Fluorine 18–tagged fluorodeoxyglucose positron emission tomographic scanning to predict lymph node metastasis, invasiveness, or both, in clinical T1 N0 M0 lung adenocarcinoma

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See related editorial on page 341.

Objective: We sought to predict lymph node metastasis and tumor invasiveness in clinical T1 N0 M0 lung adenocarcinomas, and we measured fluorodeoxyglucose uptake on positron emission tomography.

Methods: Fluorodeoxyglucose positron emission tomography was performed on 44 patients with adenocarcinomas of 1 to 3 cm in size clinically staged as T1 N0 M0 before major lung resection with lymph node dissection. Fluorodeoxyglucose uptake was evaluated by using the contrast ratio between the tumor and contralateral healthy lung tissue. Lymphatic and vascular invasion within tumors, pleural involvement, and grade of histologic differentiation were examined.

Results: The pathologic tumor stage was T1 N0 M0 in 36 patients, and a more advanced stage was found in 8 patients. Although all 22 adenocarcinomas with a contrast ratio of less than 0.5 in fluorodeoxyglucose uptake were pathologic T1 N0 M0 tumors, 8 (36%) of 22 with a contrast ratio of 0.5 or greater were of a more advanced stage than T1 N0 M0, with the difference being significant ($P = .002$). Adenocarcinomas with a contrast ratio of less than 0.5 showed less lymphatic and vascular invasion and less pleural involvement than those with a contrast ratio of 0.5 or greater ($P = .006$, $P = .004$, and $P = .02$, respectively). The grade of histologic differentiation was well differentiated in 19 of 22 adenocarcinomas with a contrast ratio of less than 0.5 (86%), which was a greater frequency than the 4 (18%) of 22 adenocarcinomas with a contrast ratio of 0.5 or greater ($P < .001$).

Conclusion: Clinical T1 N0 M0 lung adenocarcinomas with a contrast ratio of less than 0.5 usually did not have lymph node metastasis, had less tumor involvement of vessels or pleura, and were more frequently well differentiated than those with a contrast ratio of 0.5 or greater. Limited lung resection could be indicated, lymph node dissection or mediastinoscopy could be reduced, or both in this type of adenocarcinoma.

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Recent advances in low-dose helical computed tomography (CT) and video-assisted thoracoscopic surgery have enabled the diagnosis of lung cancers while still small in size.[1-6] Although limited resection procedures, such as lung wedge resection or segmentectomy, can cure some clinical T1 N0 M0 non–small cell lung cancers (NSCLCs),[7,8] lymph node metastases are still found in approximately 20% of clinical T1 N0 M0 lung adenocarcinomas.[9-11] Even for patients with pathologic T1 N0 M0 NSCLCs, tumor involvement of intratumoral vessels or the pleura can also cause local recurrence after limited resection because of the spread of tumor cells into lymphatic vessels outside the primary tumor. To predict which T1 N0 M0 lung adenocarcinomas are curable with limited resection from CT findings, several reports have evaluated the importance of ground-glass opacity (GGO) within tumors, usually indicating bronchioloalveolar carcinoma–like spread because adenocarcinomas with GGO appearance are more frequently N0 stage and have less tumor involvement of intratumoral vessels or pleura than those with a solid appearance.[12,13] The criteria of defining GGO appearance on CT scans are subjective, however, potentially leading to erroneous selection of limited surgical intervention.

In recent years, fluorodeoxyglucose (FDG) positron emission tomography (PET) has been used to evaluate pulmonary nodules and tumor stages. It has been reported that FDG uptake correlates with the proliferative activity of tumors[14,15] and is an independent prognostic factor,[16,17] particularly in lung adenocarcinoma. The prognosis in lung adenocarcinoma is known to depend on not only tumor stage but also tumor involvement of intratumoral vessels or pleura.[9,10,18] To predict lymph node metastases and tumor involvement of intratumoral vessels or pleura in clinical T1 N0 M0 lung adenocarcinomas, we measured FDG uptake to determine any correlation with lymph node metastases, lymphatic and vascular invasion, and pleural involvement.

Materials and Methods

Patients

From December 2001 through October 2003, prospective FDG-PET and CT scans were performed for 223 noncalcified pulmonary nodules. Of these, 93 nodules were malignant tumors less than 3 cm in diameter on CT. Clinical TNM stage was determined by using both CT and PET scanning. Of the 93 malignant nodules, 48 were clinical T1 N0 M0 adenocarcinomas of the lung, and these underwent major lung resection with mediastinal lymph node dissection. We excluded 4 adenocarcinomas less than 1 cm in diameter that were PET negative because the spatial resolution of the current generation of PET scanners is 0.7 to 0.8 cm, making it difficult to image pulmonary nodules of less than 1 cm. As a result, we studied 44 adenocarcinomas that were clinically staged as T1 N0 M0 of sizes from 1 to 3 cm. The medical record of each patient was examined with regard to age, sex, maximum tumor diameter, serum level of carcinoembryonic antigen (CEA; <5 ng/mL vs ≥ 5 ng/mL), operative procedure, pathologic TNM stage, vascular or lymphatic invasion within tumors (positive vs negative), pleural involvement (p0 vs p1 to p3), and grade of histologic differentiation. To identify tumor involvement of the intratumoral vessels or pleura, we routinely conducted elastica-van Gieson staining. Pleural involvement was classified as p0, p1, p2, or p3; that is, a p0 tumor did not extend beyond the elastic pleural layer, a p1 tumor invaded the visceral pleural elastic layer but did not reach the pleural surface, a p2 tumor included tumor exposure on the pleural surface, and a p3 tumor invaded the parietal pleura or chest wall. The tumor stages were based on the TNM classification of the International Union Against Cancer[19]: p2 tumors were classified as T2; p3 tumors were classified as T3; and tumors with intrapulmonary metastasis within the same lobe were classified as T4. Grades of histologic differentiation were classified as well, moderately, or poorly differentiated.

FDG-PET Scanning

Patients were instructed to fast for at least 4 hours before intravenous administration of fluorine 18–tagged FDG. The dosage of fluorine 18–tagged FDG administered was 125 μCi/kg (4.6 MBq/kg) of body weight for nondiabetic patients and 150 μCi/kg (5.6 MBq/kg) of body weight for diabetic patients. PET imaging was performed approximately 60 minutes after administration of FDG with a POSICAM.HZL mPOWER (Positron Co, Houston, Tex). No-attenuation-corrected emission scans were initially obtained in 2-dimensional, high-sensitivity mode for 4 minutes per bed position and taken from the vertical skull through to the midthighs. Immediately thereafter, a 2-bed-position attenuation-corrected examination was performed, with 6 minutes for the emission sequence and 6 minutes for the transmission sequence at each bed position. The images were usually reconstructed in a 256×256 matrix by using ordered subset expectation maximization corresponding to a pixel size of 4×4 mm, with section spacing of 2.66 mm.

PET Data Analysis

The FDG-PET data were evaluated semiquantitatively on the basis of the contrast ratio (CR) obtained as follows. The regions of interest (ROIs) were placed in the nodules and contralateral lung. Highest activities in the tumor ROI (T) and in the contralateral normal lung ROI (N) were measured. The CR was calculated by using the formula $(T - N)/(T + N)$ in each nodule as an index of FDG uptake. After correction for radioactive decay, the ROIs were also analyzed by computing the standard uptake value (SUV), which was calculated on the basis of the following equation: Tumor activity concentration/Injected dose/Body weight. The maximum SUV within the selected ROIs was also measured and compared with the results of CR.

Statistical Analysis

All data were analyzed for significance by using the 2-tailed Student *t* test. All values in the text and tables are given as means $\pm$ SD.

TABLE 1. Tumor involvements and pathologic TNM stage for each CR value

CR of FDG uptake	Total lesions	>T1 N0 M0*	Lymphatic invasion	Vascular invasion	Pleural involvement
0.3	16	0	5	1	1
0.4	19	0	5	1	1
0.5†	22	0	5	1	1
0.6	29	2	9	2	2
0.7	37	4	14	7	6
0.8	39	4	15	8	6
0.9	43	8	19	10	8
1.0	44	8	19	10	8

*Pathologically more advanced stages than T1 N0 M0. Three of the 8 cases were p2; the other 5 were p1.
†Cutoff value of CR.

TABLE 2. PET findings and patients' characteristics, tumor size, and serum level of CEA

	CR of FDG uptake		*P*
	<0.5 (n = 22)	≥0.5 (n = 22)	value
Age (y, mean ± SD)	63 ± 11	64 ± 13	NS
Male (No.)	14	10	NS
Female (No.)	8	12	
Tumor size (cm, mean ± SD)	1.9 ± 0.6	2.2 ± 0.4	NS
CEA (ng/mL)			.001
<5.0	22	10	
≥5.0	0	12	

NS, Not statistically significant.

TABLE 3. Correlation between PET findings and pathologic tumor stage

		CR of FDG uptake	
Pathologic TNM	Total (n = 44)	<0.5 (n = 22)	≥0.5 (n = 22)
T1 N0 M0	36	22*	14*
T1 N1 M0	3	0	3
T2 N0 M0	3	0	3
T4 N0 M0	2	0	2

T2 is classified from pleural involvement grade, p2. T4 is classified from intrapulmonary metastasis.
*Significant difference in the frequency of T1 N0 M0 between the CR <0.5 and CR ≥0.5 groups ($P = .002$).

Results

The pathologic tumor stage was T1 N0 M0 in 36 patients and more advanced in 8 patients (ie, T1 N1 M0 in 3 patients, T2 N0 M0 in 3 patients, and T4 N0 M0 in 2 patients). Lymphatic or vascular invasion within tumors and pleural involvement was seen in 19, 10, and 8 patients, respectively. Table 1 shows the various CR values with relation to the pathologic tumor stage, lymphatic and vascular invasion, and pleural involvement. Although all adenocarcinomas with a CR of less than 0.5 were pathologically staged as T1 N0 M0, some adenocarcinomas with a CR of 0.5 or greater were more advanced than T1 N0 M0, with more frequent lymphatic and vascular invasion and pleural involvement than the former. Therefore medical records were compared between the 22 adenocarcinomas with a CR of less than 0.5 and the 22 adenocarcinomas with a CR of 0.5 or greater.

The maximum SUVs ranged from 0.5 to 3.1 (mean, 1.1 ± 0.7) in the 22 adenocarcinomas with a CR of less than 0.5 and from 1.9 to 8.5 (mean, 3.9 ± 1.8) in the 22 adenocarcinomas with CRs of 0.5 or greater, with the difference between the 2 groups being significant ($P < .001$). Two (9%) of the 22 adenocarcinomas with CRs of less than 0.5 showed an SUV of 2.5 or greater, however, both of which were pathologically staged as T1 N0 M0 and had no involvements of intratumoral vessels or pleura. Seven (32%) of the 22 adenocarcinomas with CRs of 0.5 or greater had SUVs of less than 2.5, of which 2 had a more advanced tumor stage than T1 N0 M0, 6 had lymphatic invasion, and 1 had vascular invasion.

Table 2 shows the results of PET findings with patients' characteristics, tumor size, and serum level of CEA. None of the adenocarcinomas with CRs of less than 0.5 had increased serum levels of CEA, which was significantly less frequent than the incidence of increased CEA in the 12 (55%) of 22 adenocarcinomas with CRs of 0.5 or greater ($P < .001$). There was no significant difference between the 2 groups in mean age, sex ratio, or tumor size.

Table 3 shows the correlation between PET findings and pathologic tumor stage. All adenocarcinomas (100%) with CRs of less than 0.5 were staged as T1 N0 M0. Adenocarcinomas with CRs of 0.5 or greater were staged as T1 N0 M0 in 14 (64%) patients, T1 N1 M0 in 3 patients, T2 N0 M0 caused by p2 (tumor exposure on the pleural surface) in 3 patients, and T4 N0 M0 caused by intrapulmonary metastases in 2 patients. Adenocarcinomas with CRs of less than 0.5 were more likely to be pathologic T1 N0 M0 stage than those with CRs of 0.5 or greater ($P = .002$).

Table 4 shows the correlation between PET findings and lymphatic and vascular invasion within tumors and pleural involvement. Lymphatic invasion was seen in 5 (23%) of 22 adenocarcinomas with CRs of less than 0.5, which was significantly less frequent than 14 (64%) of 22 with CRs of 0.5 or greater ($P = .006$). Vascular invasion was seen in 1 (5%) of 22 adenocarcinomas with CRs of less than 0.5, which was significantly less frequent than 9 (41%) of 22 with CRs of 0.5 or greater ($P = .004$). Pleural involvement was seen in 1 (5%) of 22 adenocarcinomas with CRs of less than 0.5, which was significantly less frequent than 7 (32%) of 22 with CRs of 0.5 or greater ($P = .02$).

Table 5 shows the correlation between PET findings and the histologic degree of differentiation. In the adenocarcinomas with CRs of less than 0.5, well-differentiated and

TABLE 4. Correlation between PET findings and tumor involvement into intratumoral vessels or pleura

Tumor involvement	CR of FDG uptake <0.5 (n = 22)	CR of FDG uptake ≥0.5 (n = 22)	*P* value
Lymphatic invasion			.006
Yes	5	14	
No	17	8	
Vascular invasion			.004
Yes	1	9	
No	21	13	
Pleural involvement			.02
p0	21	15	
p1-p2	1	7	

TABLE 5. Correlation between PET findings and grade of histologic differentiation of adenocarcinomas

Grade of differentiation	Total (n = 44)	CR of FDG uptake <0.5 (n = 22)	CR of FDG uptake ≥0.5 (n = 22)
Well differentiated	23	19*	4*
Moderately differentiated	17	3	14
Poorly differentiated	4	0	4

There was significant difference in frequency of well-differentiated adenocarcinomas between the CR <0.5 and CR ≥0.5 groups ($P < .001$).

TABLE 6. Correlation between PET findings and tumor stages, tumor involvement of intratumoral vessels, and tumor involvement of pleura in well-differentiated adenocarcinomas

Tumor stage and invasiveness	CR of FDG uptake >0.5 (n = 19)	CR of FDG uptake ≥0.5 (n = 4)	*P* value
TNM stage			<.01
T1 N0 M0	19	2	
>T1 N0 M0	0	2	
Lymphatic invasion			<.001
Yes	3	4	
No	16	0	
Vascular invasion			.02
Yes	1	2	
No	18	2	
Pleural involvement			<.01
p0	19	2	
p1-p2	0	2	

moderately differentiated adenocarcinomas were seen in 19 and 3 patients, respectively. In the adenocarcinomas with CRs of 0.5 or greater, well-differentiated, moderately differentiated, and poorly differentiated adenocarcinomas were seen in 4, 14, and 4 patients, respectively. Adenocarcinomas with CRs of less than 0.5 were more commonly well differentiated than those with CRs of 0.5 or greater ($P < .001$).

Table 6 shows the PET findings in well-differentiated adenocarcinomas with relation to the tumor stages and tumor involvements. Of the 4 well-differentiated adenocarcinomas with CRs of 0.5 or greater, each one (25%) was a pathologic T1 N1 M0 and T4 N0 M0 carcinoma, respectively; 4 (100%) had lymphatic invasion; 2 (50%) had vascular invasion; and 2 (50%) had pleural involvement. The well-differentiated adenocarcinomas with CRs of 0.5 or greater had advanced tumor stages, lymphatic and vascular invasion, and pleural involvement more frequently than those with CRs of less than 0.5 ($P < .01$, $P < .001$, $P = .02$, and $P < .01$, respectively).

Discussion

Although a criterion for diagnosing pulmonary malignancy with FDG-PET has frequently used an SUV with a cutoff value of 2.5,[20] some authors used visual evaluation, such as comparison of FDG uptake between nodules and mediastinal uptake.[21] The present study evaluated FDG uptake with CR instead of SUV for the following reasons: (1)hyperglycemia in diabetic patients decreases both the blood clearance of FDG and the accumulation of FDG in tumor tissue, and (2) SUV could be different between fat and thin patients because it is measured by using a body weight. Actually, the mean SUV of malignant pulmonary nodules has been reported to be various, ranging from 5.5 to 10.1.[22-25] In breast cancer, Wahl and coworkers[26] have demonstrated that a CR between tumor and contralateral normal breast is a reliable indicator for diagnosing malignancy. We accordingly used CR in the present study and determined that the cutoff value to differentiate between aggressive and nonaggressive adenocarcinomas was 0.5, with which we could differentiate the degree of tumor aggressiveness more accurately than with SUV.

The important points of the present study are as follows. Compared with adenocarcinomas with CRs of 0.5 or greater, those with CRs of less than 0.5 (1) did not show an increased serum level of CEA, (2) did not have lymph node metastases, (3) had less tumor involvement of vessels or pleura, and (4) were more frequently well-differentiated adenocarcinomas. The serum level of CEA in lung adenocarcinomas has been reported to be higher in N1 or N2 disease than in N0 disease.[27] FDG uptake in lung adenocarcinomas is known to often be negative in well-differentiated adenocarcinomas.[28] It has been also reported that well-differentiated adenocarcinomas are more commonly N0 stage and have less tumor involvement of vessels or pleura than moderately or poorly differentiated lesions.[9,12,13,18] Our results agree with those of these earlier studies. There were, however, 4 well-differentiated adenocarcinomas with CRs of 0.5 or greater that had more tumor aggressiveness than the 19 well-differentiated lesions with CRs of less than 0.5. We therefore consider that an FDG

uptake on PET can predict lymph node metastases and tumor invasiveness more accurately than the grade of histologic differentiation in clinical T1 N0 M0 adenocarcinomas.

Although limited resection could be a reasonable approach for T1 N0 M0 lung cancers, it has been reported that lymph node metastases are found in about 20% of clinical T1 N0 M0 adenocarcinomas.[9-11] In 1995, the Lung Cancer Study Group reported the results of a randomized control trial comparing limited resection and lobectomy for clinical T1 N0 M0 NSCLCs.[29] This trial demonstrated the inferiority of limited resection in terms of local relapse and prognosis because some patients actually had pathologic N1 or N2 disease. This is also because tumor involvement of intratumoral vessels or the pleura can cause local recurrence after limited resection, even for pathologic N0 disease, because of the spread of tumor cells into lymphatic vessels outside the primary tumor.[30] The present study showed that clinical T1 N0 M0 adenocarcinomas with CRs of less than 0.5 usually did not metastasize to the lymph nodes and seldom invaded the intratumoral vessels or pleura. This type of lung adenocarcinoma can be cured by means of limited surgical resection, such as segmentectomy or wedge resection. Although it has been reported that NSCLCs of less than 2 cm in size can be cured by means of segmentectomy with mediastinal lymph node dissection (ie, extended segmentectomy),[7] the indication of the extended segmentectomy could be expanded for adenocarcinomas with CRs of less than 0.5 that are less than 3 cm in size.

Mediastinal lymph node dissection is a useful procedure to secure complete local control of an NSCLC, with a subsequent improvement in both survival and nodal staging.[11] However, to minimize the damage caused by mediastinal node dissection in the patients with clinical stage I NSCLC, several authors reduced the dissection of some mediastinal lymph nodal stations with respect to the location of the primary tumor (ie, that the inferior and superior mediastinal lymph node stations could be reduced in the upper lobectomy and lower lobectomy, respectively).[31,32] To expand the possibility of reduction of mediastinal lymph node dissection, a successful intraoperative sentinel lymph node biopsy has been reported.[33,34] The present study showed that lymph node dissection could be reduced for clinical T1 N0 M0 adenocarcinomas with CRs of less than 0.5, without using the sentinel lymph node biopsy.

Although FDG-PET is well known to be useful for tumor staging in lung cancer, we believe that it can also predict lymph node metastases and tumor invasiveness in clinical T1 N0 M0 lung adenocarcinomas. Limited lung resection could be indicated, lymph node dissection or mediastinoscopy could be reduced, or both in this type of adenocarcinoma.

References

1. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology*. 1996;201:798-802.
2. Yankelevitz DF, Gupta R, Zhao B, Henschke CI. Small pulmonary nodules: evaluation with repeat CT-preliminary experience. *Radiology*. 1999;212:561-6.
3. Henschke CI, Yankelevitz DF. CT screening for lung cancer. *Radiol Clin North Am*. 2000;38:487-95.
4. Nomori H, Horio H, Fuyuno G, Kobayashi R, Morinaga S, Suemasu K. Lung adenocarcinomas diagnosed by open or thoracoscopic vs. bronchoscopic biopsy. *Chest*. 1998;114:40-4.
5. Nomori H, Horio H. Colored collagen is a long-lasting point marker for small pulmonary nodules in thoracoscopic operations. *Ann Thorac Surg*. 1996;61:1070-3.
6. Nomori H, Horio H, Naruke T, Suemasu K. Fluoroscopy-assisted thoracoscopic resection of lung nodules marked with lipiodol. *Ann Thorac Surg*. 2002;74:170-3.
7. Yoshikawa K, Tsubota N, Kodama K, Ayabe H, Taki T, Mori T. Prospective study of extended segmentectomy for small lung tumors. *Ann Thorac Surg*. 2002;73:1055-9.
8. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 1997;114:347-53.
9. Suzuki K, Nagai K, Yoshida J, Nishimura M, Nishizaki Y. Predictors of lymph node and intrapulmonary metastasis in clinical stage IA non-small cell lung carcinoma. *Ann Thorac Surg*. 2001;72:352-6.
10. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Shimosato Y, Naruke T. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? *J Thorac Cardiovasc Surg*. 1996;111:1125-34.
11. Naruke T, Goya T, Tsuchiya R, Suemasu K. The importance of surgery of non-small cell carcinoma of lung with mediastinal lymph node metastasis. *Ann Thorac Surg*. 1998;46:603-10.
12. Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. Early peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg*. 2002; 74:1635-9.
13. Matsuguma H, Yokoi K, Anraku M, et al. Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: a predictor of lymph node metastasis. *J Thorac Cardiovasc Surg*. 2002;124:278-84.
14. Higashi K, Ueda Y, Yagishita M, et al. FEG PET measurement of the proliferative potential of non-small cell lung cancer. *J Nucl Med*. 2000;41:85-92.
15. 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;6:3837-44.
16. Ahuja V, Coleman RE, Herndon J, Patz EF. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with non-small cell lung carcinoma. *Cancer*. 1998;83:918-24.
17. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. Prognostic importance of the standardized uptake value on ^{18}F-fluoro-2-deoxy-glucose-positron emission tomography in non-small cell lung cancer: an analysis of 125 cases. *J Clin Oncol*. 1999;17:3201-6.
18. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer*. 1995; 75:2844-52.
19. Sobin LH, Wittekind Ch, editors. UICC: TNM classification of malignant tumours. 6th ed. New York: John Wiley & Sons; 2002. p. 99-103.
20. Coleman RE. PET in lung cancer. *J Nucl Med*. 1999;40:814-20.
21. Marom EM, Sarvis S, Herndon JE, et al. T1 lung cancers: sensitivity of diagnosis with fluorodeoxyglucose PET. *Radiology*. 2002;223: 453-9.
22. Dewan NA, Gupta NC, Redepenning LS, et al. Diagnostic efficacy of PET-FDG imaging in solitary pulmonary nodules. *Chest*. 1993;104: 997-1002.
23. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary

pulmonary nodules using fluorine-18-FDG and PET. *J Nucl Med*. 1996;37:943-8.
24. Imdahl A, Jenkner S, Brink I, et al. Validation of FDG positron emission tomography for differentiation of unknown pulmonary lesions. *Eur J Cardiothorac Surg*. 2001;20:324-9.
25. Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol*. 1998; 16:1075-84.
26. Wahl RL, Cody RL, Hutchins GD, et al. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology*. 1991;179:765-70.
27. Takamochi K, Nagai K, Yoshida J, et al. Pathologic N0 status in pulmonary adenocarcinoma is predictable by combining serum carcinoembryonic antigen level and computed tomographic findings. *J Thorac Cardiovasc Surg*. 2001;122:325-30.
28. Higashi K, Ueda Y, Seki H. F-18 FDG PET imaging is negative in bronchiolo-alveolar lung carcinoma. *J Nucl Med*. 1998;39:1016-20.
29. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg*. 1995;60:615-22.
30. Ichinose Y, Yano T, Yokoyama H, Inoue T, Asoh H, Katsuda Y. The correlation between tumor size and lymphatic vessel invasion in resected peripheral stage I non-small cell lung cancer. A potential risk of limited resection. *J Thorac Cardiovasc Surg*. 1994;108:684-6.
31. Naruke T, Tsuchiya R, Kondo H, Nakayama H, Asamura H. Lymph node sampling in lung cancer: how should it be done? *Eur J Cardiothorac Surg*. 1999;16(suppl):S17-24.
32. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systemic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastases and prognosis. *J Thorac Cardiovasc Surg*. 1999;117:1102-11.
33. Liptay MJ, Masters GA, Winchester DJ, et al. Intraoperative radioisotope sentinel lymph node mapping in non-small cell lung cancer. *Ann Thorac Surg*. 2000;70:384-90.
34. Nomori H, Horio H, Naruke T, Orikasa H, Yamazaki K, Suemasu K. Use of technetium-99m tin colloid for sentinel lymph node identification in non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2002; 124:486-92.

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