Clinicopathologic study of resected, peripheral, small-sized, non–small cell lung cancer tumors of 2 cm or less in diameter: Pleural invasion and increase of serum carcinoembryonic antigen level as predictors of nodal involvement

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Objective: The number of surgical interventions for small-sized lung cancer has increased with the development of computed tomography. We attempted to identify clinicopathologic characteristics of peripheral, small-sized, non–small cell lung cancer to show the limitation of partial resection or segmentectomy.

Methods: A retrospective analysis of 143 patients who underwent a complete resection for a peripheral non–small cell lung cancer of 2 cm or less in diameter was performed. The relationships between nodal involvement and other clinical factors were also assessed in patients who underwent a lobectomy plus node dissection.

Results: The overall 5-year survival rate was 88.1%. The 5-year survival rate was 100% for patients with a tumor of 1.5 cm or less. Survival for patients with adenocarcinoma histology was significantly better than for those with nonadenocarcinoma histology ($P = .03$). The 5-year survival rate for patients without lymph node metastases was 91.6%, whereas it was 62.5% for those with nodal involvement ($P < .01$). Increase of prethoracotomy serum carcinoembryonic antigen level was an independent predictor of a poor prognosis. Lymph node metastasis was significantly increased in those with pleural invasion by the primary lesion and increased serum carcinoembryonic antigen level. Fourteen (16.9%) of 83 patients with a tumor diameter of larger than 1.5 cm had nodal metastasis.

Conclusions: Nodal involvement should be considered in patients with non–small cell lung cancer of 2 cm or less in diameter who show pleural invasion or an increased carcinoembryonic antigen level. A lobectomy with node dissection is recommended for patients with a tumor larger than 1.5 cm, suspected pleural invasion, or prethoracotomy carcinoembryonic antigen level increase.

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With the development of high-resolution computed tomography (CT), small-sized peripheral lung cancer has been more frequently encountered. At our institute, the ratio of resected cases with peripheral lung cancer tumors sized 2 cm in diameter or less has increased from 17.1% of all lung cancer cases in the period from 1992 through 1995 to more than 34.3% from 1996 through 1999 and 42.6% from 2000 through 2003. In addition, several reports have suggested the feasibility of a limited operation for stage I early lung cancer.^{1,2}

Recently, bronchioloalveolar carcinoma (BAC) showing ground-glass opacity (GGO) on chest CT images was identified as an independent entity among well-differentiated adenocarcinomas.³ Patients with BAC with a GGO appearance, which has been clarified to be less invasive, seldom have lymph node metastasis and

Abbreviations and Acronyms

- BAC = bronchioloalveolar carcinoma
- CEA = carcinoembryonic antigen
- CT = computed tomography
- GGO = ground-glass opacity

usually have better outcomes compared with patients with typical adenocarcinoma.⁴⁻⁶ Thus patients with BAC detected as a peripheral small-sized nodule could be good candidates for a limited resection. Lymph node metastasis is detected in a proportion of patients with small-sized peripheral lung cancer, even when the tumor size is smaller than 2 cm in diameter, and the risks of limited resection for these patients have been documented.^{7,8} An inappropriate limited resection can lead to an incomplete resection or misdiagnosis of nodal staging, and such patients might miss a chance to be cured or to receive adjuvant chemotherapy, which has been shown to be effective for those with completely resected non-small cell lung cancer (NSCLC).⁹ Thus it is important to identify the characteristics of small-sized lung cancer, including GGO lesions, to determine the appropriate operative mode for each patient.

Patients and Methods

Patients

The records of 565 patients with NSCLC who underwent a thoracotomy between 1992 and 2003 at Osaka University Hospital were reviewed. Of those, we analyzed 143 patients with a small-sized peripheral lesion of 2 cm or less in diameter who underwent a complete resection (Table 1). Patients treated with induction therapy or those with multiple primary lesions were excluded. Follow-up was completed in 133 of the patients, and the mean follow-up time for all was 52.1 months. We performed a lobectomy with systematic hilar and mediastinal lymph node dissection in principle. A limited resection was indicated not only for high-risk cases, including patients with low pulmonary function, cardiovascular comorbidity, advanced age, and severe diabetes mellitus, but also for patients with GGO or a peripheral lesion smaller than 1.5 cm in diameter. There were 15 compromised cases, and an intentional limited resection as a curative operation was performed in 20 patients, including 12 lesions with a GGO appearance. Preoperative staging was done with chest and abdominal CT scanning, brain magnetic resonance imaging, and bone scintigraphy. Lymph nodes larger than 1 cm in the short axis on chest CT images were defined as clinical N factor positive. Transbronchial lung biopsy or CT-guided needle biopsy was performed to obtain a histologic diagnosis. A proportion of patients with node swelling have been evaluated with fluorodeoxyglucose positron emission tomography since 1997. Postoperative staging was performed according to the TNM classification.¹⁰ We defined a GGO lesion as a tumor occupied mainly by ground-glass shadows in at least two thirds of the area on thin-section CT scans and noted as a GGO lesion by the attending radiologist. Otherwise, tumors with a partial ground-glass area were included in the solid tumor cate-

TABLE 1. Characteristics of 143 patients with resected non-small cell lung cancer of 2 cm or less in diameter

Age, y	31-82 (average, 63)
Sex	
Male	86
Female	57
Histology	
Ad	127
Sq	14
Other	2
c-Stage	
IA	131
IB	5
IIA	3
IIB	2
IIIA	2
c-N	
c-N0	136
c-N1	5
c-N2	2
CT findings	
Solid	102
GGO	41
Operative mode	
Lobectomy	108
Partial resection	35
p-Stage	
IA	123
IB	4
IIA	5
IIB	2
IIIA	9

Ad, Adenocarcinoma; Sq, squamous cell carcinoma; GGO, ground-glass opacity; partial resection, including segmentectomy.

gory. Variables used for evaluation were age, sex, tumor size, histology, tumor density, operation mode, lymph node metastases, pleural invasion, and prethoracotomy serum carcinoembryonic antigen (CEA) level.

Statistical Analyses

The probability of survival was calculated by using the Kaplan-Meier method.¹¹ The prognostic influence of variables on survival was analyzed with a Wilcoxon test and Cox regression.¹² A χ^2 test was used to compare the ratio between 2 groups.

Results

A preoperative histologic diagnosis of lung cancer was obtained in 95 patients on the basis of results of CT-guided needle biopsy in 61 patients and transbronchial lung biopsy in 34 patients. We performed fluorodeoxyglucose positron emission tomography in 16 cases. Among those cases, 14 primary tumors showed positive uptake, and 2 were negative. Positive uptake in lymph nodes was observed in 3 cases (2 with node metastases, and 1 false-positive result),

Figure 1. Probability of survival for patients with peripheral non-small cell lung cancer who underwent a complete resection according to tumor size. Survival for those with tumors of 1.5 cm or less in diameter was better than for those with tumors of 1.6 to 2.0 cm in diameter.

whereas negative results were shown in the remaining 13 patients (12 with no metastasis, and 1 false-negative result).

The overall 5-year survival rate for patients with peripheral NSCLC tumors of 2 cm or less in diameter was 88.1%, whereas that for patients with tumors of 1.5 cm or less was 100% and that for patients with tumors of 1.6 to 2 cm was 84% (Figure 1). Patients with a tumor of 1.5 cm or less in diameter survived longer than those with a tumor from 1.6

Figure 2. Probability of survival for patients with peripheral, small-sized, non-small cell lung cancer who underwent a complete resection according to histology of the primary lesion. Survival for those with adenocarcinoma histology (Ad) was significantly better than for those with nonadenocarcinoma histology (Non-Ad). Fourteen of the 16 nonadenocarcinoma cases showed squamous cell carcinoma histology.

Figure 3. Probability of survival for patients with peripheral, small-sized, non-small cell lung cancer who underwent a complete resection according to nodal involvement. Survival for those without lymph node metastases was significantly better than for those with nodal involvement.

to 2 cm in diameter. No patient with a tumor smaller than 1 cm showed recurrence over a mean follow-up period of 43.7 months.

According to histologic type, the 5-year survival rate for patients with adenocarcinoma was 89.8%, which was significantly better than that for patients with nonadenocarcinoma histology ($P = .03$, Figure 2). Patients with nonadenocarcinoma histology consisted of 14 with squamous cell carcinoma and 2 others. The 5-year survival rate for patients with a GGO lesion was 96.3%, whereas that for patients with a solid lesion was 85.1% (statistically not significant). We did not observe recurrence in any of the patients with a GGO lesion, although 1 died of respiratory failure associated with chronic constructive pericarditis. When excluding patients with GGO from the adenocarcinoma group, patients with an adenocarcinoma still showed a better survival than those with nonadenocarcinoma histology ($P = .05$).

There was no significant difference in survival rates between the 108 patients treated with a lobectomy and the 35 patients treated with a segmentectomy or partial resection according to operation mode. Among the 35 patients, hilar node sampling was preformed in 18 patients, and both hilar and mediastinal node dissection or sampling was performed in 5 patients, whereas the remaining 12 patients received no lymph node assessment. No metastasis was found in any of these resected nodes. The 5-year survival rate was 88.0% for patients treated with a lobectomy and 87.0% for those treated with a limited resection.

The 5-year survival rate for patients without lymph node metastasis was 91.6%, which was significantly better than for those with nodal involvement, who had a survival rate of 62.5% ($P < .01$, Figure 3). Pleural invasion was pathologic

Figure 4. Probability of survival for patients with peripheral, small-sized, non-small cell lung cancer who underwent a complete resection according to preoperative serum carcinoembryonic antigen (CEA) level. Survival for those with CEA level increase (≥ 5 ng/mL) was significantly worse than for those with a normal CEA level.

ically determined in 12 patients. The 5-year survival rate for patients without pleural involvement was 89.6%, whereas it was 75.8% for those with pleural invasion diagnosed pathologically (statistically not significant).

Twenty-nine (21.8%) of 133 patients showed an increase of preoperative serum CEA levels, and their 5-year survival rate was 77.6%, which was significantly worse than the rate

TABLE 2. Multivariate analyses of potential prognostic factors in patients with resected non-small cell lung cancer of 2 cm or less in diameter

Variables	Hazard ratio	95% CL	P value
Tumor size	1.136	0.900-1.433	.2835
Histology			
Ad	1.000		
Non-Ad	3.514	0.793-15.561	.978
CT finding			
GGO	1.000		
Solid	1.702	0.190-15.202	.6341
LN metastasis			
Negative	1.000		
Positive	1.645	0.414-6.539	.4798
Pleural invasion			
Negative	1.000		
Positive	2.674	0.442-16.189	.2842
Preoperative CEA level			
WNL	1.000		
≥ 5 ng/mL	4.666	1.161-18.751	.0299

CL, Confidence limit; Ad, adenocarcinoma; CT, Computed tomographic; GGO, ground-glass opacity; LN, lymph node; CEA, carcinoembryonic antigen (cutoff value is 5 ng/mL); WNL, within normal limit.

TABLE 3. Relationship between clinical factors and lymph node metastasis in patients with small-sized non-small cell lung cancer

Factors	Patient with LN metastases	P value
Tumor size		
0-1.5 cm	2/26 (7.7%)	NS
1.6-2.0 cm	14/82 (17%)	
Pleural factor		
pP0	12/100 (12%)	.05
pP1-2	4/8 (50%)	
Serum CEA		
WNL	8/78 (10.3%)	.02
≥ 5 ng/mL	7/24 (29.2%)	
CT finding		
GGO	0/29 (0%)	NA
Solid	17/79 (21.5%)	

LN, Lymph node; NS, statistically not significant; pP0, tumor without pleural involvement beyond the elastic layer; pP1, tumor extending to elastic layer but not to the pleural surface; pP2, tumor extending to the pleural surface, according to Japanese Lung Cancer Society criteria; CEA, carcinoembryonic antigen (cutoff value is 5 ng/mL); WNL, within normal limit; CT, computed tomography; GGO, ground-glass opacity; NA, not assessed.

of 92.1% for those with a normal CEA level ($P < .01$, Figure 4). Multivariate analyses using tumor size, histology, CT finding (solid or GGO), lymph node metastasis, pleural invasion, and prethoracotomy serum CEA level as variables identified only CEA level as an independent prognostic factor (Table 2).

In addition, we analyzed the frequency of lymph node metastasis by small-sized NSCLC in 108 patients treated with a lobectomy plus systematic hilar and mediastinal node dissection. Regarding the accuracy of preoperative nodal evaluation with CT scanning, sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 18.8%, 95.6%, 84.3%, 87.1%, and 42.9%, respectively. The relationships between nodal metastasis and clinical factors are summarized in Table 3.

Lymph node metastasis was found in 1 (9.1%) of 11 and 1 (6.7%) of 15 patients with tumors sized less than 1 cm and from 1.1 to 1.5 cm in diameter, respectively, whereas 14 (17%) of 82 patients with a tumor larger than 1.5 cm in diameter had nodal involvement (statistically not significant). Eight patients were associated with pathologic pleural invasion, of whom 4 (50%) had nodal metastases. The ratio of metastasis-positive lymph nodes was significantly higher in patients with pleural involvement ($P = .05$). In addition, patients with an increased prethoracotomy serum CEA level had lymph node metastasis more frequently than those with a normal CEA level. Nodal involvement was found in 8 (10.3%) of 78 patients with normal CEA levels, whereas 7 (29.2%) of 24 with increased CEA levels had nodal metastases ($P = .02$). Notably, nodal involvement was observed

in 6 (60%) of 10 patients with a CEA level greater than the 2-fold cutoff. We found no lymph node metastasis in patients with a GGO lesion.

Discussion

In the present study we focused on patients who underwent resection of a peripheral, small-sized NSCLC tumor of 2 cm or less in diameter and identified 3 prognostic factors, adenocarcinoma histology, pathologic nodal metastases, and preoperative serum CEA level, with the latter shown to be the only independent prognostic predictor by means of multivariate analysis. We also identified pleural invasion and prethoracotomy serum CEA level increase as clinical factors related to lymph node metastasis in an analysis of patients treated with a lobectomy plus systematic node dissection. In addition, preoperative nodal staging with CT imaging for small-sized NSCLCs revealed a high specificity and positive predictive value, whereas sensitivity and negative predictive value were quite low.

Tumor size has been reported to be related to the survival of patients with stage IA NSCLC and a nodule size of less than 2 cm in diameter and has also been identified as a prognostic factor.¹³ Survival analyses based on tumor size in patients with stage I NSCLC have shown statistically significant differences among those with tumors sized from 5 to 15 mm, 16 to 25 mm, and 26 to 36 mm.¹⁴ Another report showed that tumor size was an independent prognostic factor in pN0 resected cases.¹⁵ In the present study we found node metastases in one sixth of our patients with a tumor larger than 1.5 cm in diameter compared with previous studies that found lymph node metastasis in 28% of patients with tumors smaller than 2 cm,⁷ 15% of patients with subcentimeter-sized solid tumors,⁸ and 7% of patients with subcentimeter-sized tumors.¹⁶ Thus a limited resection or omission of nodal clearance requires careful assessment of node status. For tumors larger than 1.5 cm in diameter, we recommend that a lobectomy with systematic node dissection be chosen as a general practice. These results could be part of the basic data to promote the prospective trial regarding sublobar resection for small-sized lung cancer.

Nodal staging with CT imaging was reported to show a sensitivity ranging from 50% to 81%, specificity from 56% to 94%, and accuracy from 59% to 85% in studies published in the last decade.¹⁷⁻²¹ However, the accuracy of nodal staging focused on small-sized lung cancer has not been clarified. The present results revealed a high specificity and positive predictive value for evaluation of metastatic nodes by using CT scanning for small-sized NSCLC tumors compared with those for all tumors because there were few false-positive results in preoperative nodal evaluations. Thus lymph node swelling associated with small-sized NSCLCs should be considered as a sign of metastasis.

High-resolution CT scanning can sometimes detect GGO lesions. The proportion of GGO area and tumor shadow disappearance rate, calculated by using mediastinal and lung windows in the CT images, have been shown to have a correlation with patient outcome.^{4,6} Another study reported that most pure GGO tumors smaller than 1 cm in diameter were BAC or atypical adenomatous hyperplasia, which are suitable candidates for thoracoscopic limited resection.²² Furthermore, a recent prospective study concluded that limited resection procedures with intraoperative histologic diagnosis for pulmonary nodules of 2 cm or smaller were satisfactory, showed accurate diagnoses corresponding with those of frozen sections, and demonstrated no recurrence.²³ Because patients with GGO lesions did not show nodal involvement or postoperative recurrence in the present study, we can propose a limited resection for patients with NSCLC with GGO lesions of 2 cm or less in diameter.

Prethoracotomy serum CEA level has been reported to be a good predictor of poor prognosis for patients with stage I NSCLC²⁴⁻²⁶ and was the only independent prognostic predictor in the present study of small-sized NSCLC. It is considered that a combination of CEA level and CT or histologic findings might be more valuable to identify a patient group with poor outcome.^{27,28} We also found a correlation between CEA level and nodal involvement in small-sized peripheral NSCLC. Interestingly, more than half of our patients with serum CEA levels that increased to greater than the 2-fold cutoff had node metastasis. Because the slight increase of CEA level could be caused by smoking or other pulmonary disorders, we also analyzed the frequency of node metastases for patients with CEA levels higher than 2-fold cutoff. These results indicate that a limited resection should be avoided in patients with CEA level increase. Therefore we propose that measurement of CEA level is useful to select patients with advanced disease among those with peripheral, small-sized NSCLC.

Pleural invasion was frequently found in patients with lymph node metastases, and several other studies have shown pleural involvement to be a prognostic factor and noted its clinical importance.^{29,30} However, a preoperative accurate evaluation of pleural factors is difficult to obtain by means of CT or magnetic resonance imaging, and macroscopic findings during surgical intervention are unreliable. It was recently reported that a unique CT finding, the so-called pitfall sign, was able to predict pleural invasion.³⁰ Thus we consider that peripheral lung cancer with suspected pleural involvement on CT or intraoperative findings should be treated with a lobectomy plus node dissection, even if the tumor is smaller than 2 cm in diameter.

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References

1. Yoshikawa K, Tsubota N, Kodama K, Ayabe H, Taki T, Mori T. Prospective study of extended segmentectomy for small lung tumors: the final report. *Ann Thorac Surg.* 2002;73:1055-9.
2. Koike T, Yamato Y, Yoshiya K, Shimoyama T, Suzuki R. Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. *J Thorac Cardiovasc Surg.* 2003;125:924-8.
3. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer.* 1995;75:2844-52.
4. Okada M, Nishio W, Sakamoto T, Uchino K, Hanioka K, Ohbayashi C, et al. Correlation between computed tomographic findings, bronchioloalveolar carcinoma component, and biologic behavior of small-sized lung adenocarcinomas. *J Thorac Cardiovasc Surg.* 2004;127:857-61.
5. 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.
6. Matsuguma H, Yokoi K, Anraku M, Kondo T, Kamiyama Y, Mori K, 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.
7. Nonaka M, Kadokura M, Yamamoto S, Kataoka D, Kunimura T, Kushima M, et al. Tumor dimension and prognosis in surgically treated lung cancer: for intentional limited resection. *Am J Clin Oncol.* 2003;26:499-503.
8. Asamura H, Suzuki K, Watanabe S, Matsuno Y, Maeshima A, Tsuchiya R. A clinicopathological study of resected subcentimeter lung cancers: a favorable prognosis for ground glass opacity lesions. *Ann Thorac Surg.* 2003;76:1016-22.
9. Pisters KMW, Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. *J Clin Oncol.* 2005;23:3270-8.
10. Mountain CF. Revisions in the international system for staging lung cancer. *Chest.* 1997;111:1710-7.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-81.
12. Cox DR. Regression models and life-tables. *J R Stat Soc [B].* 1972;34:187-220.
13. Birim Ö, Kappetein AP, Takkenberg JJM, van Klaveren RJ, Bogers AJJC. Survival after pathological stage IA nonsmall cell lung cancer: tumor size matters. *Ann Thorac Surg.* 2005;79:1137-41.
14. Wisnivesky JP, Yankelevitz D, Henschke CI. The effect of tumor size on curability of stage I non-small cell lung cancers. *Chest.* 2004;126:761-5.
15. Takeda S, Fukai S, Komatsu H, Nemoto E, Nakamura K, Murakami M. Impact of large tumor size on survival after resection of pathologically node negative (pN0) non-small cell lung cancer. *Ann Thorac Surg.* 2005;79:1142-6.
16. Miller DL, Rowland CM, Deschamps C, Allen MS, Trastek VF, Pairolero PC. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg.* 2002;73:1545-51.
17. Sazon DA, Santiago SM, Soo Hoo GW, Khonsary A, Brown C, Mandelkern M, et al. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. *Am J Respir Crit Care Med.* 1996;153:417-21.
18. Guhlmann A, Storck M, Kotzerke J, Moog F, Sunder-Plassmann L, Reske SN. Lymph node staging in non-small cell lung cancer: evaluation by [¹⁸F]FDG positron emission tomography (PET). *Thorax.* 1997;52:438-41.
19. Steinert HC, Hauser M, Allemann F, Engel H, Berthold T, von Schulthess GK, et al. Non-small cell lung cancer: nodal staging with FDG PET versus CT with correlative lymph node mapping and sampling. *Radiology.* 1997;202:441-6.
20. Gupta NC, Tamim WJ, Graeber GG, Bishop HA, Hobbs GR. Mediastinal lymph node sampling following positron emission tomography with fluorodeoxyglucose imaging in lung cancer staging. *Chest.* 2001;120:521-7.
21. Cerfolio RJ, Ojha B, Bryant AS, Bass CS, Bartalucci AA, Mountz JM. The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. *Ann Thorac Surg.* 2003;76:861-6.
22. Nakata M, Sawada S, Saeki H, Takashima S, Mogami H, Teramoto N, et al. Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. *Ann Thorac Surg.* 2003;75:1601-5.
23. Yoshida J, Nagai K, Yokose T, Nishimura M, Kakinuma R, Ohmatsu H, et al. Limited resection trial for pulmonary ground-glass opacity nodules: fifty-case experience. *J Thorac Cardiovasc Surg.* 2005;129:991-6.
24. Sawabata N, Ohta M, Takeda S, Hirano H, Okumura Y, Asada H, et al. Serum carcinoembryonic antigen level in surgically resected clinical stage I patients with non-small cell lung cancer. *Ann Thorac Surg.* 2002;74:174-9.
25. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Prognostic significance of perioperative serum carcinoembryonic antigen in non-small cell lung cancer: analysis of 1,000 consecutive resections for clinical stage I disease. *Ann Thorac Surg.* 2004;78:216-21.
26. Bucchieri G, Ferrigno D. Identifying patients at risk of early postoperative recurrence of lung cancer: a new use of the old CEA test. *Ann Thorac Surg.* 2003;75:973-80.
27. Sakao Y, Sakuragi T, Natsuaki M, Itoh T. Clinicopathological analysis of prognostic factors in clinical IA peripheral adenocarcinoma of the lung. *Ann Thorac Surg.* 2003;75:1113-7.
28. Takamochi K, Yoshida J, Nishimura M, Yokose T, Sasaki S, Nishiwaki Y, et al. Prognosis and histologic features of small pulmonary adenocarcinoma based on serum carcinoembryonic antigen level and computed tomographic findings. *Eur J Cardiothorac Surg.* 2004;25:877-83.
29. Shimizu K, Yoshida J, Nagai K, Nishimura M, Ishii G, Morishita Y, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2005;130:160-5.
30. Li M, Ito H, Wada H, Tanaka F. Pit-fall sign on computed tomography predicts pleural involvement and poor prognosis in non-small cell lung cancer. *Lung Cancer.* 2004;46:349-55.