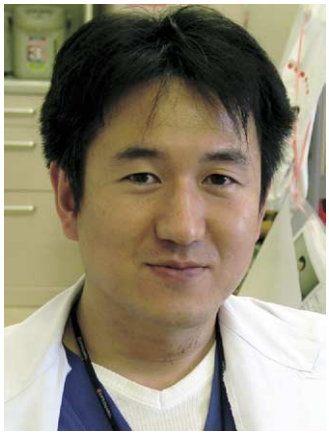
Visceral pleural invasion is an invasive and aggressive indicator of non–small cell lung cancer

Kimihiro Shimizu, MD,[a,b] Junji Yoshida, MD,[a] Kanji Nagai, MD,[a] Mitsuyo Nishimura, MD,[a] Genichiro Ishii, MD,[c] Yasuo Morishita, MD,[b] and Yutaka Nishiwaki, MD[a]



Dr Shimizu

Objective: Although visceral pleural invasion by non–small cell lung cancer is considered a poor-prognostic factor, further information is lacking, especially in relation to other clinicopathologic prognostic factors. We assessed the relationship between visceral pleural invasion and other clinicopathologic characteristics and evaluated its significance as a prognostic factor.

Methods: We reviewed 1074 patients with surgically resected T1/2 non–small cell lung cancer for their clinicopathologic characteristics and prognoses. The patients were divided into 2 groups according to visceral pleural invasion status (visceral pleural invasion group and non–visceral pleural invasion group). Both groups were compared with regard to age, sex, histology, tumor size, tumor differentiation, lymph node involvement, lymphatic invasion, vascular invasion, scar grade, nuclear atypia, mitotic index, serum carcinoembryonic antigen level, and survival. Univariate and multivariate analyses were conducted.

Results: Visceral pleural invasion was identified in 288 (26.8%) of the resected specimens. Survival was 76.0% at 5 years and 53.2% at 10 years in the non–visceral pleural invasion group and was 49.8% at 5 years and 37.0% at 10 years in the visceral pleural invasion group. The difference between groups was highly significant ($P < .0001$). Visceral pleural invasion was also significantly associated with a higher frequency of lymph node involvement. However, regardless of N status (N0 or N1/2), there was a significant difference in survival when the visceral pleura was invaded. Visceral pleural invasion was observed significantly more frequently in tumors with factors indicative of tumor aggressiveness/invasiveness: moderate/poor differentiation, lymphatic invasion, vascular invasion, high scar grade, high nuclear atypia grade, high mitotic index, and high serum carcinoembryonic antigen level. By multivariate analysis, visceral pleural invasion proved to be a significant independent predictor of poor prognosis in non–small-cell lung cancer patients with or without lymph node involvement.

Conclusions: Visceral pleural invasion is a significant poor-prognostic factor, regardless of N status. Our analyses indicated that visceral pleural invasion is an independent indicator of non–small cell lung cancer invasiveness and aggressiveness.

From the Division of Thoracic Oncology, National Cancer Center Hospital East,[a] Chiba, Japan, Division of Thoracic and Visceral Organ Surgery, Gunma University Faculty of Medicine,[b] Gunma, Japan, and Pathology Division, National Cancer Center Research Institute East,[c] Chiba, Japan

This work was supported in part by a grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare, Japan.

Received for publication Sept 21, 2004; revisions received Oct 31, 2004; accepted for publication Nov 9, 2004.

Address for reprints: Kimihiro Shimizu, MD, Division of Thoracic and Visceral Organ Surgery, Gunma University Faculty of Medicine, 3-39-15, Showa-machi, Maebashi, Gunma, 371-8511, Japan (E-mail: kmshimiz@showa.gunma-u.ac.jp)

J Thorac Cardiovasc Surg 2005;130:160-5

0022-5223/$30.00

doi:10.1016/j.jtcvs.2004.11.021

Visceral pleural invasion (VPI) is one of the most important prognostic factors in patients who undergo complete resection for non–small cell lung cancer (NSCLC).[1-3] VPI was adopted as a specific description in the TNM classification of the International Union Against Cancer staging system in the mid 1970s[4] and has remained unchanged: a tumor of any size that invades the visceral pleura is classified as T2. Whereas a tumor 3 cm or less, if it has VPI, is upgraded to T2, a tumor larger than 3 cm remains T2 in this system. The system lacks detail in VPI definition.

In a previous report,[3] we examined the significance of pleural invasion extent as a prognostic factor and proposed a refined TNM classification based on VPI. We demonstrated that VPI should be defined as tumor extension beyond the elastic layer

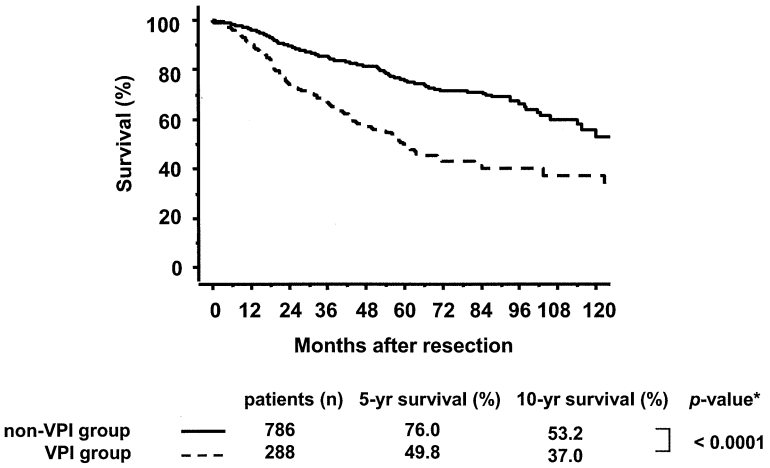


Figure 1. Survival curves and overall 5- and 10-year survival for non-VPI and VPI groups. *P value by log-rank test.

of the visceral pleura, regardless of its exposure on the pleural surface. Our proposal was that a tumor 3 cm or smaller with VPI should be upgraded to T2 and that a tumor larger than 3 cm with VPI should be upgraded to T3 in the NSCLC TNM classification.[3]

However, VPI in association with other clinicopathologic prognostic factors is not well understood. The purpose of this study was to correlate VPI and other clinicopathologic prognostic factors in NSCLC patients and to evaluate the significance of VPI as a prognostic factor.

Patients and Methods

From February 1979 through March 2001, 1074 patients with T1 and T2 NSCLC underwent pulmonary resection (segmentectomy or more) and systematic mediastinal lymph node dissection, as described previously,[5] at our institution. All resections were curative, defined as complete removal of ipsilateral hilar and mediastinal lymph nodes together with the primary tumor. Patients who had induction chemotherapy or radiotherapy; patients with evidence of residual tumor at the resection margin, malignant effusion, satellite lesions, or distant metastasis verified during surgery or by postoperative pathologic examination; patients with pathologic N3 disease; T2 patients with interlobar invasion (interlobar p3); and patients with tumors involving the main bronchus, 2 cm or more from the carina, were excluded from this study.

Histopathologic studies were performed according to World Health Organization criteria,[6] and VPI was examined in detail. Tumor sections were stained with hematoxylin and eosin (HE) and Victoria blue–van Gieson stains for evaluation of the VPI and vascular invasion. VPI was classified according to the Japan Lung Cancer Society criteria[7]: p0, tumor with no pleural involvement beyond its elastic layer; p1, tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface; and p2, tumor that is exposed on the pleural surface but does not involve adjacent anatomic structures. All patients were divided into 2 groups according to VPI status (non-VPI group, p0; VPI group, p1 or p2).[3] Lymphatic and vascular invasion indicated tumor cells identifiable in the lymphatic or blood vessel lumen, respectively.

Scar grade was classified into 4 grades: grade 1, tumors had foci of alveolar collapse with resulting condensation of elastic fibers but no or minimal fibroblastic tissue with collagen; grade 2, tumors had fibroblastic tissue with a small amount of collagen fibers; grade 3, tumors had fibroblastic tissue with a moderate or abundant amount of collagen fibers; and grade 4, tumors showed hyalinization. Categorization of nuclear atypia was based on the most atypical nuclei on sections and was divided into 3 grades as follows: grade 1 denoted nuclei that were uniform in size and equal to or only slightly larger than those of reactive type II alveolar epithelial cells, grade 2 denoted nuclei that were uniform in size and up to twice the size of those of reactive type II alveolar epithelial cells, and grade 3 denoted the presence of giant tumor cells. Mitotic index was classified into 3 groups based on the findings on several sections: grade 1 denoted 5 or fewer mitotic cells per 10 high-power fields (HPF), grade 2 denoted 6 to 15 mitotic cells per 10 HPF, and grade 3 denoted 16 or more mitotic cells per 10 HPF.[8] The lymph nodes were classified according to Naruke and colleagues'[9] lymph node map for NSCLC. Contiguous and skip N2 metastases were defined as N2 node metastases with and without hilar node involvement, respectively.

A χ^2 test was used to evaluate the significance of the relationship between VPI and other clinicopathologic factors. Clinicopathologic factors were entered into univariate and multivariate analyses to determine which clinicopathologic factors had a greater effect on the 5-year survival. The median follow-up period for the 1074 living patients was 38 months. The length of survival was defined as the interval in months between the day of surgical resection of lung carcinoma and the date of either death or the last follow-up. An observation was censored at the last follow-up when the patients were alive or lost to follow-up. The survivals were calculated by the Kaplan-Meier method,[10] and univariate analyses were performed by the log-rank test.[11] Multivariate analyses were performed by using the

GTS

TABLE 1. Characteristics of 2 groups according to clinicopathologic factors

Characteristic	Non-VPI group, n (%)	VPI group, n (%)	*P* value	Total
Total	786 (73.2)	288 (26.8)		1074
Age (y)				
<65	390 (75.3)	136 (24.7)	.3426	526
≥65	496 (73.3)	152 (27.7)		548
Sex				
Male	426 (72.1)	165 (27.9)	.3667	591
Female	360 (74.5)	123 (25.5)		483
Histology				
Adenocarcinoma	643 (72.9)	239 (27.1)		882
Squamous cell carcinoma	107 (77.5)	31 (22.5)	.2512	138
Large cell carcinoma	16 (57.1)	12 (42.9)	.0662	28
Adenosquamous	20 (77.0)	6 (33.0)	.6437	26
Size (cm)				
≤3	505 (80.8)	120 (19.2)	<.0001	625
>3	281 (62.6)	168 (37.4)		449
Tumor differentiation*				
Well	384 (83.6)	81 (17.4)	<.0001	465
Moderate or poor	374 (66.5)	188 (33.5)		562
Pathologic N status				
N0	618 (78.8)	166 (21.2)		784
N1	78 (61.4)	49 (38.6)	<.0001†	127
N2	90 (55.2)	73 (44.8)	<.0001‡	163
Lymphatic invasion				
Negative	552 (83.0)	113 (17.0)	<.0001	665
Positive	234 (57.2)	175 (42.8)		409
Vascular invasion				
Negative	499 (84.6)	91 (15.4)	<.0001	590
Positive	287 (59.3)	197 (40.7)		484
Scar grade				
1 or 2	214 (93.4)	15 (6.6)	<.0001	229
3 or 4	572 (67.7)	273 (32.3)		845
Nuclear atypia grade				
1 or 2	437 (78.7)	118 (21.3)	<.0001	555
3	349 (67.2)	170 (32.8)		519
Mitotic index grade				
1 or 2	641 (74.6)	218 (25.4)	.0336	859
3	145 (67.4)	70 (32.6)		215
CEA (ng/mL)*				
<5.0	415 (79.8)	105 (20.2)	<.0001	520
≥5.0	210 (62.7)	125 (37.3)		335

VPI, Visceral pleural invasion; *CEA,* carcinoembryonic antigen. *Data are lacking in some patients for these characteristics. †The *P* value was calculated between the N0 and N1 groups. ‡The *P* value was calculated between the N0 and N2 groups. There were no significant differences between the N1 and N2 groups ($P = .2884$).

Cox proportional hazards model on StatView software (version 5.5; SAS Institute, Inc, Cary, NC).[12] Forward and backward stepwise procedures were used to determine the combination of factors that were essential in predicting prognosis.

Results

VPI was identified in 288 patients (26.8%; VPI group). Survival was 76.0% at 5 years and 53.2% at 10 years in the non-VPI group and was 49.8% at 5 years and 37.0% at 10 years in the VPI group (Figure 1). The difference between groups was highly significant ($P < .0001$).

The relationship between clinicopathologic prognostic factors and VPI is shown in Table 1. There were significantly more tumors with VPI in patients with a tumor of moderate or poor differentiation, positive lymphatic invasion, positive vascular invasion, high scar grade, high nuclear atypia grade, high mitotic index, and high serum carcinoembryonic antigen (CEA) level. VPI was observed in 19.2% of tumors 3 cm or smaller—this was significantly less frequent compared with 37.4% of tumors larger than 3 cm in their greatest dimension. VPI was also observed less frequently in N0 patients than in patients with nodal involvement (N1/2). However, regardless of tumor size (≤3 or >3 cm) or N status (N0 or N1/N2), there was a significant difference in survival according to VPI status (Figures 2 and 3).

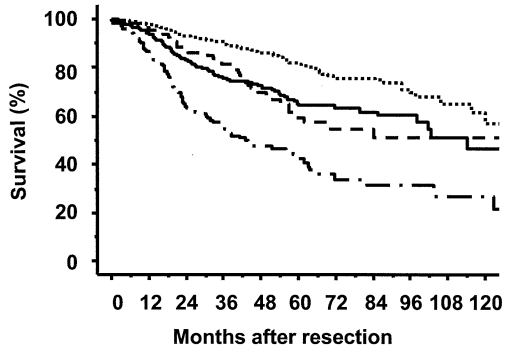
Among N2 patients, there was no statistically significant difference in node station multiplicity according to VPI status (N2 multiple-station patients: 30 of 73 VPI patients vs 38 of 90 non-VPI patients; $P = .8847$). However, when N2 patients were divided into skip and contiguous N2 groups, there were fewer skip N2 patients in the VPI group than in the non-VPI group (skip N2 patients: 17 of 73 VPI patients vs 36 of 90 non-VPI patients; $P = .0235$).

The 5-year survival according to clinicopathologic factors is shown in Table 2. The overall 5-year survival in the 1074 patients was 68.9%. Univariate analyses revealed the following clinicopathologic factors as significant: age, sex, tumor size, differentiation, pathologic N status, VPI, lymphatic invasion, vascular invasion, scar grade, nuclear atypia, mitotic index, serum CEA level, and type of surgical resection (Table 2).

By multivariate analyses, age at operation (patients 65 years or older), sex (male), tumor differentiation (moderate or poor), pathologic N status (N1/N2), VPI, lymphatic invasion, and vascular invasion were the independent poor-prognostic predictors for patients overall (Table 3). For pathologic stage I (N0) patients, multivariate analyses revealed the following independent poor-prognostic predictors: age at operation (patients 65 years or older), sex (male), VPI, lymphatic invasion, and vascular invasion (Table 4).

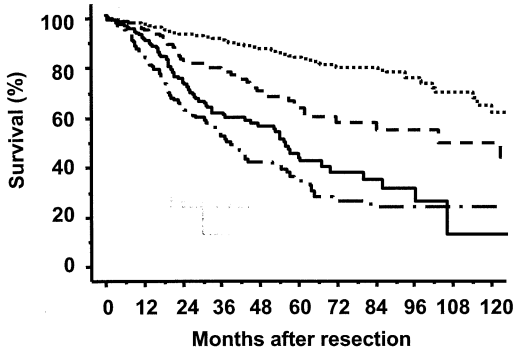
Discussion

In our study, VPI was observed in 26.8% of the surgically resected NSCLC specimens; this was higher than the 19.1% reported by Manac'h and colleagues[1] or the 23.6% by Takizawa and colleagues.[13] These reports, however, de-



	patients	p-stage (I / II / III)	5-yr survival (%)	10-yr survival (%)	p-value*
≦3cm without VPI	507	424 / 36 / 47	81.9	57.1	0.0006
≦3cm with VPI	120	87 / 12 / 21	57.5	51.4	0.9407
>3cm without VPI	279	194 / 42 / 43	65.2	46.7	<0.0001
>3cm with VPI	168	79 / 37 / 52	42.6	26.8	

Figure 2. Survival curves and overall 5- and 10-year survival of NSCLC patients according to visceral pleural invasion and tumor size. *P value by log-rank test.



	patients (n)	5-yr survival (%)	10-yr survival (%)	p-value*
non-VPI without N#	618	84.5	65.2	<0.0001
VPI without N #	166	63.7	50.2	
non-VPI with N#	168	42.2	13.0	0.0420
VPI with N#	122	33.2	22.4	

Figure 3. Survival curves and overall 5-year and 10-year survival of NSCLC patients according to visceral pleural invasion and lymph node metastasis. *P value by log-rank test; #lymph node metastasis (N1/N2).

GTS

scribed few technical details in VPI evaluation. We conducted uniform HE and Victoria blue–van Gieson stains on all tumors and performed histologic review in all cases with a special interest in VPI. Bunker and associates[14] reported that elastic stain results changed pathologic stages in 4% of resected lung carcinoma cases overall and VPI status in 10% of cases whose status was indeterminate by HE staining. Their results explain our high positive VPI rate.

We observed poor survival in patients with VPI regardless of nodal metastasis status. Brewer[15] speculated that poor prognosis of lung cancer in the subpleural location was attributable to rapid invasion of the pleura followed by diffuse dissemination of cancer cells throughout the pleural cavity by pleural fluid. Manac'h and associates[1] observed that VPI was more frequent in N2 patients and that there were more multiple-station N2 cases among them compared with N2 patients without VPI. They also demonstrated that cancer-related deaths were more frequent in patients with VPI and were mainly caused by distant metastases. Riquet and associates[16] demonstrated that positive pleural lavage cytology was correlated with the presence of VPI. Okiemy and associates[17] demonstrated that the lymphatic drainage of the medial portion of the diaphragmatic pleura traveled through the peritracheobronchial lymph node chains. These

TABLE 2. Clinicopathologic factors and 5-year survival in patients with surgically resected NSCLC by univariate analyses

Characteristic	No.	5-y survival (%)	*P* value
Total	1074	68.9	
Age (y)			
<65	526	73.5	.0007
≥65	548	63.5	
Sex			
Male	591	63.5	<.0001
Female	483	74.6	
Histology			
Adenocarcinoma	882	70.1	.0672
Nonadenocarcinoma	192	58.8	
Size (cm)			
≤3	625	77.3	<.0001
>3	449	56.7	
Tumor differentiation*			
Well	465	82.9	<.0001
Moderate or poor	562	55.4	
Pathologic N status			
N0	784	80.3	<.0001
N1 or N2	290	38.2	
Visceral pleural invasion			
Negative	786	76	<.0001
Positive	288	49.8	
Lymphatic invasion			
Negative	665	82.7	<.0001
Positive	409	46	
Vascular invasion			
Negative	584	84.4	<.0001
Positive	490	48.4	
Scar grade			
1 or 2	229	88.5	<.0001
3 or 4	845	61	
Nuclear atypia grade			
1 or 2	555	78.3	<.0001
3	519	57.2	
Mitotic index grade			
1 or 2	859	73.1	<.0001
3	215	51.7	
CEA (ng/mL)*			
<5.0	520	78.5	<.0001
≥5.0	335	56.6	
Type of resection			
Pneumonectomy or bilobectomy	77	45.8	<.0001†
Lobectomy	975	70.7	
Segmentectomy	22	46.1	

NSCLC, Non–small cell lung cancer; *CEA,* carcinoembryonic antigen. *Data are lacking in some patients for these characteristics. †The *P* value was calculated between the lobectomy group and the pneumonectomy or bilobectomy group. There were no significant differences between the lobectomy group and the segmentectomy group ($P = .2738$) or between the pneumonectomy or bilobectomy group and the segmentectomy group ($P = .1630$).

TABLE 3. Multivariate analyses of prognostic factors in NSCLC patients overall

Variable	Hazard ratio	95% CI	*P* value
Age (≥65 vs <65)	1.665	1.300-2.133	<.0001
Sex (male vs female)	1.373	1.061-1.776	.0159
Differentiation (moderate or poor vs well)	1.545	1.157-2.062	.0032
Pathologic N status (N1 or N2 vs N0)	2.309	1.738-3.067	<.0001
Visceral pleural invasion (positive vs negative)	1.670	1.299-2.148	<.0001
Lymphatic invasion (positive vs negative)	1.421	1.062-1.902	.0180
Vascular invasion (positive vs negative)	2.062	1.536-2.769	<.0001

NSCLC, Non–small cell lung cancer; *CI,* confidence interval.

TABLE 4. Multivariate analyses of prognostic factors in patients with pathologic stage I (N0) NSCLC

Variable	Hazard ratio	95% CI	*P* value
Age (≥65 vs <65)	2.639	1.835-3.797	<.0001
Sex (male vs female)	2.121	1.463-3.077	<.0001
Visceral pleural invasion (positive vs negative)	1.626	1.121-2.360	.0104
Lymphatic invasion (positive vs negative)	1.882	1.301-2.723	.0008
Vascular invasion (positive vs negative)	2.192	1.512-3.179	<.0001

NSCLC, Non–small cell lung cancer; *CI,* confidence interval.

observations suggest a possible cancer cell pathway from a tumor with VPI through the pleural cavity and diaphragmatic lymph drainage into the mediastinal lymph nodes. Such a pathway should result in more extensive mediastinal node involvement and, because the pathway bypasses pulmonary/hilar lymphatics, in more skip N2 metastases. However, we observed no relationship between VPI and N2 station multiplicity. We even found fewer skip N2 patients in the VPI group than in the non-VPI group ($P = .0235$). Kondo,[18] Buhr,[19] Dresler,[20] and their associates demonstrated that pleural lavage cytology status was not correlated with node status. From these findings, we suggest a possible VPI tumor cell pathway through the subpleural lymphatics and hilar lymph nodes into the mediastinal lymph nodes.

Several clinicopathologic prognostic factors for NSCLC have been identified. These factors include vascular invasion,[21,22] lymphatic invasion, degree of nuclear atypia,[21] mitotic index,[21,22] degree of histologic differentiation,[23,24]

GTS

serum CEA level[25] and other histologic parameters associated with stromal invasion, such as scar grade.[24,26] We found significant and positive association between positive VPI and all these poor-prognostic factors (Table 1). Vascular invasion,[21,22] lymphatic invasion,[21] and scar grade[24,26] are morphologic parameters indicative of tumor invasiveness. Histologic differentiation,[22,23] nuclear atypia,[21] mitotic index,[21,22] and serum CEA level[25] are indicative of tumor proliferation and aggressiveness. Our findings suggest that VPI in NSCLC patients indicates an invasive and aggressive tumor biology. We believe that the invasive and aggressive nature of tumor with VPI is highly contributory to poor prognosis of VPI NSCLC patients.

In conclusion, VPI is a significant and independent poor-prognostic predictor regardless of tumor size or N status. VPI is a good indicator of NSCLC invasiveness and aggressiveness. Patients with a tumor with VPI may benefit from adjuvant chemotherapy.

We thank Professor J. Patrick Barron (International Medical Communication Center, Tokyo Medical University) for reviewing the English manuscript.

References

1. Manac'h D, Riquet M, Medioni J, Le Pimpec-Barthes F, Dujon A, Danel C. Visceral pleura invasion by non-small cell lung cancer: an underrated bad prognostic factor. *Ann Thorac Surg.* 2001;71:1088-93.
2. Ichinose Y, Yano T, Asoh H, Yokoyama H, Yoshino I, Katsuda Y. Prognostic factors obtained by a pathologic examination in completely resected non–small cell lung cancer: an analysis in each pathologic stage. *J Thorac Cardiovasc Surg.* 1995;110:601-05.
3. Shimizu K, Yoshida J, Nagai K, Nishimura M, Yokose T, Ishii G, et al. Visceral pleural invasion classification in non-small cell lung cancer: a proposal on the basis of outcome assessment. *J Thorac Cardiovasc Surg.* 2004;127:1574-8.
4. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-7.
5. Naruke T, Suemasu K, Ishikawa S. Surgical treatment for lung cancer with metastasis to mediastinal lymph nodes. *J Thorac Cardiovasc Surg.* 1976;71:279-85.
6. The World Health Organization histological typing of lung tumors. 3rd ed. Geneva: World Health Organization; 1999.
7. The Japan Lung Cancer Society. General rule for clinical and pathological record of lung cancer [in Japanese]. 5th ed. Tokyo: Kanehara; 1999.
8. Suzuki K, Nagai K, Yoshida J, Nishimura M, Takahashi K, Yokose T, et al. Conventional clinicopathologic prognostic factors in surgically resected nonsmall cell lung carcinoma. A comparison of prognostic factors for each pathologic TNM stage based on multivariate analyses. *Cancer.* 1999:86:1976-84.
9. Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg.* 1978;76:832-9.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-81.
11. Peto R, Peto J. Asymptomatically efficient rank invariant test procedures (with discussion). *J R Stat Soc A.* 1972;135:185-207.
12. Cox D. The analysis of binary data. London: Methuen; 1970.
13. Takizawa T, Terashima M, Koike T, Watanabe T, Kurita Y, Yokoyama A, et al. Lymph node metastasis in small peripheral adenocarcinoma of the lung. *J Thorac Cardiovasc Surg.* 1998;116:276-80.
14. Bunker ML, Raab SS, Landreneau RJ, Silverman JF. The diagnosis and significance of visceral pleural invasion in lung carcinoma. Histologic predictors and the role of elastic stains. *Am J Clin Pathol.* 1999;112:777-83.
15. Brewer LA. Patterns of survival in lung cancer. *Chest.* 1977;71:644-50.
16. Riquet M, Badoual C, Le Pimpec Barthes F, Lhote FM, Souilamas R, Hubsch JP, et al. Visceral pleura invasion and pleural lavage tumor cytology by lung cancer: a prospective appraisal. *Ann Thorac Surg.* 2003;75:353-5.
17. Okiemy G, Foucault C, Avisse C, Hidden G, Riquet M. Lymphatic drainage of the diaphragmatic pleura to the peritracheobronchial lymph nodes. *Surg Radiol Anat.* 2003;25:32-5.
18. Kondo H, Asamura H, Suemasu K, Goya T, Tsuchiya R, Naruke T, et al. Prognostic significance of pleural lavage cytology immediately after thoracotomy in patients with lung cancer. *J Thorac Cardiovasc Surg.* 1993;106:1092-7.
19. Buhr J, Berghauser KH, Gonner S, Kelm C, Burkhardt EA, Padberg WM. The prognostic significance of tumor cell detection in intraoperative pleural lavage and lung tissue cultures for patients with lung cancer. *J Thorac Cardiovasc Surg.* 1997;113:683-90.
20. Dresler CM, Fratelli C, Babb J. Prognostic value of positive pleural lavage in patients with lung cancer resection. *Ann Thorac Surg.* 1999; 67:1435-9.
21. Takise A, Kodama T, Shimosato Y, Watanabe S, Suemasu K. Histopathologic prognostic factors in adenocarcinomas of the peripheral lung less than 2 cm in diameter. *Cancer.* 1988;61:2083-8.
22. Kurokawa T, Matsuno Y, Noguchi M, Mizuno S, Shimosato Y. Surgically curable "early" adenocarcinoma in the periphery of the lung. *Am J Surg Pathol.* 1994;18:431-8.
23. Eto T, Suzuki H, Honda A, Nagashima Y. The changes of the stromal elastotic framework in the growth of peripheral lung adenocarcinomas. *Cancer.* 1996;77:646-56.
24. Fukushima M, Fukuda Y, Kawamoto M, Yamanaka N. Elastosis in lung carcinoma: immunohistochemical, ultrastructural and clinical studies. *Pathol Int.* 2000;50:1004-13.
25. Takamochi K, Nagai K, Suzuki K, Yoshida J, Ohde Y, Nishiwaki Y. Clinical predictors of N2 disease in non–small cell lung cancer. *Chest.* 2000;117:1577-82.
26. 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.

GTS