Screening-Detected Lung Cancers
Is Systematic Nodal Dissection Always Essential?

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Background: To address whether systematic lymph node dissection is always necessary in early lung cancer, we identified factors predicting nodal involvement in a screening series and applied them to nonscreening-detected cancers.

Methods: In the 97 patients with clinical T1–2N0M0 lung cancer (<3 cm), enrolled in the Continuous Observation of Smoking Subjects computed tomography (CT) screening study, who underwent curative resection with radical mediastinal lymph node dissection, we examined factors associated with hilar extrapulmonary and mediastinal nodal involvement. Nodule size plus positive/negative positron emission tomography (PET)-CT (usually as maximum standard uptake value [maxSUV]) were subsequently evaluated retrospectively for their ability to predict nodal involvement in 193 consecutive patients with nonscreening-detected clinical stage I lung cancer.

Results: Among Continuous Observation of Smoking Subjects patients, 91 (94%) were pN0, and six (6.2%) were pN+. All patients with maxSUV <2.0 ($p = 0.08$) or pathological nodule ≤10 mm ($p = 0.027$) were pN0 (62 cases). Nodal metastases occurred in 6 cases among the 29 (17%) patients with lung nodule >10 mm and maxSUV ≥2.0 ($p = 0.002$ versus the other 62 cases). In the nonscreening series, 42 of 43 cases with negative PET-CT (usually maxSUV <2.0) or nodule ≤10 mm were pN0; 33 of 149 (22%) cases with positive PET-CT (usually maxSUV ≥ 2.0) and nodule >10 mm were pN+ ($p = 0.001$ versus the 43 cases).

Conclusions: This limited experience suggests that in early-stage clinically N0 lung cancers with maxSUV <2.0 or pathological nodule size ≤10 mm, systematic nodal dissection can be avoided as the risk of nodal involvement is very low.

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With advances in imaging technology and the introduction of lung cancer screening, many more early-stage lung cancers are being diagnosed than in the past.[1–3] In our Continuous Observation of Smoking Subjects (COSMOS) screening study,[2] more than 80% of the lung cancers diagnosed were stage I or II, and most were less than 1 cm in diameter. Very early-stage lung cancers may be less aggressive than those conventionally diagnosed,[4] suggesting that a less aggressive surgical approach that reduces morbidity and improves quality of life might be appropriate, provided cure rate can be maintained. A less aggressive surgical approach might also enhance the effectiveness of computed tomography (CT) screening,[5] reducing the duration and complications of surgery,[6] and overall cost of screening.

The current standard surgical treatment for localized non-small cell lung cancer (NSCLC) is lobectomy or pneumonectomy,[7–9] irrespective of the size of the tumor or its metabolic features on positron emission tomography (PET). Nevertheless, this approach may be overtreatment for very small cancers.[10,11] Similarly, systematic nodal dissection, considered essential for accurate intrathoracic staging of NSCLC,[12–16] may be unnecessary in selected clinical stage I cases, as most are N0.[17] If N0 cases could be reliably identified before nodal dissection, systematic nodal dissection could be avoided. A reliable preoperative predictor of N0 disease would also have implications for future studies analyzing the role of limited resection in very early peripheral lung cancers.

To address the issue of systematic lymph node dissection in early lung cancer, we analyzed a consecutive series of patients with clinically N0 screening-detected lung cancer (including cases other than NSCLC) who underwent preoperative staging with ^{18}F-fluorodeoxyglucose (FDG) PET/CT, with anatomical resection of the primary tumor and systematic lymph node dissection. Our immediate aim was to identify variables predicting patients with N0 disease and subsequently to refine indications for systematic nodal resection.

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Subsequently, we investigated the utility of the predictive factors identified in a retrospective series of nonscreening-detected lung cancers.

PATIENTS AND METHODS

We recruited 5201 asymptomatic volunteers to our single-center prospective COSMOS screening study in 2004 and 2005[2] and followed up them annually for 5 years. Those eligible were aged 50 years or older, heavy (≥20 pack-years) smokers or former heavy smokers who stopped not more than 10 years previously. All gave written informed consent to receive annual low-dose CT for 5 consecutive years. The CT machine was a High Speed Advantage multidetector (General Electric, Milwaukee, WI); contrast was not used for screening scans, which were taken in a single breath with the machine set at 140 kVp and 30 mA, with 2.5 mm slice thickness. Patients with suspicious lung nodules underwent FDG-PET-CT using an in-line system (Discovery LS, GE Medical Systems Waukesha, WI) consisting of an Advance NXi PET scanner and an eight-slice Light Speed Plus CT scanner. Nodules that were PET-CT positive or growing at repeat scans underwent surgical biopsy and additional interventions.

PET findings were recorded either as maximum standard uptake value (maxSUV) of FDG or positive or negative by visual assessment. CT-PET was considered positive if the maxSUV was more than 2.0 in the region of interest calculated automatically on lesions identified by CT. We used this low threshold because the consequence (treatment delay) of a false negative was more undesirable than that of a false positive (unnecessary biopsy or surgery).[2]

Patient data were recorded prospectively. In this study, we were interested in patients with clinical stage T1-2N0M0 disease (single lung nodule <3 cm maximum diameter, with no abnormal FDG uptake at hilar or mediastinal nodal stations) who underwent curative anatomical resection plus systematic node dissection between 2004 and 2009. Those with history of lung malignancy, requiring extended lung resection (such as sleeve resection, pneumonectomy, and chest wall resection) or who received PET-CT more than 2 months before surgery, were excluded.

Patients were fasted 6 hours, and after checking that blood glucose was less than 150 mg/dl, they were administered 5 MBq/kg FDG intravenously; they then waited in calm conditions (minimum movement and no speaking) for 50 to 60 minutes. Images were acquired with a combined CT-PET in-line system (Discovery LS, GE Medical Systems) consisting of an Advance NXi PET scanner and an eight-slice Light Speed Plus CT scanner. Patients were first positioned head-first supine and moved to the CT scanning position. A scout scan was acquired to define the axial imaging range, which for whole-body CT-PET typically extended from the lower jaw to the upper thighs. CT settings were 140 kV and 80 mA. Patients were instructed to breathe normally.

Results for FDG-PET (as maxSUV), nodule size on preoperative CT, position of the lesion (central or peripheral), and nodule size at intropeative pathological evaluation (using the fixed cutoff values ≤10 mm, more than 10 ≤20 mm, and more than 20 mm) were investigated together with patient and tumor characteristics (age, sex, type of surgery, side, site, and histology) to assess their role in predicting lymph node status. Similar findings were then examined in an independent series of consecutive patients with nonscreening-detected cancers and comparable clinical characteristics who underwent surgical resection at our institute during the same period. In this group, PET findings were recorded either as maxSUV (157 cases) or positive or negative by visual assessment (36 cases); negative cases were assumed to have maxSUV less than 2. All cases underwent systematic lymph node dissection, defined as removal of hilar extrapulmonary nodes and mediastinal nodes from stations 2, 4, 7, 8, 9, and 10 on the right side, and stations 5 to 10 on the left, in accordance with international guidelines.[13,15] Confirmation of systematic lymph node dissection was obtained by review of the number of explored stations and number of lymph nodes removed from the surgical and pathological reports. The nodule was considered as peripheral if the center of the tumor was located in the outer third of the lung in the transverse, coronal, or sagittal plan.

Statistical Analysis

We used the Mantel-Haenszel χ^2 test for trend and Fisher's exact test to assess associations between lymph node status (ordinal variables pN0, pN1, and pN2) and clinical and pathological characteristics. We then combined the discriminatory variables for lymph node status at univariate analysis in the screening group (tumor size and positive/negative PET) to assess their joint predictive value. Survival was represented by Kaplan-Meier curves and the log-rank test used to assess the significance of differences in survival experience. All tests were two sided. The analyses were performed with SAS, version 8.2 (Cary, NC).

RESULTS

During the study period, a lung cancer was detected by screening in 162 COSMOS patients; of these, 97 satisfied the inclusion criteria of the present analysis. We also analyzed 193 consecutive patients with clinical stage I lung cancer not detected by screening and treated in our Division during the same period. Table 1 lists the clinical and pathological characteristics of both groups.

In the screening group, 91 (94%) patients were N0 at pathological examination, and six (6.2%) were N+. Three variables were associated with nodal status in the screening group: pathological nodule size, maxSUV, and nodule location (central versus peripheral). It is noteworthy that all patients with maxSUV less than 2.0 ($p = 0.08$ versus maxSUV ≥2.0) or lung nodule ≤10 mm ($p = 0.027$ versus nodule >10 mm) or both—a total of 62 cases (Table 2)—were N0 at pathological examination, whereas one patient with peripheral nodule more than 10 mm and maxSUV less than 2 had pN2 disease (Table 2). All other nodal metastases occurred among the 29 patients with both nodule more than 10 mm and maxSUV ≥2.0. The rate of nodal involvement in the latter group was 17.1% (six patients) ($p = 0.002$ versus those with maxSUV less than 2.0 or nodule ≤10 mm). Radiological module size on preoperative CT was a less reliable indicator than pathological size: two cases in the

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TABLE 1. Clinical and Pathological Characteristics of 97 Patients with Screening-Detected Stage I Lung Cancer and 193 Patients with Nonscreening-Detected Stage I Lung Cancer Who Underwent Anatomical Resection and Systematic Nodal Dissection

	Screening (N = 97)				Nonscreening (N = 193)			
	pN0	pN1	pN2	p^a	pN0	pN1	pN2	p^a
All	91	4	2		159	16	18	
Sex								
Men	64	2	2		102	11	6	
Women	27	2	0	0.80	57	5	12	0.03
Age (yr)								
<60	37	1	1		43	5	8	
60–69	47	2	0		74	7	6	
70+	7	1	1	0.55	42	4	4	0.16
MaxSUV								
<2	39	0	0		34	0	1	
≥2	52	4	2	0.05	125	16	17	0.03
Clinical T								
cT1	89	4	2		136	15	13	
cT2	2	0	0	0.73	23	1	5	0.30
Tumor size (mm)								
≤10	47	2	0		15	0	0	
11–20	34	2	1		89	9	11	
>20	10	0	1	0.18	41	7	7	0.10
Missing	0	0	0		14	0	0	
Type of surgery								
Lobectomy	86	4	2		153	11	14	
Bilobectomy	0	0	0		2	2	2	
Segmentectomy	5	0	0		3	1	0	
Pneumonectomy	0	0	0	ND	1	2	2	0.0002
Side								
Right	56	2	2		95	9	11	
Left	35	2	0	0.52	64	7	7	1.00
Site								
Upper	50	4	0		109	8	10	
Middle	6	0	0		12	0	1	
Lower	35	0	2		35	4	4	
Upper + middle	0	0	0		2	0	0	
Lower + middle	0	0	0	ND	0	2	1	0.04
Missing	0	0	0		1	2	2	
Location								
Central	30	4	1		57	9	8	
Peripheral	61	0	1	0.02	94	6	9	0.19
Pathological size (mm)								
≤10	48	0	0		23	0	0	
11–20	31	4	1		95	8	10	
>20	12	0	1	0.05	41	8	8	0.006
Pathological T								
pT1	80	3	1		122	11	12	
pT2	9	1	1		35	4	6	
pT4	2	0	0	0.36	2	1	0	0.34
Histology								
Squamous	10	0	2		25	3	1	
Adenocarcinoma	71	4	0		96	12	17	
SCLC	2	0	0		5	0	0	
Carcinoid	3	0	0		24	0	0	
Other	5	0	0	0.17	9	1	0	0.21

SUV <2 and pathological size <1 cm are predictive of pathological N0 disease.

[a] p values for sex, age, maxSUV, clinical T, tumor size, side, pathological size, and pathological T from Mantel Haenszel test for trendm, and p values for type of surgery, tumor site, and histology from Fisher's exact test.

ND, not done; SCLC, small cell lung cancer; SUV, standard uptake value.

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TABLE 2. Relationship of Pathological Node Status to Metabolic Activity (maxSUV) and Tumor Size in Screening-Detected and Symptoms-Detected Tumors

	Screening (n = 97)		Nonscreening (n = 193)[a]	
Node Characteristics	**pN0**	**pN+**	**pN0**	**pN+**
All	91	6 (6.2%)	159	34 (17.6%)
≤10 mm and SUV <2 (or visually negative)	25	0	14	0
≤10 mm and SUV ≥2 (or visually positive)	23	0	9	0
>10 mm and SUV <2 (or visually negative)	14	0	20	1 (4.8%)
>10 mm and SUV ≥2 (or visually positive)	29	6 (17.1%)	116	33 (22.2%)
p (Fisher's exact test)	0.014		0.024	

In both groups, patients with both SUV <2 and pathological nodule size ≤10 mm are at very low risk of nodal involvement.
[a] In the nonscreening group, seven cases were visually negative on PET, and 29 cases were visually positive.
SUV, standard uptake value.

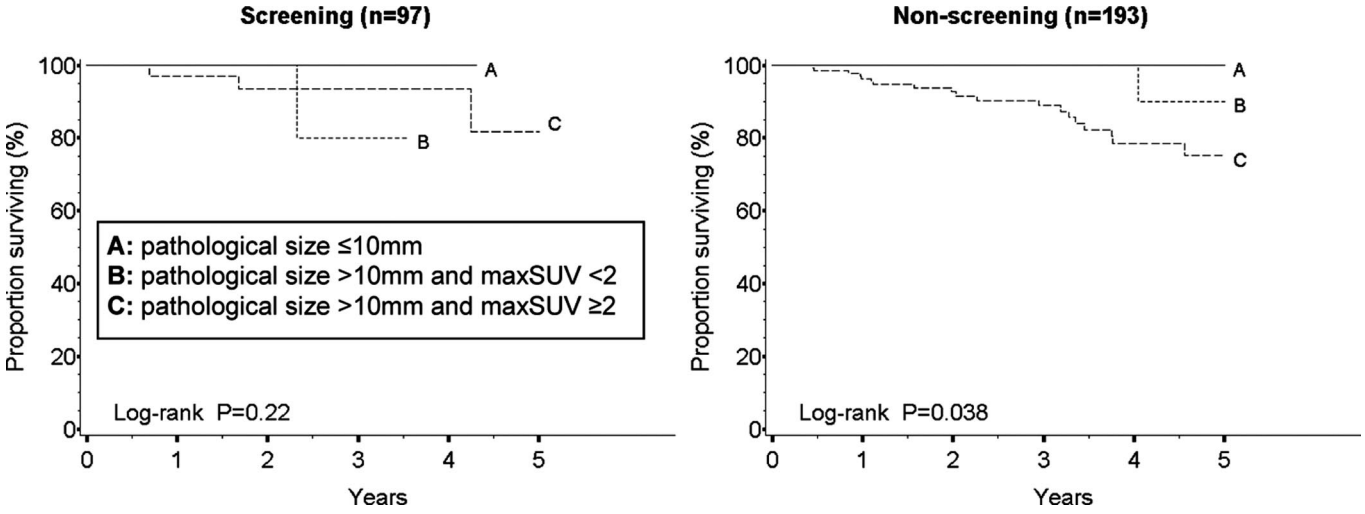

FIGURE 1. Overall survival according to metabolic activity (total standard uptake value [SUV]) and tumor size in screening-detected and symptoms-detected tumors.

screening-detected group with maximum tumor diameter ≤10 mm on preoperative CT had N1 disease at definitive pathological examination; however, in both cases, pathological size was more than 10 mm, the tumors were located centrally, and only one peribronchial lymph node was involved. Thus, these cases would not have influenced the decision on whether to perform systematic lymph node resection.

In the nonscreening group, nodule location was not significantly associated with nodal status (Table 1). Fourteen patients had negative CT-PET (by visual assessment or maxSUV <2) and nodule ≤10 mm; nine had positive CT-PET (by visual assessment or maxSUV ≥2) and nodule ≤10 mm; and 21 had negative CT-PET and nodule more than 10 mm; of these 43 cases, 42 (97.6%) were pN0 at pathological examination. Among the remaining 149 cases with positive CT-PET and nodule more than 10 mm, 33 (22%) had pathological nodal involvement (p = 0.001 versus the group of 43 patients).

Figure 1 suggests that the overall survival of patients with subcentimeter or low FDG uptake nodules (curves A and B) was better than that of patients with larger nodules and high FDG uptake, both in screening and nonscreening-detected tumors (curve C). The three curves did not differ significantly for screening-detected cancers (p = 0.22) but did differ for nonscreening-detected cancers (p = 0.038). The median follow-up of all 290 patients was 2.4 years, range 0.1 to 6.8 years.

DISCUSSION

The prognosis of lung cancer is determined mainly by the presence and extent of mediastinal lymph node involvement,[18] so mediastinal staging is usually considered essential to determine treatment. Contrast-enhanced CT is useful for noninvasive NSCLC staging but is insufficiently reliable either for detecting or for excluding lymph node metastases.[14] Histopathologic studies show that 21% of metastases occur in normal sized lymph nodes,[15] whereas no malignancy is found in 40% of enlarged lymph nodes.[16]

PET with FDG provides metabolic characterization of tissues and is the most accurate noninvasive modality available for staging mediastinal lymph nodes in lung cancer,[19] being able to detect increased metabolism even in normal-

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sized lymph nodes[20]; nevertheless, the prevalence of occult N2 disease even after negative FDG-PET at lymph node stations is approximately 8 to 10%.[20–22]

With the spread of screening[1–3] and consequent increase in the proportion of lung cancers diagnosed at a very early stage, the need to find a reliable method of identifying mediastinal node involvement before node dissection (and preferably preoperatively) has become more pressing, so as to avoid lymph node dissection in cases with true N0 disease.

In this study, we identified two simple variables—the metabolic activity of the lung nodule on FDG-PET-CT and its maximum pathological diameter—significantly related to nodal involvement in a screened population. We found that these variables were subsequently able to predict nodal involvement with high reliability in a nonscreening series with clinical stage I lung cancers. When all 290 patients were considered, the rate of occult nodal involvement when one other variable was below cutoff was less than 1% (1/106), versus 21.2% (39/184) for patients with both variables above the cutoff. Although positive nodal status was significantly associated with central nodule location in the screening group, this was not the case for nonscreening patients. In this latter group, we suggest that the larger overall nodule size may have abolished the relationship of central location with node positivity.

Unfortunately, preoperative lesion size on CT was less accurate than pathological size in predicting nodal status. Two screening-detected cancers with CT diameter ≤10 mm had N1 disease, although the pathological size of these lesions turned out to be more than 10 mm. We would, therefore, recommend intraoperative measurement of lesion size immediately after resection, which can be done by the surgeon in the operating room and takes about 5 minutes, and using this variable (together with preoperative maxSUV) to decide whether systematic lymph node dissection should be performed. Intraoperative measurement by the surgeon should be close to pathological size; however, a study to confirm this supposition is necessary, as tumor size is prone to change after fixation.

We found, unexpectedly, that extent of surgery was significantly related to nodal status in our nonscreened group (Table 1) with high proportions of nodal involvement among cases treated by pneumonectomy and bilobectomy. This is probably a selection bias related to the retrospective nature of the study: a less than 3-cm lesion treated by pneumonectomy is likely to be centrally located with inherently greater risk of nodal involvement, whereas bilobectomy is associated with intraoperative discovery of interlobe adenopathy.

The two variables we have identified as predictors of nodal status correlate with each other[24,25]; however, we found that combining them increased the predictive value of the test. We are also aware that, although the maxSUV cutoff of 2 was predictive in our series, SUV determination varies between scanners and institutes, in relationship to differing ways of estimating this variable and correcting it for confounding factors.[25]

A previous study[26] found that several clinical and pathological factors, including pathological tumor size and maxSUV, were unrelated to the presence of occult N2. Nevertheless, the authors adopted cutoffs of 3 cm for nodule size and 14 for maxSUV. By contrast, on the basis of our empirical findings, we adopted cutoffs of 10 mm for nodule diameter and 2 for maxSUV, and these enabled us to reliably distinguish patients with nodal involvement from those without such involvement.

In the study of Ishida et al.,[27] 17% of 1.1 to 2 cm tumors were associated with occult lymph node involvement, whereas none of the tumors less than 1 cm had lymph node involvement. Konaka et al.[28] also reported absence of lymph node metastases in subcentimeter lung cancers. The authors of both studies[27,28] concluded that lymph node dissection could be omitted for subcentimeter cancers. By contrast, Zhoua et al.[29] found nodal metastases in 6 of 41 (15%) patients with subcentimeter NSCLC and recommended systematic nodal dissection in the presence of subcentimeter disease, although they considered that it might be possible to omit dissection in female patients, those with normal carcinoembryonic antigen, or those with ground-glass opacity tumors or Noguchi type A or B tumors. Nevertheless, in this study,[29] preoperative PET staging was not performed, and five cases of clinical stage II or III, disease, in which systematic nodal dissection is usually indicated, were included.

In addition to providing information on lymph node status, tumor FDG uptake has also been shown to have a prognostic role in lung cancer.[4,30] In a study on screening-detected cancers,[4] maxSUV below 2.5 correlated with 100% cancer-specific survival. This is in line with our finding of 100% survival in patients with pathological size ≤10 mm (Figure 1) most of whom had maxSUV less than 2.

To conclude, our analyses of two limited series of patients indicate that in the presence of clinical stage 1 disease, systematic lymph node dissection can be omitted if preoperative FDG-PET-CT shows maxSUV less than 2 (or negative visual assessment) and if maximal diameter at intraoperative examination is ≤10 mm. These results require confirmation by further studies with long-term follow-up; however, they suggest that these two simple variables might be reliable predictors of lymph node involvement in early-stage lung cancer, making it possible to avoid nodal dissection in a considerable number of patients, reducing operating time and invasiveness, and also reducing the morbidity associated with nodal dissection such as recurrent nerve injury and chylothorax.[6] By contrast, when both variables are above the cutoffs identified in this study, radical lymph node dissection is advisable, even in clinically node-negative patients, as the risk of occult nodal involvement is fairly high.

REFERENCES

1. Henschke CI, Yankelevitz DF, Libby DM, et al. International Early Lung Cancer Action Program Investigators. Survival of patients with stage 1 lung cancer detected on CT screening. *N Engl J Med* 2006;355: 1763–1771.
2. Veronesi G, Bellomi M, Mulshine, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. *Lung Cancer* 2008;61:340–349.
3. New York Early Lung Cancer Action Project Investigators. CT screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project. *Radiology* 2007;243:239–249.

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4. Pastorino U, Landoni C, Marchianò A, et al. Fluorodeoxyglucose uptake measured by positron emission tomography and standardized uptake value predicts long-term survival of CT screening detected lung cancer in heavy smokers. *J Thorac Oncol* 2009;4:1352–1356.
5. Mulshine JL, Sullivan DC. Clinical practice. Lung cancer screening. *New Engl J Med* 2005;352:2714–2720.
6. Allen MS, Darling GE, Taine TV, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;81:1013–1020.
7. Rubinstein LV, Ginsberg RJ. Lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1996;62:1249–1250.
8. Landreneau RJ, Sugarbaker DJ, Mack MJ, et al. Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 1997;113:691–700.
9. Miller DL, Rowland CM, Deschamps C, et al. Surgical treatment of non–small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg* 2002;73:1545–1551.
10. Available at: http://clinicaltrials.gov/ct2/show/NCT00499330. Accessed December 3, 2010.
11. Nonaka M, Kadokura M, Yamamoto S, et al. Tumor dimension and prognosis in surgically treated lung cancer for intentional limited resection tumor dimension and prognosis in surgically treated lung cancer for intentional limited resection. *Am J Clin Oncol* 2003;26:499–503.
12. Veeramachaneni NK, Battafarano RJ, Meyers BR, et al. Risk factors for occult nodal metastasis in clinical T1N0 lung cancer: a negative impact on survival. *Eur J Cardiothorac Surg* 2008;33:466–469.
13. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2006;30:787–792.
14. American Thoracic Society. Clinical staging of primary lung cancer. *Am Rev Respir Dis* 1983;127:659–664.
15. Kramer H, Groen HJM. Current concepts in the mediastinal lymph node staging of non small cell lung cancer. *Ann Surg* 2003;238:180–188.
16. Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Ann Surg* 1998;227:138–144.
17. Sugi K, Nawata K, Fujita N, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. *World J Surg* 1998;22:290–294.
18. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest* 2009;136:260–271.
19. Cerfolio RJ, Ojha B, Bryant AS, et al. The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with non-small cell lung cancer. *Ann Thorac Surg* 2004;78:1017–1023.
20. Park HK, Jeon K, Koh WJ, et al. Occult nodal metastasis in patients with non-small cell lung cancer at clinical stage IA by PET/CT. *Respirology* 2010;15:1179–1184.
21. Takizawa H, Kondo K, Matsuoka H, et al. Effect of mediastinal lymph nodes sampling in patients with clinical stage I non-small cell lung cancer. *J Med Invest* 2008;55:37–43.
22. Lee PC, Port JL, Korst RJ, et al. Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007;84:177–181.
23. Hsu PK, Huang HC, Hsieh CC, et al. Effect of formalin fixation on tumor size determination in stage I non-small cell lung cancer. *Ann Thorac Surg* 2007;84:1825–1829.
24. Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18]fluorodeoxyglucose uptake by positron emission tomography. *Clin Cancer Res* 2000;6:3837–3844.
25. Vesselle H, Freeman JD, Wiens L, et al. Fluorodeoxyglucose uptake of primary non-small cell lung cancer at positron emission tomography: new contrary data on prognostic role. *Clin Cancer Res* 2007;13:3255–3263.
26. Al-Sarraf N, Aziz R, Gately K, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. *Eur J Cardiothorac Surg* 2008;33:104–109.
27. Ishida T, Yano T, Maeda K, et al. Strategy for lymphadenectomy in lung cancer three centimeters or less in diameter. *Ann Thorac Surg* 1990;50:708–713.
28. Konaka C, Ikeda N, Hiyoshi T, et al. Peripheral non-small cell lung cancers 2.0 cm or less in 290 diameter: proposed criteria for limited pulmonary resection based upon clinicopathological presentation. *Lung Cancer* 1998;21:185–191.
29. Zhoua Q, Suzuki K, Anami Y, et al. Clinicopathologic features in resected subcentimeter lung cancer—status of lymph node metastases. *Interact Cardiovasc Thorac Surg* 2010;10:53–57.
30. Nair VS, Barnett PG, Ananth L, et al. Positron emission tomography (PET) 18F-fluorodeoxyglucose (FDG) uptake and prognosis in patients with resected, clinical stage Ia non-small cell lung cancer. *Chest* 2010;137:1150–1156.

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