to 7.5 Gy, V20 below 5 to 10% and V5 below 40 to 50%).

Conclusions: IMRT following EPP resulted in a high local control rate. RT of locoregionally recurrent MPM was not associated with sustainable disease control. Optimized IMRT planning using stringent constraints with low probability for subsequent toxicity are recommended.

Disclosure: All authors have declared no conflicts of interest.

263O

A RETROSPECTIVE ANALYSIS OF SECOND-LINE CHEMOTHERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

A. Bramati[1], A. Moretti[1], M.C. Garassino[2], R. Califano[3], G. Farina[4], M. Lo Dico[5], M. Cinquini[6], G.N. Michetti[7], M. Tiseo[8], P.A. Zucali[9] *[1]Medical Oncology, A. O. Ospedale Fatebenefratelli e Oftalmico, Milan/ITALY, [2]Oncology, Fatebenefratelli and Ophtalmic Hospital, Milano/ITALY, [3]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester/UNITED KINGDOM, [4]Oncology, Ospedale Fatebenefratelli e Oftalmico, Milan/ITALY, [5]Division of Medical Oncology, Civil Hospital Livorno, Livorno/ITALY, [6]Oncology, Mario Negri Institute, Milano/ITALY, [7]Oncology/pneumology, Ospedali Riuniti, Bergamo/ITALY, [8]Medical Oncology, Parma Hospital, Parma/ITALY, [9]Department of Oncology, Istituto Clinico Humanitas IRCCS, Istituto Clinico Humanitas, Rozzano/ITALY*

Background: Chemotherapy is the only option for MPM. Cisplatin + pemetrexed became the standard in the first-line (FL), while the role of a second-line (SL) remains controversial.

Materials and methods: We retrospectively collected data of all consecutive MPM patients (pts), from 8 institutions, receiving SL chemotherapy after a platinum based FL treatment from 1996 to 2008. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), best overall response rate (ORR) and prognostic factors. Kaplan Meier curves and Log Rank were used for statistical analysis.

Results: Of 414 MPM pts treated in FL setting, 161 underwent a SL chemotherapy (63% male; median age 62,5 years). Main regimens were: platinum rechallenge (21 pts, 13,1%), pemetrexed rechallenge: (23 pts - 14,4%), pemetrexed + platinum rechallenge (32 pts - 20%), biological agents (23 pts - 14,3%) and others (62 pts-38,2%). 89 pts achieved disease control (partial remission + stable disease) with a SL regimen (55,6%) (median OS 10,23 months (mths), median PFS 5,72 mths). OS was statistically significantly higher in pts rechallenged with platinum + pemetrexed (20.56 vs 8.49 mths – HR 0.39 95%IC 0.21-0.71; $p=0.0015$), while PFS wasn't (9.77 vs 5.39 mths – HR 0.71 95%IC 0.47-1.08; $p=0.111$). PFS ($p<0,0001$) and OS ($p<0,0001$) were statistically significant in pts responding to FL and with an epithelial histology ($p=0,0008$). Univariate and multivariate logistic analysis showed that the only factors for the choice of SL regimen were response after FL and smokers.

Conclusions: The benefit of SL is strictly dependent on histology and response to FL. According to our data, rechallenge with platinum-based regimens seems the best option. No benefit has been proven in favour of polichemotherapy regimens in respect to single agents. The superiority of cisplatin + pemetrexed rechallenge has been demonstrated also at the multivariate analysis adjusted for time to SL and histology. The role of platinum-based rechallenge in SL should be further investigated, considering also that a SL has palliative intent on the basis of histology and of the extent of response to FL treatment.

Disclosure: All authors have declared no conflicts of interest.

264O

INDUCTION OF SENESCENCE MARKERS BY NEO-ADJUVANT CHEMOTHERAPY OF MALIGNANT PLEURAL MESOTHELIOMA AND ASSOCIATION WITH CLINICAL OUTCOME: AN EXPLORATORY ANALYSIS

E. Felley-Bosco[1], R. Sidi[1], G. Pasello[1], I. Opitz[2], A. Soltermann[3], M.N. Tutic[4], W. Weder[2], R.A. Stahel[5] *[1]Oncology, University Hospital Zurich, Zurich/SWITZERLAND, [2]Division of Thoracic Surgery, University Hospital Zurich, Zurich/SWITZERLAND, [3]Institute of Pathology, University Hospital Zurich, Zurich/SWITZERLAND, [4]Thoracic Surgery, Thoracic Surgery, Zurich/SWITZERLAND, [5]Klinik und Poliklinik für Onkologie, Universitätsspital, Zürich/SWITZERLAND*

Purpose: The aim of this study was to assess the induction of senescence markers versus apoptosis pathways in malignant pleural mesothelioma (MPM) tumor samples before and after neo-adjuvant platinum-based chemotherapy and to investigate their relationship with clinical outcome.

Experimental Design: Specific senescence pathways were assessed by quantifying the expression of p21 and plasminogen activator inhibitor-1 (PAI-1) for the p21-p53 pathway, IGBP7 for the IGF pathway and ALDH3A for the IFN pathway. p21 and PAI-1 expression was also assessed by immunohistochemistry. In addition, beta-galactosidase activity staining at pH 6.0 was performed. Apoptosis was determined by TUNEL assay. Clinical outcome was assessed by modified RECIST criteria and progression-free and overall survival.

Results: In a training set (n=9 patients) paired comparison demonstrated a significant increase in p21 and PAI-1 expression and apoptosis after chemotherapy. The patients with the highest increase in senescence markers expression had stable disease, while patients with little change accompanied by a high increase in apoptosis had an objective response after chemotherapy. The hypothesis that stable disease might be associated with an increased senescence markers was confirmed in a tissue microarray (n=26 patients) using p21 and PAI-1 immunohistochemistry as readout. In the 21 patients where survival data was available, a decrease in senescence markers was significantly associated with a better outcome.

Conclusions: Our results demonstrated induction of senescence markers by neo-adjuvant chemotherapy to be associated with outcome.

Disclosure: All authors have declared no conflicts of interest.

265O

VALIDATION AND COMPARISON OF PUBLISHED PROGNOSTIC CLASSIFICATIONS FOR SURVIVAL IN PATIENTS (PTS) WITH SMALL CELL LUNG CANCER (SCLC)

M.N. Paesmans[1], J.J. Lafitte[2], J.N. Lecomte[3], T. Berghmans[4], A.N. Efremidis[5], A.P. Meert[6], N.N. Leclercq[7], J. Sculier[8] *[1]Data Centre, Institut Jules Bordet, Brussels/BELGIUM, [2]Pneumology, CHRU Lille, Lille/FRANCE, [3]Pneumology, CHU de Charleroi, Charleroi/BELGIUM, [4]Medicine, Institut Jules Bordet, Brussels/BELGIUM, [5]Medicine, St-Savas Hospital, Athens/GREECE, [6]Soins Intensifs et Cancerologie Pulmonaire, Institut Jules Bordet, Brussels/BELGIUM, [7]Institut Jules Bordet, Brussels/BELGIUM, [8]Department of Intensive Care and Thoracic Oncology, Jules Bordet Institute, Brussels/BELGIUM*

Background: Several prognostic classifications are available for predicting survival in pts with SCLC : Albain et al (1), Sagman et al (2), Paesmans et al (3), Sculier et al (4), Foster et al (5), (5) focusing on pts with extensive disease (ED). We had as objective to validate them and to compare their discriminant ability.

Methods: We pooled the data collected in phase III clinical trials: 2 in pts with ED treated by chemotherapy and 1 in pts with limited disease treated by chemoradiotherapy. We selected pts registered before 31/10/2007. We used Cox regression models and calculated concordance probability estimates (CPE).

Results: We included 693 pts: 82% male pts, 81% performance status 80 or more, 54% older than 60 years and 66% with ED. Depending on the models, rates of pts with the best predicted prognosis ranged from 9% to 28% and with the poorest predicted prognosis from 11% to 26%. All the classifications had a highly significant impact on survival with hazard ratios (HR) (95% confidence intervals) being respectively: (1) 1.57 (1.44-1.71), (2) 1.85 (1.64-2.10), (3) 1.67 (1.52-1.83) and (4) 1.57 (1.45-1.71) (all $p<0.001$). Median survival times were for the best group: 17, 22, 19 and 16 and for the poorest group 7, 6, 6 and 7 months. Most of the paired comparisons were also statistically significant. Restricting the analysis to ED pts, HR were: (1) : 1.84 (1.48-2.29), (2) 1.67 (1.32-2.08), (3) 1.43 (1.26-1.64), (4) 1.79 (1.46-2.21) and (5) 1.25 (1.14-1.38). In 3 studies, Cox models were also published. The HR ratios for a single covariate derived from them are in all pts : (3) 2.86 (2.41-3.40), (4) 3.74 (3.04-4.61) and in pts with ED : (3) 2.35 (1.76-3.14), (4) 4.39 (2.73-3.05) and (5) 4.08 (2.70-6.17). CPEs ranged from 0.58 to 0.63 for prognostic classifications and from 0.63 to 0.65 for Cox models (all pts) and from 0.52 to 0.57 and 0.58 to 0.60 (pts with ED) with overlapping confidence intervals.

Conclusion: All the classifications are validated and suitable for use, for instance, in clinical trials for stratification purposes. Expectedly, prediction at an individual level remains poor. A specific model for pts with ED does not seem more useful.

Disclosure: All authors have declared no conflicts of interest.

266O

OUTCOME OF PROPHYLACTIC CRANIAL RADIOTHERAPY IN EXTENSIVE-STAGE SMALL CELL LUNG CANCER: THE CHRISTIE EXPERIENCE OVER TWO YEARS

N. Ghosal[1], K. Gupta[2], C.E. Lee[3], P. Lorigan[4], F. Blackhall[5], R. Swindell[1], N. Bayman[1], N. Thatcher[6], C. Faivre-Finn[3] *[1]Clinical Oncology, The Christie Hospital, Manchester/UNITED KINGDOM, [2]Clinical Oncology, The Christie Hospital, manchester/UNITED KINGDOM, [3]Clinical Oncology, christie, manchester/UNITED KINGDOM, [4]Department of Medical Oncology, Christie Hospital, Manchester/UNITED KINGDOM, [5]Department of Medical Oncology, Christie Hospital NHS Trust, Manchester/UNITED KINGDOM, [6]Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester/UNITED KINGDOM*

Objective: Prophylactic cranial irradiation (PCI) in extensive-stage small cell lung cancer does not only reduce the risk of developing brain metastases (BM) but also prolongs disease-free and overall survival [1]. We adopted this treatment as standard in patients who responded to chemotherapy, PS 0-2 and age ≤75 years. We present the outcome data of patients treated in our institution over a period of 2 years.

Methods: We reviewed the casenotes of all patients treated with PCI between January 2007 and December 2008. Patients did not routinely undergo imaging of the brain prior to receiving PCI or chemotherapy if there was no clinical suspicion of BM. The median follow up was 14 months.

Results: There were 51 patients in total (25 males and 26 females). The median age was 63 yrs (43-75). Prior to radiotherapy 29 patients had documented WHO performance (PS) status 0-1, 14 patients had PS 2, 1 had PS 3 and in 6 cases the PS was not documented. Patients received either 4 (=15), 5 (n=5) or 6 (n=31) cycles of cisplatin or carboplatin and etoposide chemotherapy. All patients responded to chemotherapy (at least stable disease). All patients received 20 Gy in 5 daily fractions of whole brain prophylactic cranial radiotherapy. 13 patients (25%) developed BM. The survival figures are shown in table 1.

Table 1. Survival Figures

	Median Survival	1 yr Survival
Calculated from date of diagnosis	331 days	42%
Calculated from 4 weeks prior to start of PCI	199 days	20%
Slotman study (calculated from randomisation)	201 days	27%

Conclusion: Using the same inclusion criteria as described in the Slotman study the rates of BM (and survival) after PCI were in keeping with the published data in our institution. It is encouraging that the results of the randomised controlled trial are applicable to a standard population.

1. Slotman, B., et al., Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*, 2007;357(7): p. 664–72.

Disclosure: All authors have declared no conflicts of interest.

Table 1. Results

Masaoka Staging System	No (%)	SUV_{max} (mean ± SD)	SUV_{M} (mean ± SD)	$SUV_{T/M}$ (mean ± SD)
Stage I	5 (22.7)	3.8 ± 0.90	1.7 ± 0.29	2.4 ± 1.31
Stage II	8 (36.4)	4.7 ± 1.20	1.8 ± 0.35	2.4 ± 1.46
Stage III	5(22.7)	12.1 ± 6.87	2.5 ± 0.38	3.6 ± 0.19
Stage IV	4 (18.2)	17.6 ± 6.24	2.0 ± 1.40	11.5 ± 0.19
WHO Classification				
Type A	2 (9.1)	3.5 ± 0.80	1.7 ± 0.05	0.9 ± 0.74
Type AB	5 (22.7)	4.0 ± 1.68	1.9 ± 0.34	2.0 ± 0.45
Type B1	4 (18.2)	4.9 ± 0.85	2.2 ± 0.13	2.1 ± 0.28
Type B2	2 (9.1)	6.6 ± 1.00	1.4 ± 0.15	4.9 ± 0.15
Type B3	2 (9.1)	9.4 ± 3.60	2.8 ± 1.20	3.4 ± 0.18
Type C	5 (22.7)	14.3 ± 4.25	2.0 ± 0.70	7.2 ± 6.36
Carcinoid	2 (9.1)	18.7 ± 12.63	1.7 ± 0.10	11.1 ± 7.60
Groups of risk classification				
Low risk	11 (55.0)	4.2 ± 1.70	2.0 ± 0.46	1.9 ± 0.70
High risk	9 (45.0)	13.3 ± 7.62	2.0 ± 0.92	7.1 ± 5.94

267O

STANDARDIZED UPTAKE VALUES OF POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (PET/CT) AS MALIGNANT PREDICTOR IN THYMOMA

L. Bertolaccini[1], G. Rizzardi[1], P. Scanagatta[1], A. Bianchi[2], A. Biggi[2], A. Campione[3], A. Comino[3], A. Terzi[1] *[1]Thoracic Surgery, S. Croce e Carle Hospital, Cuneo/ITALY, [2]Nuclear Medicine, S. Croce e Carle Hospital, Cuneo/ITALY, [3]Pathology, S. Croce e Carle Hospital, Cuneo/ITALY*

To evaluate the role of PET/CT as predictor of pathological type and stage of thymomas, 22 patients (13 M, 9 F; mean age 58 ± 14 ys) were assessed by PET. Maximum standardized uptake value (SUV_{max}) and tumour SUV_{max}/background mediastinal SUV_{max} (T/M) ratio were recorded. Thymomas were classified according to World Health Organization (WHO) classification, and divided in two groups based on histological finding: low-risk thymoma (LRT), including types A, AB and B thymoma; high-risk thymoma (HRT), including types B2, B3 and thymic carcinoma. Thymic epithelial tumours were staged according to Masaoka staging system. Two-tailed t-tests (normally distributed data) or Wilcoxon–Mann–Whitney U-test (not-normally distributed data) were used for evaluating significance of differences between group means. Significance of any proportional differences in attributes were evaluated using Fisher's Exact Test. Correlation between variables was evaluated using Bravais-Pearson linear correlation coefficient and using Spearman rank correlation coefficient. Results are showed in Table 1 In Masaoka staging system, differences between mean of SUV_{max} are significant ($p=0.0231$), but differences between mean of $SUV_{T/M}$ are not statistically significant. Considering Masaoka staging system, differences between mean of SUV_{max} are significant ($p=0.0098$) but differences between mean of $SUV_{T/M}$ are not statistically significant. Highly statistical correlation is shown between SUV_{max} and Masaoka staging system ($\rho=0.7869$), and $SUV_{T/M}$ and Masaoka system ($\rho=0.9455$). In groups of risk classification, differences between mean of SUV_{max} and $SUV_{T/M}$ are highly significant ($p=0.0073$), despite small statistical sample. We found highly significant correlation with comparison of SUV_{max} ($\rho=0.8759$) and $SUV_{T/M}$ ($\rho=0.9844$) with group of risk subdivision. In conclusion, $SUV_{T/M}$ is directly correlated to advanced stage of disease and to higher degree of malignity.

Disclosure: All authors have declared no conflicts of interest.

268P

MULTIPLE MICRORNA ARE DYSREGULATED IN MESOTHELIOMA

C.D. Hoang[1], Y. Xu[1], M. Zheng[1], G. Peltz[1], J. Shrager[1], R. Kratzke[2] *[1]Cardiothoracic Surgery, Stanford University, Stanford/USA, [2]Medicine, University of Minnesota, Minneapolis/USA*

Objective: microRNA (miRNA) expression profiles of mesothelioma (MM) tumors were investigated to better understand the molecular mechanisms involved in disease development.

Methods: Total RNA was extracted from 25 fresh frozen specimens of biopsy proven human MM (18 epithelial, 4 sarcomatoid, and 3 biphasic) and 6 specimens of normal pleura. miRNA microarray profiling was performed on the Illumina miRNA expression profiling panel containing 858 miRNA. To assess for significant miRNA in our data, we used a stringent adjusted p-value of < 0.01. Various computational tools were used for analysis: principle component analysis, hierarchical clustering, TargetScan mRNA gene prediction software, and DAVID network analysis software. We also used the NIH gene expression omnibus database of MM for additional analyses. Validation techniques included TaqMan real-time RT-PCR and western blotting.

Results: We detected 119 miRNA with significant differential expression between the tumor and normal pleural groups; 55 miRNA were over-expressed and 64 miRNA were under-expressed. Gene mapping identified ~17,000 different mRNA target sites corresponding to the 119 miRNA. In order to assess biologically important miRNA:mRNA pairings, we queried a MM mRNA public database to find the subset of mRNA targets common to our in-silico predictions. This resulted in a set of 572 genes. Network analysis of this reduced subset of target genes revealed groups of genes related to: cell signaling, cell differentiation, regulation of RNA polymerase, metal and ion-binding processes, nucleic acid metabolism, RNA biosynthesis, and cell cycle regulation. Notably, hsa-miR-133b was down-regulated by 16.7-fold in MM specimens. This miRNA negatively regulates members of the BCL-2 gene family which is known to participate in cell survival; and thus loss of expression of miR-133b correlates with escape from apoptosis/uncontrolled cell growth.

Conclusion: We identified many novel miRNA that are significantly altered in MM. Our results suggest that various miRNA are extensively involved in

the pathogenesis of MM and represent potential therapeutic targets. These results also serve as a database for functional characterization of miRNA in MM.

Disclosure: All authors have declared no conflicts of interest.

269P

FOLLOW-UP OF ASBESTOS-EXPOSED INDIVIDUALS USING MESOTHELIOMA SERUM BIOMARKERS

K. Hollevoet[1], J. Van Cleemput[2], J. Thimpont[3], P. De Vuyst[4], L. Bosquée[5], K.N. Nackaerts[6], Y. Kishi[7], C. Legrand[8], J.R. Delanghe[9], J.P. van Meerbeeck[10] *[1]Respiratory Medicine, 7K12, Ghent University Hospital, Ghent/BELGIUM, [2]Occupational Diseases, Eternit NV, Kapelle-op-den-Bos/BELGIUM, [3]Occupational Diseases, Occupational Diseases Fund, Brussels/BELGIUM, [4]Respiratory Medicine, Erasme Hospital ULB, Brussels/BELGIUM, [5]Pulmonology, CHU Sart Tilman, Liege/BELGIUM, [6]Pulmonology, UZ Leuven, Leuven/BELGIUM, [7]Medical & Biological Laboratories, Co. Ltd., Ina Institute, Nagano/JAPAN, [8]Institut De Statistique, Université Catholique de Louvain, Louvain-la-Neuve/BELGIUM, [9]Clinical Chemistry, Ghent University Hospital, Ghent/BELGIUM, [10]Department of Respiratory Medicine, University Hospital, Ghent/BELGIUM*

Introduction: Prediction of malignant mesothelioma (MM) risk in asbestos-exposed individuals is hampered by the limited accuracy of current screening techniques and the low prevalence of MM. Serum biomarkers might increase the former by enriching the population at risk. This abstract reports the follow-up of asbestos-exposed individuals with soluble mesothelin (SM) and megakaryocyte potentiating factor (MPF).

Methods: Individuals with professional asbestos exposure were recruited at the Belgian Occupational Diseases Fund, 2 companies, and the participating departments of Respiratory Medicine. After 1 year, participants were contacted for a 2nd blood sample. Serum SM (nM) and MPF levels (ng/mL) were assayed with the Mesomark® and Human MPF ELISA kit, respectively, and cut-offs were set at 2.00 nM and 12.38 ng/mL [Hollevoet, 2010]. Glomerular filtration rate (GFR), a confounder of these biomarkers [Hollevoet, 2009], was determined with the CKD-EPI equation (mL/min/1.73 m^2).

Results: From the 214 individuals included at baseline, 9 had both SM and MPF levels above cut-off, while respectively 4 and 5 were either MPF or SM-positive. The GFR of these 18 individuals (median-IQR: 65-44 mL/min/1.73 m^2) was significantly lower (Mann Whitney U, $p<0.001$) than those with a negative test (median-IQR: 80-23 mL/min/1.73 m^2). In the 133 individuals who already gave a 2nd sample, biomarker levels correlated highly significantly between the 2 time points (Spearman rank, $p<0.001$), and Bland-Altman analysis revealed a mean difference of 0.29 ng/mL and 0.26 nM, respectively, with acceptable limits of agreement. Currently, no participants presented a malignancy. Updated results will be presented at the meeting.

Conclusion: In asbestos-exposed individuals, SM and MPF levels reveal a long-term stability and a manageable percentage of positive test results. At present, it is not possible to conclude whether an elevated biomarker level reflects an insidiously developing malignancy or merely a false positive, e.g. due to renal failure. As such, only further long-term follow-up can establish whether triaging asbestos-exposed populations based on biomarker levels indeed results in a population with increased MM prevalence.

Disclosure: J.P. van Meerbeeck: I received a research grant from Cis bio International (25 000 €). All other authors have declared no conflicts of interest.

270P

COMPLETE RESPONSE TO CHEMOTHERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA - WHAT NEXT?

M. Feigen[1], N. Alam[2], S. White[3] *[1]Radiation Oncology Centre, Austin Health, Heidelberg/AUSTRALIA, [2]Thoracic Surgery, East Melbourne Heart and Lung Foundation, Fitzroy/AUSTRALIA, [3]Oncology, Warringal Medical Centre, Heidelberg/AUSTRALIA*

Background: This is a case report of a 56 year old man diagnosed in November 2007 with stage IV malignant pleural mesothelioma. He was treated with palliative chemotherapy and had a complete response on CT and PET scan followup.

Methods: A CT scan performed to investigate right chest pain showed pleural thickening at the right lung base and an effusion. Pleural biopsy found epithelioid mesothelioma and a PET/CT scan showed intense FDG activity involving thickened pleura over the entire right hemithorax, including the fissures, paraoesophageal, retrocardiac and retrocrural spaces and costophrenic recess, IMIG stage T4NxM0. Six cycles of cisplatin and pemetrexed were given from January to June 2008. A progress CT scan showed a marked reduction in all the previous disease with pleural thickening under 1 cm and a PET/CT scan showed minimal nonspecific residual FDG uptake. The mesothelin level fell from 29.0 to 0.7 nmol/L.

Results: A pleurectomy/decortication was performed in September 2008 finding residual low volume disease on the right hemidiaphragm and parts of the visceral pleura. Followup scans showed a recurrence in the right 8th rib in March 2009 and at other sites in the right hemithorax and retrocrural nodes in October. These did not respond to four cycles of the same chemotherapy he had two years earlier.

Conclusion: Less than 1% of mesothelioma patients have a complete radiological response to chemotherapy. A careful observation policy with close followup is recommended as future relapse is likely and the expectation that this may be responsive to the initial chemotherapy may be unsustained.

Disclosure: All authors have declared no conflicts of interest.

271P

MMP-9, TIMP-1 AND VEGF IN SMALL CELL LUNG CANCER PATIENTS

E.L. Wojcik[1], B.N. Sas-Korczynska[2], J.N. Jakubowicz[2], Z.N. Stasik[1], P.P. Skotnicki[3], J.K. Kulpa[1] *[1]Clinical Biochemistry, Center of Oncology, Krakow/POLAND, [2]Radiotherapy, Center of Oncology, Krakow/POLAND, [3]Surgery, Center of Oncology, Krakow/POLAND*

Introduction: Small cell lung cancer (SCLC) is an aggressive and rapidly growing neoplasms that represents a strong tendency to dissemination. Matrix metalloproteinases are thought to play an important role in stromal invasion and degradation of the extracellular matrix components. Elevated expression of some of them, especially MMP-2 and MMP-9, has been reported in several types of human cancer, including small cell lung cancer. Currently, special attention is given to serum level of these metalloproteinases and their inhibitor in respect to the patients prognosis. The aim of presented study was the evaluation of relationship between MMP-9, TIMP-1, VEGF, IL-6 versus NSE and ProGRP in respect to SCLC patients survival.

Material and methods: MMP-9, TIMP-1, VEGF, IL-6, NSE, and ProGRP determinations were performed in 55 SCLC patients and in the reference group consisting of 44 healthy persons. Whereas NSE was determined using ECL method (cobas e411 analyzer), ProGRP – CMIA method (Architect i2000), for the remaining parameters ELISA method and Bender MedSystem reagents were applied.

Results: In SCLC patients there were found significantly higher levels of all assessed parameters than in the reference group. Frequency of elevated results were, respectively: for MMP-9 – 41.8%, TIMP-1 – 34.5%, VEGF – 47.3, IL-6 – 50.9, NSE and ProGRP – 72.7%. In the studied group of patients were observed relationships between MMP-9 and TIMP-1 ($r = 0.381$), as well as MMP-9 and VEGF ($r = 0.364$) and lack of them between metalloproteinase as well as its inhibitor, with tumor markers. Moreover, there was shown influence of IL-6 on the levels of the "cascade metastasis" markers. Spearman's correlations with IL-6 were: for MMP9 $r_s = 0.560$, for TIMP-1 $r_s = 0.400$, for VEGF $r_s = 0.289$ and for NSE $r_s = 0.257$. The analysis of relationships between pretreatment levels of studied parameters and patients survival revealed that apart from the extent of disease, TIMP-1, NSE and ProGRP also have significant impact on prognosis.
Conclusions: Relationships between IL-6 and MMP-9, TIMP-1 as well as VEGF may indicate complex mechanisms leading to development of invasive phenotype in SCLC patients. Elevated pretreatment TIMP-1, NSE, and ProGRP levels are associated with worse prognosis of SCLC patients.
Disclosure: All authors have declared no conflicts of interest.

272P

PROTEIN EXPRESSION AND GENE COPY NUMBER OF INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR (IGF1R) IN SMALL CELL LUNG CANCER (SCLC)

A. Badzio[1], M.W. Wynes[2], R. Dziadziuszko[3], M. Pardo[4], D. Merrick[4], J. Ranger-Moore[5], A. Kowalczyk[1], W. Rzyman[6], J. Jassem[7], F.R. Hirsch[8]
[1]Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND, [2]Medicine-division of Medical Oncology, University of Colorado Denver, Aurora/USA, [3]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk/POLAND, [4]Division of Medical Oncology, University of Colorado Denver, Aurora/USA, [5]Biostatistics and Data Management, Ventana Medical Systems Inc., Tucson/USA, [6]Toracic Surgery, Medical University of Gdansk, Gdansk/POLAND, [7]Oncology and Radiotherapy, Medical University, Gdansk/POLAND, [8]Medicine-oncology, University of Colorado Cancer Center, Aurora/USA

Background: IGF1R is a tyrosine kinase receptor implicated in the pathogenesis of several malignancies. In addition to mediating cell proliferation and apoptosis, IGF signalling also influences tumor cell motility and adhesion, affecting the propensity for invasion and metastasis. Consequently, IGF1R is now an attractive target for anti-cancer treatment. There is a paucity of data on the protein expression and IGF1R gene copy number, and their clinical relevance in SCLC.
Methods: We analyzed IGF1R protein expression and gene copy number in primary tumors from 90 SCLC patients who underwent pulmonary resection in a period from 1982 to 2001. This series included 67 males and 32 females 67 (74%); stage IA 6, IB 26, IIA 5, IIB 13, IIIA 24, IIIB 11, IIIB/IV 1, unknown 1. IGF1R expression was evaluated by immunohistochemistry using Ventana CONFIRM antibody and scored by three observers, taking into account percentage of positive cells (0-100%) and staining intensity (0-4). H-score was calculated as a percentage of positive cells times staining intensity. IGF1R gene copy number was evaluated using silver in-situ hybridization (SISH) technique and scored by two pathologists.
Results: Median H-scores for IGF1R protein expression was 81 (range 0-352). The positive immunostaining rates (cut-off H-score of 10) in the entire group were 77%. IGF1R expression did not correlate with any clinicopathological parameters such as age, tumor size, lymph node involvement and stage of the disease. Survival was not influenced by protein expression of IGF1R ($p=0.34$). Increased IGF1R gene copy number (average of four copies per cell or more) was found in 15 cases, gene amplification was rare in this subset and was detected in 5 patients. No correlation with clinicopathologic parameters or survival ($p=0.4$) was found. Gene copy number did not correlate with IGF1R expression ($p=0.54$).
Conclusions: Increased IGF1R gene copy number and IGF1R protein overexpression was found in numerous SCLC patients, but did not affect prognosis. These findings support potential role of targeting IGF1 signalling pathway in SCLC and warrant further investigations in this field.
Disclosure: J. Ranger-Moore: Employment: Ventana Medical Systems, Roche Tissue Diagnostics F.R. Hirsch: Advisory Boards: AstraZeneca, Merck Serono, BMS/Imclone, Syndax, Pfizer, Boehringer-Ingelheim, Lilly Oncology, GSK, OSI/Genenetech/Roche Research Funding: AstraZeneca, OSI, Genentech, Syndax, Biogen-Idec, Ventana-Roche, Merck, Genmab. All other authors have declared no conflicts of interest.

273P

OUTCOME PREDICTION IN LIMITED DISEASE SMALL CELL LUNG CANCER ON THE BASIS OF EARLY TREATMENT RESPONSE ASSESSMENT WITH 18FDG-PET

J. van Loon[1], C. Offermann[1], M. Ollers[1], W. van Elmpt[1], P.N. Lambin[1], D. De Ruysscher[2]
[1]Radiotherapy, Maastro Clinic, Maastricht/NETHERLANDS, [2]Department of Radiation Oncology (Maastro Clinic), Maastricht University Medical Center + GROW Research Institute, Maastricht/NETHERLANDS

Background: The majority of patients with limited disease (LD) SCLC still show disease progression short after the completion of concurrent chemoradiotherapy (CRT). Therefore, it is of great value to select patients early during treatment with the highest probability of benefit, avoiding ineffective treatment in the group with poor prognosis. Early metabolic response would be a logical choice. In contrast to NSCLC, data on the predictive value of an early metabolic response in SCLC are scarce. Thus, the purpose of the current study was to evaluate whether metabolic response early after the start of chemotherapy has predictive value in LD-SCLC.
Methods Patients: with LD-SCLC treated with CRT who had both an FDG-PET scan available before the start of chemotherapy and after the first cycle of chemotherapy, before the start of radiotherapy, were evaluated. Minimum follow-up was 18 months. The volume of FDG-uptake areas was quantified both within the primary tumour as in the involved nodal stations using the 40% (MV40) and 50% (MV50) threshold of the SUVmax. Metabolic response was assessed by the % change in the metabolic volume (MV) between both time points, and analyzed for its association with overall survival (OS) by univariate cox regression analysis.
Results: 15 patients, with an age of 48-85 years, were included. The median OS was 20 months. The time interval between the two PET-scans was 20 ± 8.4 days. The metabolic response as assessed by the % change in MV40 and MV50, was $-32 \pm 38\%$ (131.6 cm^3 to 89.8 cm^3) and -41 ± 38 % (86,0 cm^3 to 48,5 cm^3), respectively. Both the metabolic response based on MV40 and MV50 showed a significant association with survival ($HR = 1.02$, $p=0.042$; $HR = 1.02$ and $p=0.048$ respectively), indicating a 2% reduction in survival hazard for 1% reduction in metabolic volume. The mean tumour volume delineated on CT before the start of RT was 103.5 cm^3. Neither this parameter, nor the MV at any time point was associated with survival.
Conclusions: This study shows that the metabolic response assessed with PET early after the start of chemotherapy has the potential to predict outcome in SCLC. On basis of these data, a prospective study is planned in a larger patient population to allow multivariate analysis.
Disclosure: All authors have declared no conflicts of interest.

274P

PHASE II STUDY COMPARING ACCELERATED TWICE DAILY AND ONCE DAILY THORACIC RADIOTHERAPY IN PATIENTS WITH LIMITED-STAGE SMALL CELL LUNG CANCER (LS-SCLC) TREATED CONCURRENTLY WITH CHEMOTHERAPY

C.E. Lee[1], P. Lorigan[2], F. Blackhall[3], P. Taylor[4], L.F. Ashcroft[5], N. Thatcher[6], C. Faivre-Finn[1] *[1]Clinical Oncology, Christie, Manchester/UNITED KINGDOM, [2]Department of Medical Oncology, Christie Hospital, Manchester/UNITED KINGDOM, [3]Department of Medical Oncology, Christie Hospital NHS Trust, Manchester/UNITED KINGDOM, [4]Northwest Lung Centre, South Manchester University Hospital, Manchester/UNITED KINGDOM, [5]Department of Biostatistics, Christie Hospital, Manchester/UNITED KINGDOM, [6]Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester/UNITED KINGDOM*

Introduction: Over the past few decades the role of radiotherapy in SCLC has expanded and one particular study (Turrisi et al, 1999) reported improved survival rates with accelerated hyperfractionated (BDRT) versus once daily (ODRT) treatment concurrently with chemotherapy. Some however suggest that the total dose in the comparative arm (45Gy OD) was inadequate as the local relapse rate was high (52%). We conducted a phase II study to compare the BD schedule with a higher dose in the OD arm.

Methods: 38 patients were randomised from July 2004 to March 2008. They had histological and radiological confirmation of LS-SCLC, with a performance status of 0-1. In the OD arm, 66Gy in 33 fractions were delivered over 45 days and in the BD arm, 45Gy in 30 fractions over 15 days. Patients received cisplatin, 60 mg/m2 IV d1 with etoposide 120 mg/m2 IV d1-3, q3 wks × 4 cycles with concurrent RT (3D conformal without elective nodal irradiation) from cycle 2. The primary endpoint was acute grade 3 and 4 oesophagitis. Secondary endpoints were response rates, acute and late treatment toxicity and overall survival.

Results: 38 patients were randomised on a 2:1 basis (ODRT n=12; BDRT n=26) and 32 evaluated for response. The median age was 61 yrs (range 39–78). 66% were male and 82% were PS1. 15% had grade 3 acute oesophagitis in the OD arm and 25% in the BD arm. There was no grade 4 acute oesophagitis. No patients developed grade 3 or 4 late oesophagitis. Only 1 patient (4%) in the OD arm had grade 3 acute pneumonitis. 4% in the OD arm and 11% in the BD arm had grade 3 late pneumonitis at 6-9 months. There was no statistically significant difference in overall survival between the 2 arms (p=0.910). To date 26 patients have died and 12 are still alive. At a median follow up of 33.6 mths (range 15-53), the median survival for the OD arm was 16.9 months and 15.5 months in the BD arm.

Conclusions: This study shows that treatment in both arms is feasible and tolerable. The multinational randomised phase III CONVERT trial is currently recruiting with the end point of overall survival. We would encourage interested PIs to join the trial in order to establish a standard of care in LS-SCLC.

Disclosure: All authors have declared no conflicts of interest.

275P

DOSE-INTENSITY OF RADIOTHERAPY BEST PREDICTS LONG-TERM SURVIVAL IN PATIENTS WITH LIMITED DISEASE SMALL-CELL LUNG CANCER

I. Wzietek, M. Bialas, E. Nowara, R. Suwinski *Radiotherapy Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice/POLAND*

Purpose: It has been recently proposed (De Ruysscher et al. J Clin Oncol. 2006, 24: 3815-6) that time between Start of any cytotoxic treatment until the End of Radiotherapy (SER) is an important predictor of survival in limited-disease small-cell lung cancer (LD-SCLC). The purpose of this study is to verify this concept based on analysis of large database of patients treated in a single institution.

Material and methods: The analysis included 364 patients with LD-SCLC treated between 1994 and 2007. Only the patients who received radiation doses of more than 40 Gy were included. All 364 patients received Cis-Pt based chemotherapy. Timing of chest radiotherapy (RT) relative to the start of chemotherapy varied over the years resulting in heterogeneity in SER. Also, radiation prescription practice varied (split course, conventional and hyperfractionated RT) resulting in heterogeneity of treatment times, while total radiation doses were relatively uniform (45-50 Gy in most of the patients). The average dose-intensity of radiotherapy (DI) was calculated as a quotient of RT dose and RT time.

Results: SER (<120 days vs. ³120 days) did not significantly influence overall survival (RR=0.88, p=0.32). By contrast, DI (<8 Gy/week vs. ³8 Gy/week) significantly influenced overall survival (RR=0.73, p=0.02), with 2-year survival rate of 10% and 25% in the respective groups. The parameters related to chemotherapy (number of courses, time of chemotherapy) did not appear significant.

Conclusion: The results of present analysis suggest that dose-intensity of radiotherapy better predicts long-term survival in LD-SCLC than the parameter SER proposed in the literature.

Disclosure: All authors have declared no conflicts of interest.

276P

FIVE-YEAR RESULTS OF RADIOTHERAPY FOR SMALL CELL LUNG CANCER

Y.A. Ragulin[1], A.G. Zolotkov[2], Y.S. Mardynsky[2], V.N. Medvedev[1], I.N. Ivanova[2] *[1]Thoracic Department, Medical Radiological Research Center RAMS, Obninsk/RUSSIAN FEDERATION, [2]Radiology Department, Medical Radiological Research Center RAMS, Obninsk/RUSSIAN FEDERATION*

Background: Results of the treatment of small cell lung cancer are unsatisfactory. The aim of the study is to compare efficiency of nonconventional (hyperfractionated, accelerated radiotherapy with doze escalation) with traditional (conventional) radiotherapy.

Materials and methods: Between 1995 and 2003, 157 patients with locally advanced small-cell lung cancer received chemo-radiotherapy. All patients received 2 induction and 4 adjuvant cycles of platinum-based chemotherapy (cisplatin/carboplatin plus etoposide). Patient demographics, tumor characteristics, treatment details, and survival were recorded retrospectively. All patients earlier did not receive any special anticancer treatment. Group A (hyperfractionated, accelerated radiotherapy with doze escalation) - 75 patients received two daily fractions of 1.4 Gy with an interval 5–6 hours during 3 weeks, further two daily fractions of 1.6 Gy to a total dose of 60–64 Gy. Group B (conventional radiotherapy) - 82 patients: 2 Gy daily to a total dose of 60-64 Gy. Radiotherapy was carried on the linear accelerator Clinac 2100C.

Results: Five-year overall survival rate in patients Group A was 26% (20 pts) and in patients Group B 11% (9 pts), p = 0,022. Local recurrence was observed in 15 pts (20%) and in 32 pts (39%), respectively. Post-radiation esophagitis grade III developed in 18 pts Group A (24%) and in 12 pts Group B (15%). Post-radiation pneumonitis and pulmonary fibrosis developed in 15 pts (20%) and in 10 pts (12%), respectively. Complete response of a tumor to hyperfractionated, accelerated radiotherapy with doze escalation are statistically significant prognostic factors, influencing on five-year overall survival rate.

Conclusions: Hyperfractionated accelerated radiotherapy with doze escalation is more effective than traditional radiotherapy with higher levels of toxicity in small cell lung cancer. Low ability to reparation of sublethal damages increases small cell lung cancer radiosensitivity because it has

considerable part of proliferating clone, short time of tumor duplication, high ability to repopulation, heterogeneity of a new growth with prevalence of any subpopulation.
Disclosure: All authors have declared no conflicts of interest.

277P

EFFICACY AND SAFETY OF COMBINED RADIO-CHEMOTHERAPY IN LIMITED-STAGE SMALL CELL LUNG CANCER TREATMENT: A SINGLE-INSTITUTION EXPERIENCE

I. Meattini, V. Scotti, A. Rampini, P. Bastiani, C. De Luca Cardillo, C. Santomaggio, V. Di Cataldo, B. Agresti, M. Mangoni, G. Biti *Radiation-Oncology, University of Florence, Florence/ITALY*

Purpose: To evaluate the efficacy and safety of the combined modality treatment in patients with limited-stage small cell lung cancer (SCLC).
Patients and methods: Fifty-eight patients affected by limited-stage SCLC were treated between July 1987 and January 2006 at University of Florence. All patients were treated with combined early chemotherapy and thoracic radiotherapy. Median age was 62 years (range 41–77), 44 were female and 14 male. No patient underwent surgery. A total of 238 cycles of chemotherapy (range 3–8, median 5 cycles) were administered; composed of platin-etoposide (CE, 34 patients) or alternated CE and epirubicin-ifosfamide (CE/EI, 24 patients) were used. A median total dose of 6000 cGy (range 5000–6400 cGy) with 200 cGy daily fractions was given to the primary tumour and mediastinum in 45 patients (77.6%) and only to the primary tumour in 13 patients (22.4%). Prophylactic cranial irradiation (PCI) was performed in all patients with complete response after combined treatment.
Results: Median follow-up time was 20 months (range 3-159). Five-years PFS and OS rates were 27 % and 18 %, respectively. No difference in terms of PFS and OS emerged between EC and CE/EI regimens ($p=0.41$). After combined treatment we registered 55% of complete response, 39% of partial response and 6% of progressive disease. Univariate analysis showed that a total radiation dose $\geq$6000 cGy significantly improved PFS ($p<0.05$). According to the Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0) we registered 14 cases of G1-2 dysphagia and 11 cases of G1-2 esophagitis. Concerning haematological toxicity our results showed 16 cases of G1-2 neutropenia, 8 cases of G1-2 anaemia and 3 cases of G1-2 piastrinopenia. No significant differences emerged between different chemotherapy regimens ($p=0.30$).
Conclusions: Our treatment results are in accordance with the most relevant literature studies. In our experience the combined approach with radio-chemotherapy in limited-stage SCLC was effective and well-tolerated. Our results suggest that limited radiotherapy volumes and higher doses obtained with dose-escalation may improve SCLC outcome.
Disclosure: All authors have declared no conflicts of interest.

278P

CISPLATIN, ETOPOSIDE AND IFOSFAMIDE (PEI) IN THE TREATMENT OF SMALL CELL LUNG CANCER: MONOINSTITUTIONAL EXPERIENCE OF 59 CONSECUTIVE CASES

C. Boni[1], E. Radighieri[1], V. Bertolini[2], D. Formisano[3], F. Zanelli[1] *[1]Medical Oncology, Arcispedale Santa Maria Nuova, Reggio Emilia/ITALY, [2]Information Department, Arcispedale Santa Maria Nuova, Reggio Emilia/ITALY, [3]Statistics Department, Arcispedale Santa Maria Nuova, Reggio Emilia/ITALY*

Combination chemotherapy is very active in SCLC, although no improvement has been done in the last 20 years, with Cisplatin-Etoposide (PE) still considered the world-wide standard, with an average median survival of about 7 months in pts with extended disease (ED). In 1995, a randomized trial of the Hoosier Group, in 171 ED pts, showed a significant advantage in overall survival in the arm treated with PEI, compared to PE. Despite that, PEI is not a commonly used regimen in SCLC. Here we present a serie of 59 consecutive pts with SCLC that were treated at our Institution, in first and/or subsequent line with PEI: Cisplatin 20mg/m2, Etoposide 75mg/m2 and Ifosfamide 1200mg/m2, day 1 to 4, every 3 weeks. From Dec 1998 to Dec 2008, 59 pts, 40 males and 19 females, were considered; 21 with LD and 38 with ED. Median age was 59, with PS 0 in 59%, PS 1 in 32% and PS 2 in 9%. Overall, 364 cycles of PEI were given, with an average of 6 cycles and 2 lines per patient. 48 pts received PEI in first line, 24 in second, 16 in third and 4 in subsequent lines (range 4-6). In the serie of 59 pts, the PR rates were 75%, 42% and 13% and CR were 13%, 17% and 13% in 1st, 2^{d} and 3^{d} line, respectively, with a ORR of 87%, 58% and 25%. In 21 LD pts, Time To Progression was 12.7, 7.9 and 5.8 mts in 1st, 2^{d} and 3^{d} line, respectively; in 38 ED pts, TTP was 6.8, 5,0 and 3.0 mts. OS was 26.3 mts in LD pts, and 13.2 mts in ED pts, with 2 year Survival of 62% in LD and 24% in ED. Median Dose Intensity for all 3 drugs was about 89% when PEI was given in first line, 80% in second line and 87% in third line. Haematologic toxicity was the most frequent adverse event, with G3-4 Neutropenia in 56%, Anemia in 27% and thrombocytopenia in 21% of the pts, in first line. Three toxic deaths were observed, all in PS $\geq$ 1 pts: two for febrile neutropenia in pts receiving the first cycle of a third line, and one in the first cycle of a first line, for heart failure in a cardiopatic patient. In our study the regimen PEI confirmed a high activity and efficacy, both in LD and ED pts. Toxicity was manageable, with a high dose intensity also in pts heavily pretreated, that received PEI as rechallenge, after two previous lines of PEI or other Platinum based chemotherapy.
Disclosure: All authors have declared no conflicts of interest.

279P

FIRST AND SECOND LINE SYSTEMIC CHEMOTHERAPY RESPONSES IN SMALL CELL LUNG CARCINOMA

A. Besen, F. Kose, A. Sezer, A.T. Sumbul, T. Canbolat, U. Disel, O. Ozyilkan *Medical Oncology, Baskent University, Adana/TURKEY*

Introduction: Small cell lung cancer (SCLC) accounts for approximately %15 of all lung neoplasm. Treatment of limited-stage SCLC consists of combination chemotherapy and concurrent radiotherapy while chemotherapy is cornerstone of treatment in extensive-stage. Although SCLC is both chemotherapy and radiotherapy sensitive, recurrences are common during the course of the disease. Here we discuss survival rates, treatment patterns and characteristics of patients that were followed up between 2005 to 2009 in our centre.
Material-methods-results: Thirty eight patients were studied during this period and the patients characteristics were as follows: 35 patients were men and 3 patients were women. Mean age and mean cigarette smoking were 57 years old (range 38–85 years old) and 45, 9 pack-years (range 0–110 pack-years) respectively. 20 patients had limited-stage and 18 patients had extensive-stage disease at diagnosis. All patients except two of them received chemotherapy with or without radiotherapy. Cisplatin plus etoposide was initiated as a first-line chemotherapy regimen to all patients. Median overall survival time, determined by the Kaplan-Meier method, was 11 months (range 6.8–15.1 months). There was no relationship between overall survival and patients LDH and hemoglobin levels. Median progression free survival after first line chemotherapy was 7 months (range 6.1–7.8 months). Of 18 patients who were given second-line chemotherapy seven of them received cyclophosphamide, doxorubicin, vincristine (CAV) combination chemotherapy and remainder received irinotecan based therapy. Progression free survival after second line chemotherapy was 2 months (1.1–2.8 months) and there was no statistically significant difference between these two regimens.

In conclusion, SCLC is a highly aggressive tumor with a rapid doubling time. Cisplatin plus etoposide is the established regimen in the first line setting. Despite good responses to chemotherapy observed during the course of the disease, early relapses are common and further investigations are needed to determine optimal chemotherapy regimens.
Disclosure: All authors have declared no conflicts of interest.

280P

PATTERNS OF CARE AND INFLUENCE ON SURVIVAL IN SMALL CELL LUNG CANCER: A SINGLE AUSTRALIAN ONCOLOGY UNIT EXPERIENCE

K.B. Pittman[1], M. Colbeck[1], T.J. Price[1], S. Sukumaran[1], B. Hooper[1], M. Tuck[1], D. Roder[2], L. Milliken[3], J. Hardingham[1] *[1]Medical Oncology, The Queen Elizabeth Hospital, Adelaide/AUSTRALIA, [2]Epidemiology, Cancer Council South Australia, Adelaide/AUSTRALIA, [3]Epidemiology, Department of Health, Adelaide/AUSTRALIA*

Background and Aims: The Queen Elizabeth Hospital (TQEH) Clinical Cancer Registry has collected clinical data on small cell lung cancer (SCLC) for over 25 years. SCLC outcomes have changed little over the past couple of decades. The aims of this study were to identify patterns of care (POC) and survival over two 10 year time periods (1/1/1987 to 31/12/1996- Cohort A and 1/1/1997 to 31/12/2006-Cohort B).
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: Study population comprised of 392 patients (224 in A, 168 in B). The percentage of males were 70% in A compared with 55% in B. At diagnosis 38% of patients in cohort A and 24% in cohort B had limited stage disease (LD), while the remainder had extensive stage disease(ED). The majority of patients were smokers or former smokers in both groups. Combined chemotherapy and radiotherapy for LD was used in 6% in A and 58% in B. Chemotherapy drugs in cohort A included variable combinations involving Vincristine, Etoposide Cyclophosphamide and Adriamycin, whereas in B it was predominantly Carboplatin/Etoposide. The median survival for LD in cohort B was significantly higher (19.5 months), compared to A (11.8) months ($P=0.03$). In ED the median survival was 6.2 months in A and 4.3 months in B ($p=0.7$). Variables for poorer outcome were STA, male gender, ECOG >2, ED and diagnosis in cohort A.
Conclusions: This data provides information regarding changing POC and outcomes for patients with SCLC. Trends in outcomes may be indicative of more accurate staging as well as standardisation of treatment (particularly the use of chemo/radiotherapy) in the later cohort.
Disclosure: All authors have declared no conflicts of interest.

MISCELLANEOUS

281O

THE EXACTRAC SNAP VERIFICATION (SV), A NEW TOOL FOR ENSURING THE QUALITY CONTROL FOR STEREOTACTIC BODY RADIATION THERAPY (SBRT). THE FRENCH EXPERIENCE

F. Mornex[1], C. Udrescu[1], B. De Bari[1], G. Michel-Amadry[2], O. Chapet[1] *[1]Département de Radiotherapie Oncologie, Centre Hospitalier Lyon Sud, Pierre Benite/FRANCE, [2]Département de Physique Médicale, Centre Hospitalier Lyon Sud, Pierre Benite/FRANCE*

Purpose: The new system: intra-fraction patient (pt) imaging and verification provided by ExacTrac® SV allows tracking possible isocenter displacement within the pt throughout SBRT treatment and intratreatment realignment, improving radiotherapy quality. The purpose of this study was (1) to measure, for the first time, the intra-fraction variations of isocenter position, (2) to study the amplitude of variation function of the fraction duration and (3) to evaluate the impact of the table movement on pt positioning, using SV.
Methods: ExacTrac® SV uses X-ray real-time images acquired at any moment during treatment delivery or between fields to instantly detect and visualize isocenter displacement (beam on or off). The displacement can be measured using the fusion of the bony structures or the implanted markers with the DRRs. A tolerance margin indicates if a patient setup correction is needed or not. We already evaluated 18 pts irradiated for lung/liver tumors, using SBRT. The pts had a SV at each fraction, before each treatment beam. Finally, 1751 beams were verified with a measure of the isocenter displacement. The time from the pt installation on the table to each SV was systematically noted.
Results: The mean isocenter deviation for all the beams and all the fractions was 1.95 mm. The total mean time of one fraction was 21 minutes [9- 64 minutes]. The mean deviations were 1.98mm. The percentages of deviation ≥ 3 mm were 12.5% and the percentage of deviation ≥ 5 mm were 4.58%. In 12 pts, a table rotation was necessary. Pain, caugh or talk may explain the observed deviations in a few situations.
Conclusions: For the first time, it is shown that SV allows detecting isocenter deviations, which increase in amplitude and frequency with the fraction duration. It makes possible and highly suitable the intra-fraction verification during SBRT. With high-quality images at low X-ray doses, SV gives an accurate targeting from the beginning to the end of each fraction, inducing confidence to escalate the dose. SV appears to be an important tool for ensuring the quality control for SBRT. More results will be available at the time of the meeting.
Disclosure: All authors have declared no conflicts of interest.

282O

POSTOPERATIVE COMPLICATIONS AFTER LUNG CANCER SURGERY IN ELDERLY PATIENTS: SURGICAL PROCEDURES AND RISKS

S. Shiono[1], M. Abiko[1], N. Kanauchi[2], T. Sato[1] *[1]Thoracic Surgery, Yamagata Prefectural Central Hospital, Yamagata/JAPAN, [2]Thoracic Surgery, Nihonkai General Hospital, Sakata/JAPAN*

Background: Postoperative complications for elderly patients after lung cancer surgery remain higher than for young patients. Decreasing these postoperative complications in elderly patients is a major issue. Objective: To identify the risk factors of postoperative complications for elderly patients who underwent lung cancer surgery. In particular, we investigated surgical factors, including surgical time, blood loss and thoracotomy size.
Methods: From January 2000 to September 2009, 567 patients underwent lung cancer surgery at our institution. We retrospectively reviewed 157 patients aged 75 years or older for possible risk factors of postoperative complications.
Results: Patients' mean age was 78 years (range, 75-89 years). There were 105 men and 52 women. There were no perioperative or postoperative deaths. Postoperative complications developed in 47 (30%) patients, including 21 (13%) with arrhythmia, 11 (7%) with prolonged air leak, 10 (6%) with delirium, 10 (6%) with hypoxia, 8 (5%) with pneumonia, 2 (1%) with cerebrovascular disease and 2 (1%) with postoperative hemorrhage. Univariate analyses showed that males ($P=0.04$), smoking history ($P=0.03$), preoperative $PaCO^2$ ($P=0.03$), surgical time ($P<0.01$), blood loss ($P<0.01$), blood transfusion ($P=0.03$), thoracotomy size ($P=0.01$), lobectomy

(P=0.02) and the period when surgery was done (before April, 2004 vs. after May 2004) (P<0.01) were risk factors for postoperative complications. Multivariate analysis showed that surgical time (P=0.04), thoracotomy size (P=0.04) and the period for surgery (P=0.03) were independent risk factors for postoperative complications.

Conclusions: This study demonstrated that the quality of surgery was an important factor for postoperative complications. Although severe adhesion and inflammation of the lung are difficult conditions during lung cancer surgery, in the case of elderly patients, skillful and meticulous surgical technique are required.

Disclosure: All authors have declared no conflicts of interest.

283PD

CONE BEAM CT AND LUNG STEREOTACTIC BODY RADIOTHERAPY: TUMOR LOCALIZATION AND SETUP CONTROL

F. De Rose[1], G. Mantini[1], B. Meduri[1], M. Balducci[1], G.R. D'Agostino[1], G.C. Mattiucci[2], S. Margaritora[3], A.R. Larici[3], F. Varone[4], V. Valentini[1] *[1]Radiotherapy, Polyclinic, Rome/ITALY, [2]Radiology, Polyclinic, Rome/ITALY, [3]Thoracic Surgery, Polyclinic, Rome/ITALY, [6]Pneumology, Polyclinic, Rome/ITALY*

Purpose: Lung stereotactic body radiotherapy (SBRT) requires high precision in daily patients' repositioning. Given the availability of onboard cone-beam CT (CBCT) imaging at our institution, we used daily volumetric image-guidance to evaluate the reliability of simulation and planning procedure and setup accuracy.

Materials and methods: The patients' selection criteria were: (1) primary unresectable tumour or (2) oligometastatic patients (less then three metastatic lesions with maximum diameter smaller than 5 cm). Every patient formerly trained to have normal breath during simulation had 3 CT scan on three subsequent days. CT were repeated in the same technical conditions. Patients were immobilized using a fixing device built by a vacuum bag modelled on the body of the patient and a thermoplastic mask to reduce respiratory movement (3D-LINE - Body Frame). 3D localization of the target was obtained by a stereotactic body frame external to the patient. Gross Tumor Volume (GTV) was identified by every CT scan; individual GTV was defined as an extent to wrap the whole volume of the three subsequent GTV. Planning target volume (PTV) was defined by increasing GTV of 3 mm in any direction. Prior to every fraction a CBCT was acquired in treatment position, errors between planned and actual tumour position were measured and corrected.

Results: Since May 2008, 16 patients were candidate for hypofractionated sterotactic body radiotherapy. 19 treatments were performed by 6-15 MV LINAC. Diameter of the lesions was comprised between 1.5 cm and 5 cm with a median value of 3 cm. Median delivered total dose was 4200 cGy (range 4200-5000 cGy, EQD_2>100 Gy). The mean tumour motion in the 3 referencing directions were the following: lateral 2.6 mm (median 2mm, range 0 – 17 mm); longitudinal 3.8 mm (median 2.5 mm, range 0 – 23 mm); vertical 2.6 mm (median 2 mm, range 0 – 12 mm). In 168/255 (66%) cases the error detection was lesser than 3 mm.

Conclusion: The our simulation and planning procedure is reliable, but these data support the use of a daily, pre-treatment cone beam CT in stereotactic treatments in order to account for setup errors larger than 3 mm, which in our sample was present in 34% of patients.

Disclosure: All authors have declared no conflicts of interest.

284P

SURGICAL TREATMENT OF NEUROGENIC TUMORS OF THE CHEST

F. Gradica[1], A.Y. Pere[2], A. Menzelxhiu[1], S. Mulosmani[3], D. Argjiri[3], I. Skenduli[1] *[1]Thorax Surgery Department, University Hospital of Lung Disease, Tirana/ALBANIA, [2]Onkologie Department, University Hospital Center, Tirana/ALBANIA, [3]Pneumologie, University Hospital of Lung Disease, Tirana/ALBANIA*

Background: Neurogenic tumors are commonly found in the mediastinum, especially in the posterior mediastinum or in the chest wall, and have a variety of clinical and histological features. We reviewed our experience with these types of tumors and assessed diagnostic and therapeutic approaches.

Patients and methods: A series of 23 consecutive patients with a neurogenic tumor of the chest, all seen for 5 years period, was retrospectively reviewed.

Results: The mean age of the 23 patients was 40 years, including 12 males and 11 females. Preoperative symptoms were present in seven patients (30.4%). Median tumor size was 6.4 cm, ranging from 3.6 to 28 cm. The major location of the tumor was the posterior mediastinum in 19 cases (82.6%) and the chest wall in 4 cases (17.4%). The operative procedure performed was tumor extirpation in 21 cases (91.3%), in posterior thoracotomy approach was performed in twenty one patients and chest wall resection in two cases. The histological type of the tumors was neurilemmoma in 15 cases (65.2%) neuroganglioma in 2 cases (8.7%), neurofibroma in 4 cases (17.4%), and malignant schwannoma in two cases (8.7%).Tumor related death occurred in only one case with malignant schwannoma. Five patients with neurilemmoma were diagnosed by magnetic resonance imaging (MRI).

Conclusion: Almost all cases of intrathoracic neurogenic tumours were benign in nature. Therefore, surgical indications may be carefully determined in cases with no symptom and with imaging that indicate benign neurilemmoma. Dumbbell tumours require a combined thoracic and neurosurgical approach.

Disclosure: All authors have declared no conflicts of interest.

285P

COMORBIDITY RISK ASSESSMENT FOR LUNG CANCER SURGERY IN ELDERLY PATIENTS

N. Lukavetskyy[1], T. Fetsych[1], V. Myronovych[2] *[1]Oncology, Lviv Medical University, Lviv/UKRAINE, [2]Surgery, Lviv Cancer Center, Lviv/UKRAINE*

In patients with resectable non-small cell lung cancer, surgical resection is the treatment of choice. The purpose of the present study was to identify preoperative risk factors related to age of the patients focusing on comorbidities.

Materials and 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 (p<0.05). The 30-day operative mortality rates were 6.25% in elderly population, postoperative morbidity was – 40.0% - significantly higer in elderly lung cancer population (p<0.05). But type of comorbidities is not independently related to postoperative morbidity and mortalities in both group of patients (p>0.05)

Conclusions: 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.
Disclosure: All authors have declared no conflicts of interest.

286P
TREATMENT DELAYS IN NON-SMALL CELL LUNG CANCER (NSCLC) AND THEIR PROGNOSTIC IMPLICATIONS

R. Diaconescu[1], C. Lafond[2], L. Choiniere[3], C. Sirois[3], B. Laliberte[4], M. Doyon[1], R. Whittom[1] *[1]Hematology Oncology, Hopital Sacre Coeur Montreal, Montreal/CANADA, [2]Pulmonology, Hopital Sacre Coeur Montreal, Montreal/CANADA, [3]Thoracic Surgery, Hopital Sacre Coeur Montreal, Montreal/CANADA, [4]Radiation Oncology, Hopital Maisonneuve Rosemont, Montreal/CANADA*

Background: The impact of treatment delays on NSCLC patients' survival is uncertain. While later treatment could negatively affect their psychological wellbeing, the maximum acceptable waiting time has not been determined.
Methods: We analyzed consecutive patients diagnosed with NSCLC between January 2005 and May 2007 who received standard treatment at Hôpital du Sacré-Coeur de Montréal. Treatment delay was calculated from the first abnormal radiographic study. Patients were classified into three groups, based on TNM staging and the treatment received: localized (stages I and II), regional (most of stage III) and advanced (stages IIIB and IV). Cox proportional hazards analysis was used to identify predictive factors for survival among the following parameters: age, gender, histology, smoking status, type of treatment, tumor board discussion and treatment delay. Kaplan-Meier curves were used to estimate survival.
Results: Three hundred twenty eight patients were identified. Their median treatment delay was 72 days (25-75% interquartile range = 37-110 days), and distributed as follows: 85 (56-130) days for localized, 91 (37-120) days for regional and 50 (30-76) days for advanced stages ($p<0.01$ for the latter). Treatment delay did not have a significant prognostic meaning for localized or regional stages. The opposite was true for advanced disease, both in univariate ($p=0.006$) as well as multivariate ($p=0.009$) analysis; for each week that the treatment could be delayed, the hazard ratio for mortality was improved at 0.93 (95% confidence interval 0.89-0.98). Survival of advanced patients who began treatment earlier versus later than 50 days was 6.8 months compared to 11.6 months ($p=0.027$). None of the other factors were significant in uni or multivariate analyses.
Conclusions: Treatment delays did not impact outcome in patients having localized or regional stage NSCLC in our cohort. For advanced stages, shorter treatment delays were associated with shorter survival. Rather than having a direct negative impact, this likely reflects that urgent treatment carried a negative prognostic meaning, as it was preferentially offered to patients having more aggressive disease.
Disclosure: All authors have declared no conflicts of interest.

287P
RADIATION PNEUMONITIS AND PULMONARY FIBROSIS IN LUNG CANCER

Y.A. Ragulin[1], L.V. Kursova[2], I.N. Ivanova[2] *[1]Thoracic Department, Medical Radiological Research Center RAMS, Obninsk/RUSSIAN FEDERATION, [2]Radiology Department, Medical Radiological Research Center RAMS, Obninsk/RUSSIAN FEDERATION*

Background: Radiotherapy is the main method of treatment of inoperable lung cancer. The doses necessary for tumour eradication considerably exceed tolerance of a pulmonary tissue and radiation pneumonitis often develops after anticancer treatment and it is most frequently complication of radiotherapy.
Materials and methods: We observed patients with radiation pneumonitis from 2005 to 2008 in MRRC. Adjuvant course of radiotherapy of 50 Gy have received 4 patients (prs) (16%), simultaneous chemo-radiotherapy (60–70 Gy) − 9 pts (36%), photodynamic therapy with following radiotherapy (65–70 Gy) −6 pts (24%), and radiotherapy only (65–70 Gy) −6 pts (24%). Radiotherapy was administered as accelerated hyperfractionated with non-uniform (1 + 1,5 Gy) dose crushing. Most of patients (21) had tumour stage III. In most cases radiation pneumonitis was developed during the course of radiotherapy or within three months after irradiation. Radiation pneumonitis grade II (scale LENT SOMA) was observed in 10 patients, grade III in 12 pts, and grade IV in 3 pts. The performance status was about 50% (Karnofsky scale).
Results: Treatment of radiation pneumonitis in patients with lung cancer is long and complex, hospitalizations alternated with the outpatient therapy. Patients with expressed symptoms of radiation pneumonitis require hospitalization of 4–5 times in a year. Treatment of radiation pneumonitis (II–IV grade) is difficult and expensive, but it is necessary as a part of treatment and rehabilitation actions in lung cancer therapy. Within a year lung cancer progression was revealed in 5 patients, fatal pulmonary bleeding was developed in 4 pts, and fatal pulmonary embolism in 1 patient. Pulmonary fibrosis stage II as the outcome of radiation pneumonitis was developed in 7 patients, grade III - in 4 pts, grade IV - in 4 pts. Anti-inflammatory agents, infusions, antiaggregants, inhalation therapy, cardiac drugs and therapy of concomitant diseases improve patients' status, functional and biochemistry indicators.
Conclusions: Radiation pneumonitis and pulmonary fibrosis are serious medical and social problem. It is necessary to introduce new therapy techniques for improvement of results of lung cancer treatment.
Disclosure: All authors have declared no conflicts of interest.

288P
PRIMARY PULMONARY HEMANGIOENDOTHELIOMA: CT, HRCT AND PET/CT MANIFESTATIONS

U. Yilmaz Turay, A. Yilmaz, Ç. Biber, Y. Erdoğan, N.Y. Demirci, H. Yücel *Chest Disease, Ataturk Chest Disease and Surgery Education Hospital, Ankara/TURKEY*

A 26 year old man was admitted to our hospital with right sided chest pain complaint. His physical examination was revealed normal. Chest X-Ray showed bilaterally, linear and micronodular opacities predominantly lung bases. His pulmonary function tests showed restriction and diminished diffusion capacity (49% of predicted). HRCT and CT of the thorax showed aproximatelly 8 mm in diameter, perivascular, subpleural, multiple nodules predominantly in lung bases, mosaic areas of ground −glass opacity and multipl mediastinal lymphadenopathy . The working diagnosis was interstitial lung disease and transbronchial biopsy was performed. Because of this procedure nondiagnostic surgical biopsy was performed. The histological findings and immunohistochemistry tests were consistent with pulmonary epitheloid hemangioendothelioma (PEH). The patient underwent 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG-PET/CT), abdominal CT, ultrasonography to evaluate the multiple nodules and to search for a metastasis. There was no evidence of multiorgan disease, metastasis, FDG up take. PEH is rare vascular tumor of low grade malignancy. Significant factors of poor prognosis are loss of weight, anemia, pulmonary symptomps and hemorrhagic pleural effusion. Our patient didn't have any of these features. Because of rarity of PEH there is no standard for treatment. After six months of diagnosis lesions were stable and there were no progression without therapy. This case was discussed for its rarity and HRCT

findings that mimicking interstitial lung disease and in contrast to the literature there were no up take of the FDG any of the nodules and lymphadenopathy.
Disclosure: All authors have declared no conflicts of interest.

289P

A CASE REPORT: ASKIN'S TUMOR OF CHEST WALL WITH PLEURAL EFFUSION

S. Kashyap, M. Sarkar, R.S. Negi, K. Sidhu *Pulmonary Medicine, Indira Gandhi Medical College, Shimla, Shimla/INDIA*

Introduction: Askin's tumor is a very rare primitive neuroectodermal tumor of the thoraco-pulmonary region. It is generally associated with dismal prognosis. Here, we report a patient who presented with chest wall mass which on further investigations turned out to be Askin tumor.
Material and methods: A 23 year old female was admitted in the department of pulmonary medicine of our institution with pain and swelling right anterior chest wall for last 6 months, cough with mucoid expectoration and progressive dyspnea for last 3 months and low grade fever of 10 days duration. On physical examination a chest wall mass with local tenderness and right sided pleural effusion was revealed. Computed tomography scan noted a 16 × 17 cm heterogeneously enhancing mass occupying right hemi thorax with chest wall invasion, erosion of ribs and right sided pleural effusion. Fine needle aspiration cytology (FNAC) of the chest wall mass and subsequent immunohistochemistry of the aspirated material was done.
Results: FNAC of chest wall swelling was suggestive of malignant small round cell tumor which on immunohistochemical staining showed positivity to Neuron Specific Enolase (NSE), CD-99(MIC-2) but negative on Desmin staining. The final diagnosis of Askin tumor with pleural effusion was made THERAPY: Patient was given induction chemotherapy followed by surgery and post-operative radiotherapy. Pre-operative chemotherapy was given in a total of 6 cycles with alternatingVACA/IE regime (Vincristine, ActinomycinD, Cyclophosphamide, Adriamycin/Ifosfamide Etoposide).
Discussions: Askin tumor is a rare, malignant, small round cell tumour of the thoraco-pulmonary region, typically presents as a solitary mass or multiple masses in the thoracic region. Seventy-five percent of Askin's tumors have been reported in patients younger than 20 years. Conventional histological features show compact nests of small, round cells and Homer-Wright pseudorosettes. Neuron-specific enolase stain is considered as a good marker for this tumor and supports its neurogenic origin.. The treatment for Askin's tumor should consist of radical resection supplemented with radiotherapy (3500 to 5500 rads) and aggressive chemotherapy. Overall prognosis is usually dismal.
Disclosure: All authors have declared no conflicts of interest.

290P

VASCULAR EVENTS IN LUNG CANCER

N. Yilmaz Demirci[1], U. Yilmaz Turay[2], A. Yilmaz[2], Y. Erdoğan[2], Ç. Biber[2], H. Yücel[2] *[1]Chest Disease, Ataturk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara/TURKEY, [2]Chest Disease, Ataturk Chest Disease and Surgery Education Hospital, Ankara/TURKEY*

Introduction: Many factors have prognostic significance in lung cancer. Thrombocytosis is observed frequently in these patients. The association between vascular events, which are the outcomes of paraneoplastic symptom, and mortality and morbidity have evaluated in numerous studies. The aim of this study is to evaluate thrombocytosis which is observed frequently in patients with lung cancer and vascular events.
Material and method: 281 patients who were histopathologically diagnosed as lung cancer between March 2007 and August 2009 were evaluated retrospectively.
Results: In 281 patient 234 (%83.27) were male, 47(%16.72) were female with median age 60.35(31-83 year). Histopathologically 40(%14.23) were small cell lung cancer, 241 (% 85.76) were non small cell lung cancer. Totally 17(%6.04) vascular event were determined. 11(%64.70) were deep vein thrombosis, 3(%17.64) were pulmonary thromboembolism, 1(%5.88) were cerebral arterial thrombosis, 1(%5.88) were vena cava superior thrombosis. In the course of thrombosis thrombocytosis have not determined but following visits thrombocytosis presented.
Conclusion: Thrombocytosis is observed frequently in patients with lung cancer. Further prospective researches are required to evaluate the necessity of profilactic anticoagulants in these patients. The association between coagulation parameters and survival, other step of the study, continues prospectively.
Disclosure: All authors have declared no conflicts of interest.

291P

DIABETES INCIPIDUS, A RARE FIRST CLINICAL MANIFESTATION OF LUNG ADENOCARCINOMA

F. Gharemanfard, F. Malek, A. Sadeghi *Internal Medicine, Seman University of Medical Sciences, Fatemie Hospital, Semnan/IRAN*

Lung cancer is the most common cause of cancer mortality worldwide, causing approximately 1.2 million deaths per year. Adenocarcinoma account for 38 percent of lung cancer. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is frequently caused by SCLC but it is rare in NSCLC. DI as the initial manifestation of malignancy is rare. Our case was a 52 years man who visited with polyuria and polydipsia and blurred vision. Pituitary stimulation test revealed central diabetes insipidus. Retinal angiography demonstrated multiple choroid lesions suspicious to metastastic lesions. Chest X Ray and CT scan showed right sided pleural effusion and lower lobe opacity. Open lung biopsy showed adenocarcinoma.
Disclosure: All authors have declared no conflicts of interest.

292P

EFFECTIVENESS AND PROGNOSIS OF INITIAL PERICARDIOCENTESIS IN THE PRIMARY MANAGEMENT OF MALIGNANT PERICARDIAL EFFUSION

O. Arrieta[1], Á. Apodaca-Cruz[2], B. Torres-Avila[1], C. Villarreal-Garza[1], J. Torres[2], A. Meneses[1], D. Flores-Estrada[1], F. Lara-Medina[1] *[1]Medical Oncology, Instituto Nacional de Cancerologia, Mexico City/MEXICO, [2]Department of Internal Medicine, Instituto Nacional de Cancerologia, Mexico City/MEXICO,*

Introduction: The management of pericardial effusion in patients with cancer denotes a complex condition, one which is frequently encountered. In terms of determining a better selection of treatment strategies, the purpose of this study was to determine the effectiveness of initial pericardiocentesis and examine prognostic factors influencing survival in patients with solid malignant tumors and symptomatic pericardial effusion treated initially with pericardiocentesis.
Patients and methods: We retrospectively reviewed the records of 100 patients with malignant disease and symptomatic pericardial effusion initially treated with pericardiocentesis at the National Cancer Institute of

Mexico between 1985 and 2009. We analyzed predictive factors for recurrence of pericardial effusion by bi- and multivariate analyses.
Results: The group comprised 74 females and 26 males. Twenty patients had developed malignant pericardial effusion at the time of primary cancer diagnosis. Recurrence rate (RR) after pericardiocentesis was 33%. Progression-free survival for pericardial effusion at 1 year was 59% (range, 47–71%). Median overall survival after pericardiocentesis was 40.3 ± 7.9 weeks (95% Confidence interval [95% CI], 24.9–55.7). The sole factor that correlated with increased progression-free survival for pericardial effusion was the presence of bloody pericardial effusion. For overall survival, multivariate analysis yielded that female gender and presence of pericardial effusion at time of primary malignancy diagnosis were associated with higher life expectancy.
Conclusion: Initial pericardiocentesis can provide successful management of patients with a control rate of 67%. In spite of the high effectiveness of the primary management of pericardial effusion with pericardiocentesis, it might be considered for initial treatment in this type of patients, especially those with poor prognosis, leaving pericardial window as a secondary strategy for recurrence.
Disclosure: All authors have declared no conflicts of interest.

293P

CYTOREDUCTIVE OPERATIONS IN COMPLEX TREATMENT FOR LUNG METASTASES OF COLORECTAL CANCER

A.V. Reshetov[1], R.V. Orlova[2], S.M. Lasarev[1], F.M. Markin[3], P.K. Yablonsky[3], A.V. Nohrin[4], G.N. Volgin[1], S.M. Simkin[5] *[1]Thoracic Surgery, St. Petersburg Medical Academy named after I.I. Mechnikov, St. Petersburg/RUSSIAN FEDERATION, [2]Chemotherapy Department, State City Oncology Dispancer, St. Petersburg/RUSSIAN FEDERATION, [3]Thoracic Surgery, Multifield City Hospital No. 2, St. Petersburg/RUSSIAN FEDERATION, [4]Thoracic Surgery, State City Oncology Dispancer, St. Petersburg/RUSSIAN FEDERATION, [5]Thoracic Surgery, Leningrad Regional Hospital, St. Petersburg/RUSSIAN FEDERATION*

Comparative studies of different treatment methods for intrapulmonary metastases in patients with colorectal cancer have always been a hot topic.
Methods: Retrospective analysis of 121 patients with intrapulmonary metastases of colorectal cancer since 1996 till 2008 was carried out. Forty three patients received system chemotherapy, 78 were operated. Median follow-up was 34.5 months (from 13 to 74 month). On the basis of age, sex of a patient the size and the number of metastases, FDI, secondary lymphnodal involvement we formed two groups: A and B using u-criterion Mann-Whitney. Group A included 21 patients who underwent surgery, group B - 21 patients who received systemic chemotherapy only. Similarly two groups were formed from operated patients: C and D. Group C included 34 patients who underwent surgery only. In group D (29 patients) we used system chemotherapy in addition to operation. Survival was calculated by the Kaplan-Meier formula using the moment method.
Results: One-year, three-year and five-year survival were estimated to be 95%, 42%, 15% and 92%, 12%, 7% in surgical group and in chemotherapy only group respectively. Survival in group A was significantly better than in group B. Median survival was (M) was 24.5 months and 11.7 respectively $p=0.003$. We did not find significant difference in survival between group D (M - 18.9 months) and C (M - 20.1 months) $p=0.29$.
Conclusion: Cytoreductive surgical resection of lung metastasis in patients with colorectal cancer in some patients may be the treatment of choice.
Disclosure: All authors have declared no conflicts of interest.

294P

INHIBITION OF CELL SURVIVAL, TUMOR GROWTH AND HISTONE DEACETYLASE (HDAC) ACTIVITY BY THE DIETARY FLAVONOID LUTEOLIN IN HUMAN EPITHELIOID CANCER CELLS

R. Iratni[1], S. Attoub[2], A.H. Hassan[3], B. Vanhoecke[4], A.M. Gaben[5], M. Bracke[6], M. Al-Sultan[7], K. Arafat[7], C. Gespach[5], G. Petroianu[8] *[1]Biology, UAE University, Al Ain/UNITED ARAB EMIRATES, [2]Pharmacology, Faculty of Medicine and Health Sciences UAE University, Al Ain/UNITED ARAB EMIRATES, [3]Biochemistry, Faculty of Medicine and Health Sciences, UAE University, Al Ain/UNITED ARAB EMIRATES, [4]Laboratory of Experimental Cancer Research, University Hospital, De Pintelaan, Gent/BELGIUM, [5]INSERM U673 and U938, University Pierre et Marie Curie Paris VI, Paris/FRANCE, [6]3Laboratory of Experimental Cancer Research, University Hospital, De Pintelaan, Gent/BELGIUM, [7]Pharmacology, UAE University, Al Ain/UNITED ARAB EMIRATES, [8]Pharmacology and Therapeutics, Faculty of Medicine and Health Sciences, UAE University, Al Ain/UNITED ARAB EMIRATES*

Phytochemical compounds and histone deacetylase inhibitors (HDIs) are emerging as a new generation of anticancer agents with limited toxicity to cancer patients. The present study investigates the impact of luteolin, a dietary flavonoid, on survival, motility, invasion of cancer cells, and tumor growth in vivo. We found that luteolin (25-200 mM) decreased the viability of human cancer cell lines originating from the lung (LNM35). Luteolin effectively increased the sub-G1 fraction of apoptotic cells through caspases 3 and 7-dependent pathways. The effect of luteolin on cell-cell adhesion, motility and invasion was investigated. We also demonstrate that luteolin is a potent HDI and that it potentiates the cytotoxicity of cisplatin in cultured LNM35 cells and decreased the growth of LNM35 tumor xenografts after intra-peritoneal injection (20 mg/kg) in athymic mice. Our results indicate that luteolin is a promising HDI for the treatment of lung cancer in combination with standard anticancer drugs such as cisplatin.
Disclosure: All authors have declared no conflicts of interest.

295P

PYOTHORAX-ASSOCIATED LYMPHOMA: AN UNUSUAL CASE WITH BOTH T- AND B-CELL GENOTYPES

D. Kim[1], E. Ko[2], Y. Lee[1], J.J. Shim[3] *[1]Internal Medicine, Soonchunhyang University Bucheon Hospital, Gyeonggi-Do/KOREA, [2]Pathology, Soonchunhyang University Bucheon Hospital, Gyeonggi-Do/KOREA, [3]Department of Internal Medicine, Korea University Guro Hospital, Seoul/KOREA*

Pleural lymphoma is a non-Hodgkin's lymphoma that occurs exclusively in patients with long standing pyothorax. Histologically, most of these tumors are classified as diffuse large B-cell lymphoma(DLBCL) with immunoblastic morphology being the most common, but unusual types of those have also been reported. Aozasa proposed the term pyothorax-associated lymphoma (PAL) for this type of lymphoma. PAL is now accepted as a distinctive entity and has a strong association with Epstein-Barr virus (EBV) infection. In the recent WHO classification, however, PAL is not listed as a variant of DLBCL, probably due to its rarity in Western countries. We report a patient with pyothorax-associated lymphoma who exhibited a unique surface phenotype. An 73-year-old man was admitted to Soonchunhyang university hospital with pain on the left side of the chest. He has a history of having undergone surgery for artificial pneumothorax for pulmonary tuberculosis 30 years ago. Computed tomographic (CT) scan revealed the mass to be confined to the left pleural cavity affected by pyothorax. Pleural surgical biopsies performed under computed tomography and was diagnosed with

diffuse large cell lymphoma. Immuohistochemically, the tumor cells were positive for CD79a, CD3 and TIA-1 but negative for CD20, CD30, CD56. In situ hybridization for EBER mRNA revealed positive signals in the nucleus of the neoplastic cells.

Disclosure: All authors have declared no conflicts of interest.

296P

DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS OF PRIMARY PULMONARY LYMPHOMA

I.N. Subortseva[1], I. Poddubnaya[2], A.M. Kovrigina[1], N.V. Kokosadze[1], D.S. Osmanov[1] *[1]Chemotherapy of Haemoblastosis, Blokhin's Cancer Research Center of RAMS, Moscow/RUSSIAN FEDERATION, [2]Oncology, Russian Academy of Postgraduate Education, Moscow/RUSSIAN FEDERATION*

Background: Among malignant lymphomas the specific interest refers to primary extranodal non-Hodgkin's lymphoma (PENHL). According to the data of existing literature, extranodal lymphomas cover 24%-48% of all non-Hodgkin's lymphomas. PENHL of pulmonary tissue is the uncommon and poorly studied pathology. According to the data of existing literature, PENHL of lungs involves 2%–3,6% of all extranodal lymphomas, 0,4% of NHL, 0,5–1% of all primary lung tumours. Lack of specific clinical and radiology signs and symptoms causes objective difficulties in diagnosis of PENHL.

Methods: In the Blokhin's Cancer Research Center of RAMS, between 1983–2007, we observed 704 patients with PENHL; lesions in lungs were found in 13 patients (1,8%): 7 female and 6 male, age 26–79 years (median - 59 years). In all cases tumors were of B-cell immunophenotype. The most common histology variant of PENHL of lungs was MALT lymphoma - 7 patients (54%), 5 patients (38,5%) - diffuse large B-cell lymphoma (DLBCL), 1 patient (7,5%) - follicular lymphoma. Diagnosis was verified by histology and immunohistochemical analysis of biopsy of tumour tissue of the lung, and thoracotomy in 7 patients (54%), thoracoscopy in 3 patients (23%), operative surgery (lobectomy, atypical resections of a part of the lung) - 3 patients (23%). In 8 patients (61,5%) the clinical signs and symptoms of the disease were absent. Within scheduled fluorography procedure of these patients, the solitary tumour was found in 5 patients (62,5%), and multiple tumour focuses in 3 patients (37,5%). All these patients had indolent lymphomas (MALT, follicular lymphoma of type I). In 5 patients (38,5%) the diagnosis of DLBCL was established during generalization of the primary lesion developed since 6 months after detection of lung pathology: 2 patients developed the lesion of lung tissue from the opposite side, in 2 patients the lung tissue and bone marrow were involved in the pathology process, 1 patient developed the lesion of lung tissue and shoulder bone which corresponded to stage IV. Difficulties to define the character of pathology process are explained by the fact that from the moment of diagnosis of the tumour in the lung up to verification of the diagnosis, the period of 3–36 months passed (median 15 months). All patients were monitored in the district anti-tuberculosis or oncology follow up. In 3 patients (23%) the pathological focuses were evaluated as small cell lung cancer, and they received symptomatic therapy. One patient received continuous anti-tuberculosis therapy which was not successful, and the patient was subsequently directed to Blokhin's Cancer Research Center of RAMS.

Conclusions: Verification of primary pulmonary lymphomas is difficult. To clarify the true character of pathology process in such patients, it is required to conduct the careful analysis of clinical and radiographical data, subsequently using X-ray, and computer tomography. Application of such methods allows us to evaluate the character of changes in the lung parenchyma more precisely. The final diagnosis in complicated cases is established as per data of morphology analysis of biopsies received after thoracoscopy.

Disclosure: All authors have declared no conflicts of interest.