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

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Objective: In patients with clinical T1 N0 M0 lung adenocarcinoma, we investigated whether the proportion of ground-glass opacity area measured on high-resolution computed tomography was valuable for predicting the existence of lymph node metastasis, lymphatic invasion, or vascular invasion.

Methods: Between 1994 and 1999, 111 patients with clinical stage IA adenocarcinoma underwent surgical resection of the lung at our hospital. Of these, 96 patients received high-resolution computed tomography of the chest, and they constituted the study population. The tumors were semiquantitatively classified into 5 groups on the basis of the proportion of ground-glass opacity area to whole tumor shadow on high-resolution computed tomography: group I, 0%; group II, 1% to 25%; group III, 26% to 50%; group IV, 51% to 75%; and group V, 76% to 100%. Correlations of computed tomographic findings, pathologic results of lymph node metastasis and lymphatic and vascular invasion, and the histologic subtype according to the new World Health Organization classification were examined. We also investigated the characteristics of the patients with ground-glass opacity areas on high-resolution computed tomography and their value for predicting lymph node metastasis.

Results: Among the 96 patients, 15 (15.6%) had mediastinal lymph node metastases, and 3 (3.1%) had hilar node metastases. Regarding the proportion of the ground-glass opacity area of the tumors, 15 (15.6%) tumors were classified as group V, 11 (11.5%) as group IV, 9 (9.3%) as group III, 22 (22.9%) as group II, and 39 (40.6%) as group I, respectively. Of the 18 patients with lymph node metastases, no patients were found in groups IV and V, 2 (22.2%) were found in group III, 4 (18.2%) were found in group II, and 12 (30.8%) were found in group I (trend $P = .003$), respectively. Twenty-six patients classified into groups IV and V also showed neither lymphatic invasion nor recurrence. All the smaller tumors (≤ 2.0 cm) in group IV or V were histologically proved to be bronchioloalveolar carcinoma. Adjusted for smoking status and other characteristics, patients without ground-glass opacity on high-resolution computed tomography had a significantly increased risk of concurrent lymph node metastasis compared with those with ground-glass opacity.

Conclusion: In patients with clinical T1 N0 M0 adenocarcinoma, the proportion of ground-glass opacity area on thin-section computed tomography scans was a strong predictor for tumor aggressiveness and thus could be a useful index for planning limited surgical resection for these patients.

There have been two concerns regarding operations for patients with clinical stage IA non-small cell lung cancer: one is to what extent the lymph node area should be dissected, and the other is the volume of the lung parenchyma that should be resected. Many surgeons advocate that systematic nodal dissection be routinely used for accurate intrathoracic staging of non-small cell lung cancer, even if a patient's disease is classified as clinical stage IA, because no clinical or pathologic subset of patients with a negligible incidence of N2 disease has been discriminated.¹⁻³ On the basis of the results of a prospective randomized trial comparing limited resection with lobectomy for the management of patients with T1 N0 disease, limited resection should not be recommended as the treatment of choice for these patients because of the high incidence of local recurrence.⁴

Recently, the advent of high-resolution computed tomography (HRCT) has made it possible to investigate tumor shadows in more detail. Some cases of adenocarcinoma showed ground-glass opacity (GGO) at the tumor periphery that reflected the lepidic growth of the tumor cells seen in bronchioloalveolar carcinoma (BAC) microscopically.⁵ Moreover, patients with peripheral adenocarcinoma accompanied by a high BAC component showed better prognosis.^{6,7} Therefore, we reviewed HRCT scans of patients with cT1 N0 M0 peripheral adenocarcinoma to determine the value of the presence and extent of areas of GGO as a clinicopathologic indicator, especially for the extent of nodal involvement and the presence of intratumoral lymphatic and vascular invasion of tumor cells, which might reflect tumor aggressiveness.⁸⁻¹⁰ We also investigated a correlation between the proportion of GGO on HRCT and histologic findings of the tumors and characteristics of patients with GGO.

Patients and Methods

Between October 1994 and December 1999, 370 patients with primary lung cancer underwent surgical resection of the lung at our hospital. Of these, 130 patients were given a diagnosis of clinical stage IA disease, of whom 111 patients had adenocarcinoma. Among the patients, 96 received HRCT, and they constituted the study population. All patients underwent physical examination, chest radiography, bone scintigraphy, bronchoscopic examination, and magnetic resonance imaging of the brain, as well as CT of the chest and upper part of the abdomen for staging and evaluation of resectability before the operation. Serum levels of tumor markers associated with adenocarcinoma of the lung, such as carcinoembryonic antigen (normal range, ≤ 5 ng/mL), carbohydrate antigen 19-9 (≤ 37 U/mL), and sialyl Lewis(x) (≤ 38 U/mL), were analyzed preoperatively.

Fifty-seven patients were women, and the mean age was 61.6 years (range, 40-80 years). For cigarette smoking, patients who never smoked and those who ever smoked numbered 53 and 43, respectively. Surgical treatment was performed as follows: pneu-

monectomy in 1 patient, lobectomy in 79 patients, segmentectomy in 11 patients, and partial resection in 5 patients. A patient with pleural disseminated disease underwent an extrapleural pneumonectomy. Systematic lymph node dissection was performed in 77 patients, whereas sampling or no resection of mediastinal lymph nodes was done in 19 patients in whom no node metastasis was clinically suspected. Of those 19 patients, 9 underwent intentionally limited operations without systematic nodal dissection because of the tumor's less aggressive appearance, and consequently, none of these tumors have recurred. The remaining 10 patients did not undergo complete nodal staging because of the impaired condition.

The tumors were classified into 3 histologic subtypes according to the classification of the World Health Organization (WHO), with some modification: BAC, BAC with small invasive foci (≤ 5 mm), and other subtypes, including acinar, papillary, solid carcinoma with mucin, and adenocarcinoma with mixed subtype.¹¹ BAC was defined as an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. Stromal invasion is suggested by tumor cells arranged in acinar, papillotubular structures or solid tumor cells in a fibroblastic stroma, often accompanied by collagenization. BACs with invasive foci ≤ 5 mm in diameter were classified as BAC with small invasive foci. If invasive foci were larger than 5 mm, the tumors were classified into other subtypes. Pathologic stage was classified according to the International System for Staging Lung Cancer criteria.¹²

CT scanning was performed on a TCT 900S (Toshiba Medical Systems, Tokyo, Japan) or X-Vigor (Toshiba Medical Systems) scanner. HRCT scans were performed over a range of 50 mm, covering the entire lesion. The scanning parameters were a tube voltage of 120 kV, a tube current of 250 mA, 2-mm collimation, table speed of 2 mm/s, 1 rotation per second, pitch of 1, and a reconstruction interval of 2 mm by using a bone algorithm. The field of view was focused at about 20 cm in 60 patients. The images were photographed with a window level of -650 HU and a window width of 1800 HU. The analysis was made on hard-copy films. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking. In this study we defined GGO as reflection of a tumor cell lepidic growth pattern seen in BAC. Therefore, the area we thought to be secondary inflammation was not regarded as GGO. Three observers who were unaware of the pathologic staging and prognosis reviewed each HRCT scan of 96 peripheral adenocarcinomas and quantitated the percentage of lesions occupied by areas of GGO on all slices on which the tumor appeared visually. Then, according to the proportion of the GGO area, we classified the tumors into 5 groups: group I, 0%; group II, 1% to 25%; group III, 26% to 50% (Figure 1); group IV, 51% to 75%; and group V, 76% to 100% (Figure 2). Discrepancies in interpretation between observers were resolved by consensus. The reasons we estimated the proportion of GGO on all slices on which a tumor existed instead of on one level of the tumor equator were as follows. First, we thought that it was easier to classify each tumor into the 5 categories by considering more information than from one slice. Second, because the distribution of GGO was not uniform around the solid portion, all slices were superior to one slice for expressing the tumor characteristics.

Figure 1. A, HRCT showing group III tumor according to the GGO classification. B, Histologic specimen showing the tumor had an invasive area ≥ 5 mm in diameter and BAC component.

Figure 2. A, HRCT showing group V tumor according to the GGO classification. B, Histologic specimen showing the tumor was composed of BAC growth pattern with no evidence of invasion.

All lesions were surgically resected within 2 months or less after CT examination. Four-micrometer sections, including the largest piece cut from the surface of the tumor in each case, were stained with hematoxylin and eosin and elastica van Gieson stains and examined by means of light microscopy. Intratumoral vascular invasion was determined by means of the identification of tumor cells in blood vessels. Lymphatic invasion was also morphologically distinguished from vascular invasion. The patients were scheduled for checkups, chest radiography, and measurement of tumor marker serum levels every 1 to 3 months for 2 years after the

operation and every 6 months thereafter. All patients except one were followed up until death or the last date of the follow-up (March 31, 2001). The average length of follow-up was 40 months.

We investigated the association of the proportion of GGO area with maximal tumor size, lymph node metastasis, lymphatic invasion, vascular invasion, and the histologic subtype according to the new WHO classification. We also examined the characteristics of patients having a greater proportion of GGO area and the GGO classification in relation to the prediction of lymph node metastasis. The Mantel-Haenszel χ^2 test was performed to examine cor-

TABLE 1. Relationship among GGO classification, maximal tumor diameter, nodal status, and vessel invasion

	Total	Nodal status			Vessel invasion	
		N0	N1	N2	ly	v
GGO classification						
V	15	15 (100)	0 (0)	0 (0)	0 (0)	0 (0)
IV	11	11 (100)	0 (0)	0 (0)	0 (0)	1 (9.1)
III	9	7 (77.8)	1 (11.1)	1 (11.1)	0 (0)	2 (22.2)
II	22	18 (81.8)	2 (9.1)	2 (9.1)	5 (22.7)	7 (31.8)
I	39	27 (69.2)	0 (0)	12 (30.8)	13 (33.3)	13 (33.3)
Maximal tumor diameter (cm)						
≤1.0	5	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)
1.1-1.5	14	12 (85.7)	0 (0)	2 (14.3)	2 (14.3)	4 (28.6)
1.6-2.0	18	15 (83.3)	0 (0)	3 (16.7)	3 (16.7)	3 (16.7)
2.1-3.0	59	46 (80.0)	3 (5.1)	10 (17.0)	13 (22.0)	16 (27.1)
Total	96	78 (81.3)	3 (3.1)	15 (15.6)	18 (18.8)	23 (24.0)

Numbers in parentheses indicate percentages. ly, Lymphatic invasion; v, vascular invasion.

relations between the proportion of GGO and clinicopathologic factors. We also examined a relation of lymph node metastasis with selected characteristics. To further clarify the independent factors in association with lymph node metastasis, we performed multiple logistic regression analysis with the SAS software package (Statistical Analysis Systems, Inc, Cary, NC).

Results

Pathologic examination revealed that 21.8% of the tumors were BACs, and 10.4% were BACs with small invasive foci. T1 tumors were found in 90.6% of the patients, whereas T2 and T4 tumors were discovered in 5 and 4 patients, respectively. Mediastinal lymph node metastasis was found in 15 (15.6%) patients, and hilar node metastasis was found in 3 (3.1%) patients.

During the follow-up period, 23 patients had tumor recurrences. Of the 16 patients with locoregional relapse, 4 with pathologic N2 disease had lymph node recurrences beyond the dissected area of the mediastinum. No nodal recurrence was observed in patients with pathologic N0 disease.

Among the 96 tumors, 15 (15.6%) were classified as group V, 11 (11.5%) as group IV, 9 (9.3%) as group III, 22 (22.9%) as group II, and 39 (40.6%) as group I according to the proportion of GGO area. The distribution of pathologic N status and vessel invasion by proportion of GGO and maximal tumor diameter are shown in Table 1. The numbers of node-positive cases were 0 (0%) for groups V and IV, 2 (22.2%) for group III, 4 (18.2%) for group II, and 12 (30.8%) for group I, respectively. Among the patients with group V and IV tumors, no resected tumors showed lymphatic or vascular invasion, with the exception of one patient with a relatively large tumor (≥ 2 cm) with vascular invasion. The patients in groups I, II, and III had several occurrences of lymph node metastasis and lymphatic and vascular invasion. According to the tumor size, only 5 (5.2%) tumors measuring ≤ 1 cm were accompanied with

neither lymph node metastasis nor vessel invasion. On the other hand, lymph node metastasis was more often observed in patients with tumors larger than 1 cm in diameter. Except for the smallest tumors with a diameter ≤ 1 cm, the proportion of each GGO group was not different among the other 3 groups ($P = .80$).

The relationship between the proportion of GGO and patient and tumor characteristics is shown in Table 2. BACs and BACs with small foci of invasion were found in 93% of group V patients, 82% of group IV patients, 33% of group III patients, 14% of group II patients, and 5% of group I patients. In patients with tumors ≥ 2 cm in diameter, all tumors in group IV and V patients were BACs. All patients classified as having BAC or BAC with minimal invasive foci are alive without recurrence.

Women, patients who never smoked, and patients with a normal range of preoperative tumor marker values had a significantly greater portion of GGO, whereas nodal involvement, lymphatic invasion, and vascular invasion were observed more often among those with a smaller proportion of GGO (Table 2).

A multiple logistic regression analysis revealed that absence of GGO area on CT was an independent risk factor for lymph node metastasis (odds ratio, 4.87; 95% confidence interval, 1.51-15.77; Table 3). In 77 patients with complete nodal staging, the analysis also showed basically the same results (odds ratio, 4.24; 95% confidence interval, 1.17-15.38).

Discussion

Among patients with clinical T1 N0 M0 peripheral adenocarcinoma, the proportion of GGO area in the tumor shadow was related to aggressiveness of the tumor independent of tumor size. This finding will become an important factor when planning appropriate surgical treatment, especially less invasive surgical intervention.

TABLE 2. Relationship between the proportion of GGO and patient and tumor characteristics

	GGO group					Total	P value for trend
	V	IV	III	II	I		
Sex							
Male	3	2	4	9	21	39	
Female	12	9	5	13	18	57	.008
Age							
≤62 y	7	3	2	13	19	44	
>62 y	8	8	7	9	20	52	.341
Smoking status							
Never	11	9	5	12	16	53	
Ever	4	2	4	10	23	43	.007
Tumor marker							
Normal range	14	8	8	14	22	66	
High*	1	3	1	8	17	30	.006
Tumor size							
≤2.0 cm	8	3	2	7	17	37	
>2.0 cm	7	8	7	15	22	59	.917
Nodal involvement							
N0	15	11	7	18	27	78	
N1-2 (N1)	0	0	2 (1)	4 (2)	12	18 (3)	.003
Lymphatic invasion							
Negative	15	11	9	17	26	78	
Positive	0	0	0	5	13	18	.001
Vascular invasion							
Negative	15	10	7	15	26	73	
Positive	0	1	2	7	13	23	.004
Histological subtype							
BAC	12 (8)	6 (3)	1 (0)	1 (0)	1 (0)	21 (11)	
BAC invasive†	2 (0)	3 (0)	2 (1)	2 (0)	1 (0)	10 (1)	
Other	1 (0)	2 (0)	6 (1)	19 (7)	37 (17)	65 (25)	<.001‡
Recurrence							
No	15	11	8	16	23	73	
Yes	0	0	1	6	16	23	.001

Numbers in parentheses were cases of the tumor 2 cm in diameter or less.

*At least one tumor marker was elevated over the normal range (carcinoembryonic antigen, ≤5 ng/mL; carbohydrate antigen 19-9, ≤37 U/mL; and sialyl Lewis(x), ≤38 U/mL).

†BAC with small invasive foci (≤5 mm).

‡Relationship between the proportion of GGO and histologic subtype (BAC vs BAC invasive + other).

Including thoroscopic surgery, limited surgical resection might have some advantages over a standard operation for selected patients.¹³ However, patient selection was difficult because several studies revealed that mediastinal lymph node metastasis was common in patients with small peripheral adenocarcinomas.¹⁻² Therefore, if the tumor is larger than 1 cm in diameter, lobectomy with systematic lymph node dissection is now recommended as the standard treatment, with the aim of accurate staging and possible improvement of prognosis. On the other hand, patients with a tumor ≤1 cm rarely have lymph node metastasis.² Yoshida and colleagues³ found only 13 (1.2%) such cases among 1051 patients with lung cancer who underwent surgical resection. The proportion of these small tumors was only about 5% of clinical T1 N0 M0 cases and 0.8% of all surgically treated cases in our study. Therefore, a more reliable and useful indicator for predicting the possibility of lymph node metastasis in this clinical stage is desirable.

Shimosato and associates¹⁴ noted a poorer prognosis in patients with an increased amount of collagenization or hyalinization in the central fibrotic focus in the tumor. As results of analyses of various prognostic factors in resected cases, it has been shown that the size of the central fibrotic area relates to outcome in patients with adenocarcinoma.^{6,15} From a different point of view, Higashiyama and coworkers⁷ suggested that the degree of BAC involvement might reflect clinicopathologic and prognostic characteristics. In 1996, Jang and colleagues¹⁶ reported that GGO in BAC on thin-section CT was an early sign of BAC. In addition, the extent of GGO might be well correlated with that of bronchioloalveolar growth of lung adenocarcinoma.⁵ Therefore, we classified the tumors according to the proportion of GGO in the tumor shadow on HRCT and confirmed that the patients with a higher proportion of GGO had a tendency for their tumors not to metastasize to the lymph nodes. There were 26 (27%) patients with a higher proportion of GGO

TABLE 3. Relationships among selected characteristics and risk of concurrent lymph node metastasis

Factors	Lymph node metastasis		Odds ratio*	95% CI	P value
	–	+			
Sex					
Male	32	7	1.00	Reference	—
Female	46	11	0.86	0.12-5.93	.89
Smoking status					
Never	43	10	1.00	Reference	—
Ever	35	8	0.81	0.12-5.39	.83
Tumor marker					
Normal	53	13	1.00	Reference	—
High†	25	5	0.60	0.18-2.03	.41
Tumor size					
≤1.0 cm	5	0	1.65‡	0.58-4.68	.35
1.1-1.5 cm	12	2			
1.6-2.0 cm	15	3			
2.1-3.0 cm	46	13			
GGO					
Present	51	6	1.00	Reference	—
Absent	27	12	4.87	1.51-15.77	<.01

CI, Confidence interval.

*Adjusted for other characteristics in the Table.

†At least one tumor marker was elevated over the normal range (carcinoembryonic antigen ≤5 ng/mL; carbohydrate antigen 19-9, ≤37 U/mL; and sialyl Lewis(x), ≤38 U/mL).

‡An increased risk due to a 1-cm increase in diameter.

(51%-100%), and they did not have lymph node metastasis or evidence of tumor recurrence. We believe that the proportion of GGO was a powerful indicator of lymph node metastasis and a powerful indicator for identifying patients suitable for limited resection.

The Lung Cancer Study Group reported the results of a prospective randomized trial comparing limited resection with lobectomy for the management of patients with T1 N0.⁴ A total of 247 patients were eligible for analysis. The limited resection group had a significantly higher local recurrence rate than the lobectomy group. The Lung Cancer Study Group therefore concluded that limited resection should not be recommended as the resection of choice for patients with T1 N0 disease. Ichinose and associates¹⁷ reported that 44% of tumors showed lymphatic invasion in patients with resected non-small cell lung cancers classified as pathologic stage I located on the periphery of the lung. They speculated that this was the main reason that the limited resection group had a higher local recurrence rate in the Lung Cancer Study Group trial. Others reported that lymphatic vessel invasion was correlated with poorer prognosis in patients with non-small cell lung cancer.⁹ This suggested that intratumoral lymphatic invasion reflected tumor aggressiveness. Therefore, if we could select patients with tumors without lymphatic invasion, limited resection might be successfully performed without local recurrence. In our series tumors with a proportion of GGO greater than 50% did not show lymphatic invasion. According to the new WHO classification, BAC was defined as not showing in-

vative foci including vessel invasion.¹¹ In this study all the tumors that measured ≤ 2 cm in groups IV and V were histologically diagnosed as BAC. Tumors larger than 2 cm in diameter classified in group IV and V were found in 7 patients with BAC and 8 patients with BAC plus invasive foci. However, those 15 patients had neither lymphatic invasion nor nodal metastasis and are alive without recurrence. Therefore, we consider that patients with T1 tumors categorized to groups IV and V are candidates for limited resection. Meanwhile, it should be argued whether intraoperative pathologic examination would be useful to indicate a limited resection for a favorable BAC. Yamato and colleagues¹⁸ proposed limited resection for BAC on the basis of the intraoperative pathologic examination. They converted wedge resection into lobectomy if active fibroblastic foci or invasive signs were presented on the frozen section. However, it is still unclear whether BACs with small invasive foci are not candidates for limited resection. Further studies will be necessary to clarify this issue.

Recently, positron emission tomography (PET) was introduced for mediastinal staging. It was shown to have a high percentage of negative predictive value in patients with stage I disease.¹⁹ PET might provide more accurate lymph node staging than CT. However, it might not provide information on lower tumor invasiveness that could be obtained by GGO classification. Higashi and associates²⁰ reported that Fluorine-18-FDG PET imaging results were negative in 4 of 7 patients with BAC and 1 of 23 patients without BAC.²⁰ Although these results showed that PET could be

used to diagnose some cases of BAC, we consider that PET is more expensive and not as accessible as CT. We believe that GGO classification on HRCT could be more useful than PET for planning limited operations.

In conclusion, by using this novel classification based on semiquantitative analysis of the GGO area in the tumor shadow on HRCT, we identified patients with less invasive tumors. Thus, it could be a useful tool for planning therapeutic strategies, particularly for limited surgical intervention.

References

- Graham AN, Chan KJ, Pastorino U, Goldstraw P. Systematic nodal dissection in the intrathoracic staging of patients with non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 1999;117:246-51.
- Oda M, Watanabe Y, Shimizu J, Murakami S, Ohta Y, Sekido N, et al. Extent of mediastinal node metastasis in clinical stage I non-small-cell lung cancer: the role of systematic nodal dissection. *Lung Cancer.* 1998;22:23-30.
- Yoshida J, Nagai K, Yokose T, Takahashi K, Nishimura M, Goto K, et al. Primary peripheral lung carcinoma smaller than 1 cm in diameter. *Chest.* 1998;114:710-2.
- Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995;60:615-22.
- Kuriyama K, Seto M, Kasugai T, Higashiyama M, Kido S, Sawai Y, et al. Ground-glass opacity on thin-section CT: value in differentiating subtypes of adenocarcinoma of the lung. *AJR Am J Roentgenol.* 1999;173:465-9.
- Suzuki K, Yokose T, Yoshida J, Nishimura M, Takahashi K, Nagai K, et al. Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. *Ann Thorac Surg.* 2000;69:893-7.
- Higashiyama M, Kodama K, Yokouchi H, Takami K, Mano M, Kido S, et al. Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. *Ann Thorac Surg.* 1999;68:2069-73.
- Macchiarini P, Fontanini G, Hardin JM, Pingitore R, Angeletti CA. Most peripheral, node-negative, non-small-cell lung cancers have low proliferative rates and no intratumoral and peritumoral blood and lymphatic vessel invasion. Rationale for treatment with wedge resection alone. *J Thorac Cardiovasc Surg.* 1992;104:892-9.
- Brchet JM, Chevret S, Charpentier MC, Appere de Vecchi C, Capron F, Prudent J, et al. Blood vessel and lymphatic vessel invasion in resected nonsmall cell lung carcinoma. Correlation with TNM stage and disease free and overall survival. *Cancer.* 1996;78:2111-8.
- Fu XL, Zhu XZ, Shi DR, Xiu LZ, Wang LJ, Zhao S, et al. Study of prognostic predictors for non-small cell lung cancer. *Lung Cancer.* 1999;23:143-52.
- World Health Organization. Histological typing of lung and pleural tumours. 3rd ed. Geneva: World Health Organization; 1999.
- Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-7.
- Giudicelli R, Thomas P, Lonjon T, Ragni J, Morati N, Ottomani R, et al. Video-assisted minithoracotomy versus muscle-sparing thoracotomy for performing lobectomy. *Ann Thorac Surg.* 1994;58:712-7.
- Shimosato Y, Suzuki A, Hashimoto T, Nishiwaki Y, Kodama T, Yoneyama T, et al. Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. *Am J Surg Pathol.* 1980;4:365-73.
- Goldstein NS, Mani A, Chmielewski G, Welsh R, Pursel S. Prognostic factors in T1 N0 M0 adenocarcinomas and bronchioloalveolar carcinomas of the lung. *Am J Clin Pathol.* 1999;112:391-402.
- Jang HJ, Lee KS, Kwon OJ, Rhee CH, Shim YM, Han J. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. *Radiology.* 1996;199:485-8.
- 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.
- Yamato Y, Tsuchida M, Watanabe T, Aoki T, Koizumi N, Umezumi H, et al. Early results of a prospective study of limited resection for bronchioloalveolar adenocarcinoma of the lung. *Ann Thorac Surg.* 2001;71:971-4.
- Farrell MA, McAdams HP, Herndon JE, Patz EF Jr. Non-small cell lung cancer: FDG PET for nodal staging in patients with stage I disease. *Radiology.* 2000;215:886-90.
- Higashi K, Ueda Y, Seki H, Yuasa K, Oguchi M, Noguchi T, et al. Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. *J Nucl Med.* 1998;39:1016-20.