using CT scans for 10 years and demonstrated no changes in residual lesions. These cases suggest that multiplicity of pulmonary sclerosing hemangioma does not necessarily imply biological aggressiveness. Biological behavior might be different between solitary and multiple cases. However, further analysis of a larger group of patients is required.

In conclusion, we reported a rare case of multiple sclerosing hemangiomas of the lung unchanged for over 10 years. This case and review of the literature suggest that the multiplicity of multiple sclerosing hemangiomas does not necessarily indicate a dismal outcome.

Acknowledgments

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Limited resection trial for pulmonary ground-glass opacity nodules: Fifty-case experience

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Dr Yoshida

Objective: This study was undertaken to determine the recurrence rate after limited resection of small lung carcinoma and to evaluate intraoperative frozen-section examination accuracy for Noguchi classification.

Methods: Enrollment requirements were as follows: pulmonary nodule 2 cm or smaller, diagnosed or suspected clinical T1 N0 M0 carcinoma in the lung periphery, and ground-glass opacity findings and lack of evident pleural indentations or vascular convergence on high-resolution computed tomographic scan. A wedge or segmental resection specimen, removed with custom stapler cartridges, was immediately reinflated and examined by frozen-section with hematoxylin-eosin and Victoria blue–van Gieson stains. If the tumor was confirmed as Noguchi type A or B with resection margins greater than 1 cm, the patient was closed and followed up on an outpatient basis. End points were 5-year disease-free survival and intraoperative classification accuracy.

Results: From August 1998 through October 2002, a total of 50 patients were enrolled (20 men and 30 women, ages 30-77 years). Tumor sizes ranged from 2 to 21 mm (11 mm average). There were 2 Noguchi type A tumors, 23 Noguchi type B tumors, 15 Noguchi type C tumors, 5 atypical adenomatous hyperplasias, 4 fibroses, and 1 granuloma. Frozen-section accuracy was approximately 98% (39/40). One intraoperative type B diagnosis was revised to type C after postoperative pathologic study. No morbidity, mortality, or recurrence has been seen with a median follow-up of 50 months.

Conclusion: Noguchi type A and B tumors may well be in situ carcinomas, and frozen-section examination was highly accurate. Neither local recurrence nor distant metastases have been found to date. Limited resection initial results appear promising.

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The Lung Cancer Study Group has performed the only prospective, randomized trial of limited resection versus lobectomy to date. They concluded that lobectomy was the appropriate surgical treatment for T1 N0 M0 non–small cell lung carcinomas, because limited resection resulted in greater local recurrence.[1] The Lung Cancer Study Group trial did not include many small cancers, and ground-glass opacity (GGO)[2] nodules were not recognized at the time of the study. Since then, several researchers have reported, although in retrospective study designs, that limited resection could be an acceptable alternative for patients with T1 N0 M0 disease.[3,4] We decided to do more investigations and evaluations. In 1998, we reviewed peripheral lung cancers smaller than 1 cm in diameter and found that almost half of them displayed an invasive nature. We concluded that tumor size alone cannot be a positive indicator for limited resection.[5]

Shimosato and colleagues[6] retrospectively evaluated cancer fibrotic focus or scarring and patient prognosis. They found that increasing fibrotic focus or scarring

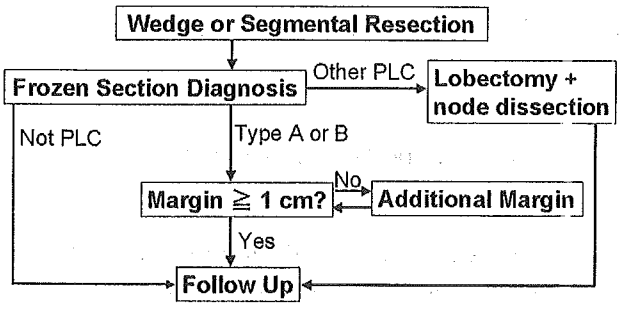

Figure 1. Treatment sequence. *PLC,* Primary lung cancer

GTS

was positively related to pleural invasion, lymph node metastasis, and blood vessel invasion. Patient prognosis was poorer with increased focus or scarring. They believed that scarring and resulting pleural indentations occurred with tumor development.

Noguchi and associates[7] developed a six-category classification for lung adenocarcinomas less than 2 cm in diameter. They concluded, on the basis of histologic characteristics and outcomes, that localized bronchioloalveolar carcinoma (type A) and localized bronchioloalveolar carcinoma with foci of collapse (type B) were pathologically and biologically in situ noninvasive peripheral carcinomas, whereas localized bronchioloalveolar carcinoma with foci of fibroblastic proliferation (type C) was an advanced invasive stage of types A and B. This differentiation required careful histologic examination.

We speculated that if Noguchi type A and B tumors truly are in situ, noninvasive carcinomas, limited resection might be the procedure of choice. With this goal in mind, we developed some unique tools and methods for intraoperative diagnosis of these tumor types. With these methods, we found that we were able to reliably differentiate Noguchi types A and B from type C during the surgical procedure. As a result, in 1998 at our institution we started a prospective limited resection clinical trial to confirm the reliability of the tumor type differentiation methods and to determine the survival of those with limited resection based on the tumor differentiation results for probable in situ adenocarcinoma in the lung periphery. We describe the study design, unique tools and methods, and preliminary results after completion of the planned 50 patient enrollment.

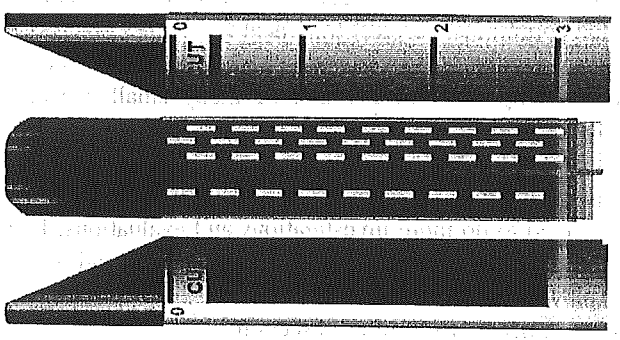

Figure 2. Customized stapler (ENDO-GIA 30 3.5/3-1; Tyco Healthcare Japan, Tokyo, Japan).

Patients and Methods

Our objectives were to evaluate intraoperative frozen-section examination in the identification of Noguchi type A or B tumors, to perform limited resection for Noguchi A and B and other benign or noninvasive nodules, and to determine the extent of local recurrence or distant metastases in all patients at 5-year follow-up. Enrollment required patients with a tumor less than 2 cm in diameter diagnosed or suspected as a clinical T1 N0 M0 carcinoma in the lung periphery on the basis of a computed tomographic (CT) scan. They had to have a high-resolution CT scan with findings suggestive of a Noguchi type A or B tumor: GGO and lack of evident pleural indentations or vascular convergence.[8] Written informed consent was obtained from each participant. Patients with a malignancy history within the past 5 years and those not candidates for lobectomy and systematic lymph node dissection were excluded.

Figure 1 shows the treatment flow chart. We performed wedge or segmental resection, depending on the tumor location. When a tumor was deep in the middle of a segment, segmentectomy was chosen. Also, when a tumor could not be localized during surgery, we performed a segmentectomy to avoid missing the tumor. Our pathologist (T.Y.) examined the frozen-section specimen immediately. If the tumor was confirmed as Noguchi type A or B with a resection margin greater than 1 cm, the patient was closed up and followed up on an outpatient basis. If the margin was not sufficient, additional margin was resected. If the tumor was a primary malignancy, but not type A or B, lobectomy and systematic lymph node dissection were performed. Patients are followed up on an outpatient basis at least every 6 months by physical check-up, plain chest radiograph, and laboratory tests. Patients who underwent limited resection for Noguchi type A or B disease have chest CTs every year.

It is fairly difficult to perform Noguchi classification from a simple frozen section. To facilitate the examination, we used several innovative tools and techniques in our trial. We believe these contributed significantly to the trial results. Figure 2 shows the stapler cartridge (ENDO-GIA 30 3.5/3-1; Tyco Healthcare Japan, Tokyo, Japan), custom modified as requested by our chief thoracic surgeon (K.N.). Rather than three lines of staples on both sides, it has a single staple line on the black, resected specimen side. This makes it easier to cut a narrow pathologic examination specimen margin strip for negative cut-end confirmation.

With no obvious specimen bronchus or bronchiole for phosphate-buffered saline solution injection, specimen inflation to facilitate alveolar structure observation is difficult. To inflate the resected specimen's alveolar structure, our pathologist used a technique known, but not normally used in neoplastic lung disease diagnosis.[9] With the specimen in a closed, phosphate-buffered saline solution–filled syringe, the piston was pulled back quickly and repeatedly, reinflating the alveolar structure by replacing alveolar air with phosphate-buffered saline solution (Figure 3). After

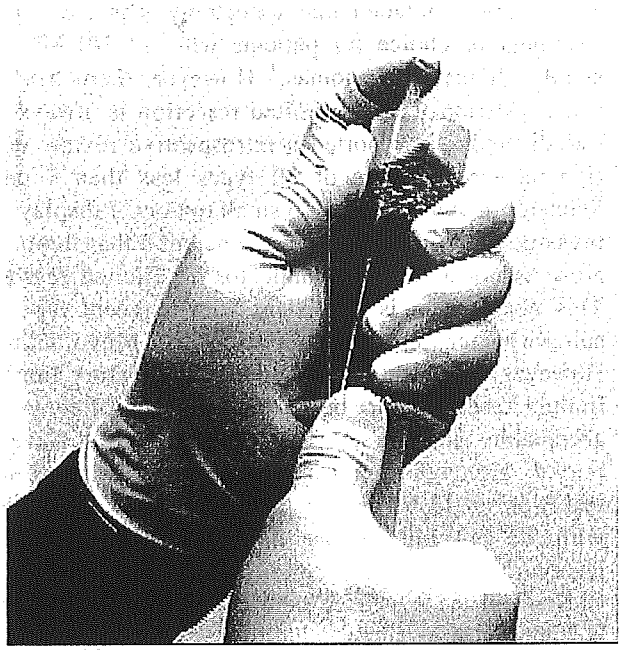

Figure 3. Specimen vacuum reinflation.

slicing the specimen into 2-mm thick slices and a second reinflation, the pathologist stereoscopically examined the slices, looking for the most severe structure destruction indications. The maximum stromal destruction slices or the largest area slice were cut by cryostat, stained with hematoxylin-eosin, and examined microscopically.

In addition to routine hematoxylin-eosin staining, our pathologist (T.Y.) thought Victoria blue–van Gieson (VvG) staining would improve Noguchi classification accuracy, because it reveals whether the alveolar wall elastic fibers are intact,[10] providing a powerful aid in improving intraoperative classification accuracy. If the elastic fibers were destroyed by tumor cells, as shown in Figure 4, *A*, the tumor was diagnosed as Noguchi type C, whereas if they were intact, as in Figure 4, *B*, the classification was type A or B. This diagnostic judgment was based on our group's previous report (Yokose and associates[11]) that patients without stromal destruction, as shown by VvG staining, survived 5 years without recurrence.

Noguchi and associates[7] reported no cancer recurrences at 5 years after lobectomy and lymph node dissection in the type A and B population.[7] Statistically, it is impossible to compare the limited resection outcome for these tumors with the event-free standard surgery outcome. We reported an 85% 5-year survival rate among patients with tumors 2 cm or smaller and T1 N0 M0 pathologic class who underwent lobectomy and systematic lymph node dissection at our institution.[12] Allowing 4 local recurrences in 50 patients, a 90% confidence interval of 86% to 98% results, and the lower limit would be better than our earlier study. We therefore decided to recruit 50 patients, with a trial-quitting rule of 5 local recurrence cases.

The first end point was accurate frozen-section examination results for carcinoma invasiveness. The second, and more important, end point was 5-year disease-free survival. This study protocol was reviewed by the National Cancer Center Hospital East institutional review board and was approved in July 1998.

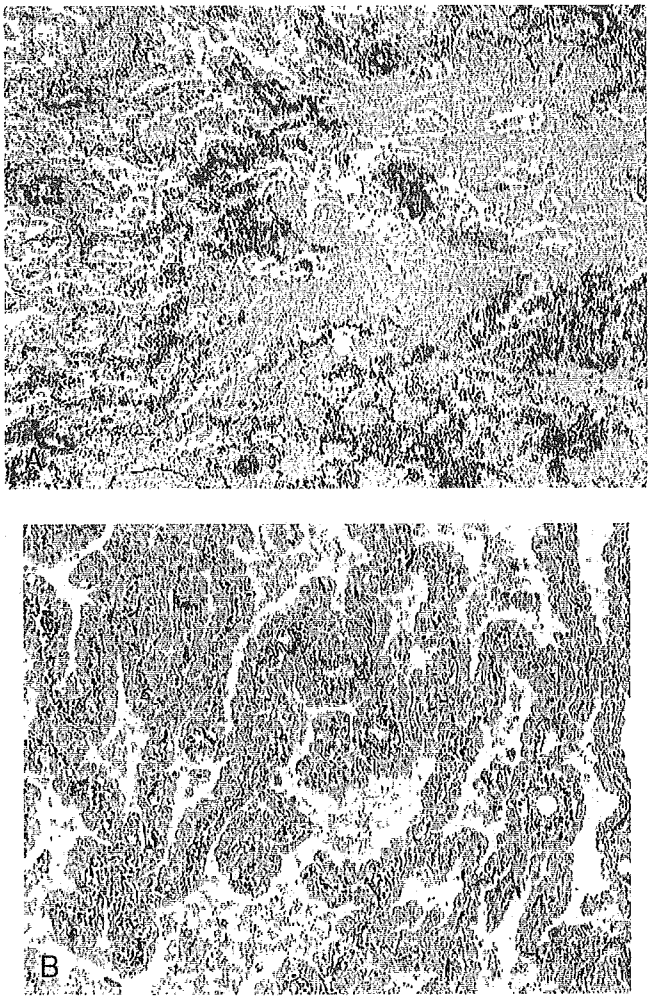

Figure 4. VvG staining showing elastic fiber destruction in type C tumor (A) and intact elastic fibers in type A tumor (B). (Magnification 100×.)

Results

This prospective study (August 1998–October 2002) enrolled 50 patients comprising only 5.3% of all patients with resected lung cancer at our institution during this period. There were 20 men and 30 women, with ages ranging from 30 to 77 years (average 61 years). Tumor sizes ranged from 2 to 21 mm (average 11 mm). Thirty patients had wedge resection, 6 segmentectomy, and 14 lobectomy with lymph node dissection. Nineteen of the 30 wedge procedures were performed thoracoscopically by three-port access, and the other 11 needed a small thoracotomy.

Three-port procedures were performed when the tumor was subpleural or when the tumor was shallow or hard

TABLE 1. Histologic subtype and tumor size distribution in resected specimens

Subtype	No. of cases	Range (mm)	Median (mm)	Resection type (W/S/L)
Type A	2	9-10	—	1/1/0
Type B	23	6-21	12	21/2/0
Type C	15	10-19	14	1/0/14
Atypical adenomatous hyperplasia	5	5-14	8	2/3/0
Fibrosis	4	6-15	10	4/0/0
Granuloma	1	6	—	1/0/0

W/S/L, Wedge resection/segmentectomy/lobectomy plus lymph node dissection, in numbers of patients.

enough to directly palpate with one or two fingers through the ports. Initially, because of the nature of GGOs, we were not sure that we would be able to palpate and localize these lesions. However, we found the GGO-containing lung parenchyma to have a different texture than the surrounding normal parenchyma. When it was impossible to determine the tumor location or periphery through the thoracoscopy ports, the procedure was converted to a small thoracotomy. Segmentectomy and lobectomy were done through a muscle-sparing thoracotomy, typically about 12 cm in length.

During the trial, Noguchi classification assessment took about an hour because of the extensive image recording required for study purposes. There were 2 Noguchi type A tumors, 23 Noguchi type B tumors, 15 Noguchi type C tumors, 5 atypical adenomatous hyperplasias (AAH), 4 fibroses and 1 granuloma. Their size distribution is summarized in Table 1. In addition to the intraoperative slides, further postoperative slides were prepared and studied. The postoperative slides did not differ significantly from the intraoperative slides. One initial frozen-section type B diagnosis was revised to type C after postoperative pathologic study. We discussed this with the patient in detail, and he chose not to have any further treatment. He is still alive without any signs of recurrence after more than 5 years.

No morbidity or mortality has been seen. During the follow-up period, with a range of 19 to 68 months (median 50 months), as this is being written (May 2004), there have been no recurrences. Enrollment concluded without a forced quit.

Discussion

The Lung Cancer Study Group conducted a prospective randomized trial to evaluate the role of limited resection versus lobectomy for T1 N0 M0 non–small cell lung carcinomas. They reported significantly increased local recurrence and marginally but not significantly higher cancer death rates in the limited resection group relative to the lobectomy group. On the basis of their observations, they concluded that lobectomy was the surgical treatment of choice for patients with T1 N0 M0 non–small cell lung carcinomas.[1] However, there has been some question whether limited resection is always contraindicated. We reported a retrospective review of peripheral lung cancers of all types less than 1 cm in diameter in 1998.[5] Of the 16 small tumors, 7 displayed an invasive nature. We therefore concluded that tumor size alone is not a sufficient indicator for limited resection. This observation is consistent with a recent report on subcentimeter lung cancers from the Mayo Clinic.[13] However, in patients with impaired respiratory function, limited resection has been tried and has often yielded acceptable outcomes.[14] Several researchers have reported, although in retrospective studies, that limited resection could be an acceptable alternative in patients with T1 N0 M0 disease and insufficient pulmonary reserve.[3,4]

Noguchi and associates[7] conjectured that type A and type B tumors are in situ carcinomas, whereas type C is an advanced stage of types A and B. If Noguchi type A and B peripheral tumors are truly in situ, noninvasive carcinomas, limited resection would be the management of choice for these tumors. As a result, in August 1998 we started this prospective clinical trial with intraoperative frozen-section examination to establish the Noguchi classification and limited resection for probable in situ adenocarcinoma with GGO characteristics in the lung periphery.

As noted, Shimosato and associates[6] evaluated cancer fibrotic focus or scarring and patient prognosis. Increased lymph node metastasis and pleural and blood vessel invasion were present with greater scarring and fibrotic focus. Aoki and colleagues[15] noted the pleural indentation and vascular convergence increased with tumor development in Noguchi type B and C tumors. This information was incorporated into our patient selection criteria.

A concern in our trial was the accuracy of frozen-section examination. The correct classification as atypical adenomatous hyperplasias or Noguchi type A,[16] or as Noguchi type B or type C tumors,[7] has been reported as being difficult, even more so with frozen sections. We think that the equipment developed for this trial and the methods and techniques applied contributed significantly to our outcomes. Finding the GGO "spongelike" structure could be felt in the lung made locating the lesion and ensuring sufficient resection margin much easier. The customized stapling cartridge and negative-pressure specimen inflation were useful in frozen-section preparation. They made it much easier to work with the specimen. Stereoscopic microscopy enabled the pathologist to locate regions of interest for detailed examination. For Noguchi subtype determination, VvG staining proved to be a powerful aid in separating Noguchi type A and B

from type C. These tools, methods, and techniques, together with the expertise of our pathologist, resulted in high frozen-section examination accuracy: only 1 type B lesion in 50 cases was recategorized as type C postoperatively. This patient underwent only a wedge resection and, after being fully informed of the underdiagnosis, potential outcomes, and additional treatment options, decided not to undergo any further treatment. He is still alive after more than 5 years without recurrence.

The other patients with 14 Noguchi type C tumor, whose diagnoses were confirmed by postoperative pathologic study, underwent lobectomy and systematic lymph node dissection after the frozen-section diagnosis. Detailed pathologic study after the operation revealed no nodal involvement, pulmonary metastases, lymphatic permeation, or vascular invasion in the specimens. It is likely that these patients will survive. Kondo and colleagues[17] studied air-containing lesions 2 cm or smaller, including GGO or subsolid tumors. These lesions were of interest if their opacity area decreased by more than 50% on the mediastinum-setting CT from the lung-setting CT. They reported that this patient cohort survived 5 years without recurrences after either standard or limited resection, and most of them had no node metastases or vessel involvement. So although Noguchi type C tumors are invasive, they may well represent an early invasive stage. On the basis of our finding of no nodal involvement, lymphatic permeation, or vascular invasion, and Kondo and colleagues' similar results and survival rates,[17] we conjecture that Noguchi type C tumors in our trial might well also have been curatively treated by limited resection. However, we did not address this issue in our trial.

During the trial, Noguchi classification assessment took about an hour. This was mostly because we extensively recorded sample images for study purposes. Our pathologist believes that in routine practice, without extensive image recording, the determination can be accomplished in 15 to 20 minutes.

There was no definite difference in size distribution among subtypes. However, all Noguchi type C tumors were 1 cm or larger, whereas other subtypes included subcentimeter tumors. This strengthens the suggestion that limited resection is indicated when a GGO tumor is smaller than 1 cm. Although this contradicts our previous review[5] and a recent report on subcentimeter lung cancers by the Mayo Clinic,[13] that is probably because those series included non-GGO lesions.

In conclusion, Noguchi classification type A and B tumors appear to be in situ, noninvasive carcinomas, and limited resection achieves the goals of local control and survival. With about 5.5 years total on this study, it may be still too early for strong conclusions. Considering the probable slow-growing nature of GGO lesions,[18] 5 years of follow-up is not long enough to conclude that the disease is cured. We will probably have to continue our follow-up for an additional 5 years. However, initial results are encouraging. With the customized stapling cartridges, negative-pressure specimen preparation and inflation, stereoscopic microscopy, VvG staining, and a skilled pathologist, frozen-section classification of Noguchi subtype has been highly accurate. Our results suggest that lung tumors 2 cm or less in diameter with high-resolution CT scan findings of GGO and without evident pleural indentations or vascular convergence may be safely managed with only limited resection.

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GTS

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

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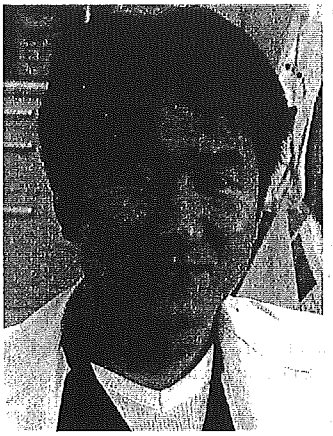

Dr Shimizu

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.

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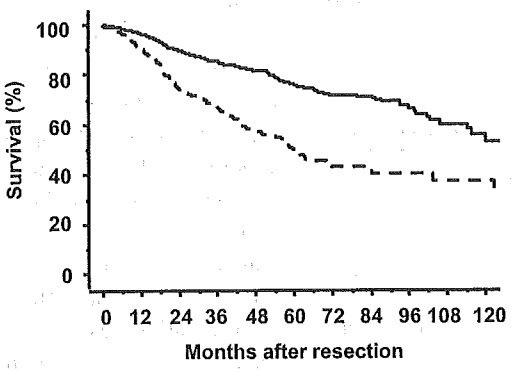
Visceral pleural invasion (VPI) is one of the most important prognostic factors in patients who undergo complete resection for non–small cell lung cancer (NSCLC).[1-3] VPI was adopted as a specific description in the TNM classification of the International Union Against Cancer staging system in the mid 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



		patients (n)	5-yr survival (%)	10-yr survival (%)	p-value*
non-VPI group	——	786	76.0	53.2	< 0.0001
VPI group	- - -	288	49.8	37.0	

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

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).

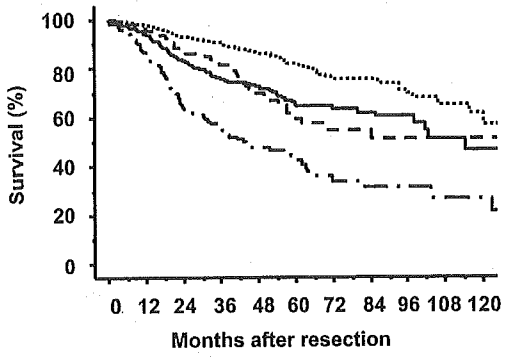
Among N2 patients, there was no statistically significant difference in node station multiplicity according to VPI status (N2 multiple-station patients: 30 of 73 VPI patients vs 38 of 90 non-VPI patients; $P = .8847$). However, when N2 patients were divided into skip and contiguous N2 groups, there were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

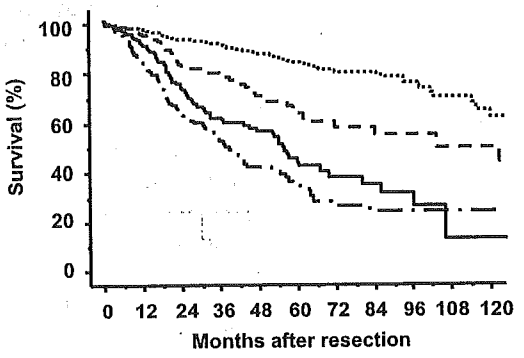
Discussion

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).

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

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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]

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.

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Pleural Lavage Cytology Before and After Lung Resection in Non-Small Cell Lung Cancer Patients

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Background. The aim of this study was to analyze on a multivariate basis the prognostic significance of pre-resection and post-resection pleural lavage cytologies in surgically resected primary non-small cell lung cancer (NSCLC) patients, in relation to pathologic TNM factors in a large cohort of almost 1,200 patients.

Methods. From August 1992 through March 2001, pleural lavage cytology (PLC) was performed in 1,214 NSCLC patients without pleural effusion or dissemination undergoing pulmonary resection. The cytologic evaluation was classified into three categories: negative, suggestive, and positive. To investigate the impact on patient survival, PLC results were analyzed with conventional clinicopathologic factors.

Results. Definitive pre-resection PLC result was obtained in 1,194 patients and 38 had a positive result. The 5-year survival rates were 27% if pre-resection PLC was positive and 71% if negative. Of 1,198 patients 54 had a positive post-resection PLC result. The 5-year survival rates were 10% if post-resection PLC was positive and 73% if negative. On multivariate analysis, post-resection PLC was an independent prognostic factor as significant as established clinicopathologic factors.

Conclusions. Pre-resection and post-resection PLC should be recognized as an essential prognostic factor and should be performed in NSCLC patients without pleural effusion and dissemination. Post-PLC, compared with pre-PLC, had a greater and independent impact on survival and needs to be incorporated in the pathologic staging of NSCLC in the future.

(Ann Thorac Surg 2006;81:298–304)

Pleural lavage cytology (PLC) has been reported to be a possible prognostic factor in patients with resected non-small cell lung cancer (NSCLC). However, many of the reports are that only PLC immediately after thoracotomy, before lung resection, (pre-PLC) has been studied in detail. The pre-PLC impact on patient outcome has been studied, chiefly, on a univariate basis and has not been studied in relation to the conventional pathologic TNM by multivariate analysis. Although pre-PLC has been reported to be a poor prognosis predictor, a positive result is currently not recognized as equivalent to T4 or a factor indicating incomplete resection. Although PLC after radical NSCLC resection, before chest closure, (post-PLC) has also been studied, significance of post-PLC remains controversial. Higashiyama and associates [1] performed pre-PLC and post-PLC in 325 lung cancer patients, but neither pre-PLC nor post-PLC results were an independent prognostic factor. Dresler and associates [2], who reported the pre-PLC and post-PLC analysis in 137 patients, stated that the 3-year survival rate was significantly better in negative post-PLC patients than in positive patients. We thought further analyses on post-PLC were needed. In the present study, we analyzed both pre-PLC and post-PLC on a multivariate basis, in relation to pathologic TNM factors in a large cohort of almost 1,200 patients.

Material and Methods

From August 1992 through March 2001, a total of 1,387 patients underwent surgical resection for primary NSCLC at the National Cancer Center Hospital East. Intraoperative PLC, which was approved for this observational study by the institutional review board, was prospectively performed in all patients without pleural effusion and dissemination, totaling 1,214 patients, and all were enrolled in this study. As the largest sample size for PLC study was 1,000 before this study, we aimed at accruing well more than 1,000 patients before analysis. Preoperative evaluation included a detailed history, physical examination, bronchoscopy, contrast-enhanced computed tomography (CT) of the chest, and distant metastasis screening (bone, brain, liver, and adrenals). Histologic typing was determined according to the World Health Organization classification [3]. Disease stages were determined based on the TNM classification of the International Union Against Cancer [4]. Immediately after

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thoracotomy, the pleural cavity was carefully washed with 500 mL physiologic saline before any pulmonary parenchyma manipulation. A sample of 50 mL was retrieved for cytologic evaluation (pre-PLC). We performed lung resection (segmentectomy or greater) and complete mediastinal lymph node dissection in 1,199 patients, and lung resection and mediastinal lymph node sampling in 15 patients. Before chest closure, a pleural cavity lavage sample was also retrieved (post-PLC) in the same fashion as pre-PLC. Samples were centrifuged at 1,500 rpm for 5 minutes. The sediment was stained using Papanicolaou's methods. A single cytologist blinded to the clinical-pathologic information evaluated the specimen and classified it into three categories: Papanicolaou classes I and II as negative, class III as suggestive, and classes IV and V as positive. In the survival analyses, we studied only cases with definitive cytologic diagnoses, excluding Papanicolaou class III. To investigate the impact on patient survival, the following conventional clinicopathologic factors were reviewed and analyzed: age, gender, smoking index (< 400 vs ≥ 400), serum carcinoembryonic antigen (CEA) level (< 5.0 mg/mL vs ≥ 5.0 mg/mL), clinical T factor (cT: cT2-4 vs cT1), clinical lymph node status (cN: mediastinal node involvement as cN2 vs less extensive as cN0-1), histologic type of tumor (adenocarcinoma versus others), pleural involvement of surgical (sP0-1 vs sP2-3) and pathologic finding (p0 vs p1-3), lymphatic invasion (positive versus negative), vascular invasion (positive versus negative), pathologic N status (pN: pN2-3 vs pN0-1), degree of fibrotic scarring (scar grade 1-2 vs grade 3-4), nuclear atypia (grade 1 or 2 vs grade 3), mitotic activity (mitotic index 1 or 2 vs 3), and surgical resection completeness (incomplete versus complete). Complete resection was defined as negative surgical margin and no highest mediastinal lymph node involvement. Incomplete resection was defined as positive surgical margin or highest mediastinal lymph node involvement. The smoking index was defined as the product of the number of cigarettes smoked per day and the number of years of smoking. We defined cN2 as mediastinal lymph node(s) greater than 1.0 cm in the shortest dimension on preoperative conventional CT. Pleural involvement was classified according to the Japan Lung Cancer Society criteria: p0; tumor did not extend beyond the elastic pleural layer, p1; tumor invaded the visceral pleura elastic layer but was not exposed on the pleural surface, p2; tumor was exposed on the pleural surface and p3; tumor invaded the parietal pleura or chest wall. Surgeons determined pleural involvement (sP factor) macroscopically before resection. Pathologic pleural involvement (p factor) were diagnosed on the resected specimens by a single pathologist blinded to the surgeons' findings [5]. Lymphatic invasion and vascular invasion indicated tumor cells identifiable in the lymphatic and vascular vessel lumen, respectively. Scar grade was classified into 4 grades: grade 1; tumor had foci of alveolar collapse with resulting condensation of elastic fibers but no or minimal fibroblastic tissue with collagen, grade 2; tumor had fibroblastic tissue with a small amount of collagen fibers, grade 3; tumor had fibroblastic tissue with moderate or abundant amount of collagen fibers, and grade 4; tumor showed hyalinization [6]. Nuclear atypia categorization was based on the most atypical nuclei on sections and divided into 3 grades as follows: grade1; nuclei that were uniform in size and equal to or only slightly larger than those of reactive type II alveolar epithelial

Table 1. Patient Characteristics (n = 1,214)

Characteristics	Results	
Gender		
Male	781	(64)
Female	433	(36)
Histology		
Adenocarcinoma	792	(65)
Squamous cell carcinoma	284	(23)
Others	138	(12)
Clinical T factor		
T1	593	(49)
T2	490	(40)
T3	111	(9)
T4	20	(2)
Clinical N factor		
N0	1,005	(83)
N1	116	(10)
N2	92	(8)
N3	1	(<1)
Clinical stage		
IA	550	(45)
IB	376	(31)
IIA	17	(1)
IIB	129	(11)
IIIA	113	(9)
IIIB	24	(2)
IV	5	(<1)
Pathologic T factor		
T1	543	(45)
T2	434	(36)
T3	126	(10)
T4	111	(9)
Pathologic N factor		
N0	801	(66)
N1	204	(17)
N2	202	(17)
N3	7	(1)
Pathologic stage		
IA	438	(36)
IB	256	(21)
IIA	51	(4)
IIB	147	(12)
IIIA	196	(16)
IIIB	113	(9)
IV	13	(1)

(Numbers in parentheses are percentages)

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Table 2. Pre-PLC Result and Clinicopathologic Characteristics

Factors	Pre-PLC (n = 1,194)		P Value
	Positive (n = 38)	Negative (n = 1,156)	
Age	63	63	0.740
Gender			
Male	25	746	
Female	13	410	0.873
Treatment modality (resection type)			
Lobectomy	34	1,049	
Pneumonectomy	1	64	0.177
Limited resection	3	43	(limited resection vs others)
Pathologic stage			
I	16	667	
II	3	193	0.056
III	19	283	(stage I vs others)
IV	0	13	
Histology			
Adenocarcinoma	26	751	
Squamous cell carcinoma	6	274	0.660
Large cell carcinoma	3	47	(adenocarcinoma vs others)
Other	3	84	
Pathologic pleural involvement			
p0	11	754	
p1–3	27	402	<0.001
Pathologic N status			
N0	17	774	
N1–3	21	382	0.041
Lymphatic invasion			
Positive	27	481	
Negative	11	675	<0.001
Vascular invasion			
Positive	30	633	
Negative	8	523	0.003
Resection completeness			
Complete	28	1,067	
Incomplete	10	89	<0.001
Scar grade			
1–2	0	191	
3–4	35	844	0.001
NA	3	121	
Nuclear atypia			
1–2	15	432	
3	20	607	0.863
NA	3	117	
Mitotic index			
1–2	26	813	
3	9	226	0.539
NA	3	117	

NA = data not available.

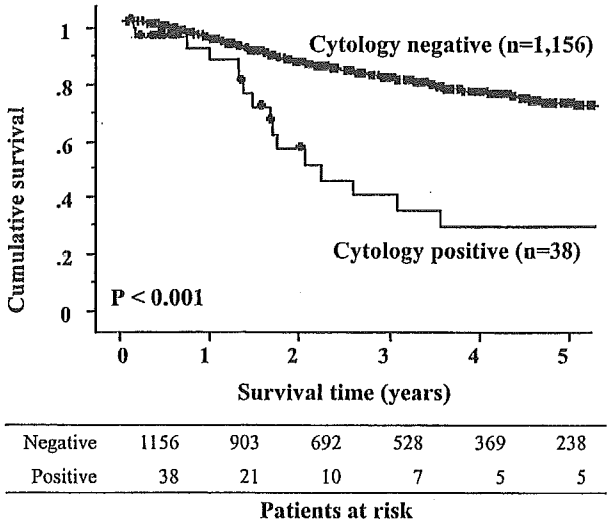
cells, grade 2; nuclei that were uniform in size and up to twice the size of those of reactive type II alveolar epithelial cells, and grade 3; presence of giant tumor cells. Mitotic index was classified into three grades based on the findings of several sections: index 1; up to 5 mitotic cells per 10 high-power fields (HPF), index 2; 6–15 mitotic cells per 10 HPF, and index 3; greater than 15 mitotic cells per 10 HPF [7]. The length of survival was defined as the interval in months between the day of surgical intervention and the date of death due to

Table 3. Post-PLC Results and Clinicopathologic Characteristics

Factors	Post-PLC (n = 1,182)		
	Positive (n = 54)	Negative (n = 1,128)	*p* Value
Age	61	63	0.363
Gender			
Male	37	725	
Female	17	403	0.524
Treatment modality (resection type)			
Lobectomy	48	1,026	
Pneumonectomy	2	63	0.129
Limited resection	4	39	(limited resection vs others)
Pathologic stage			
I	7	673	
II	3	191	<0.001
III	42	253	(stage I vs others)
IV	2	11	
Histology			
Adenocarcinoma	41	731	
Squamous cell carcinoma	4	270	0.094
Large cell carcinoma	4	46	(adenocarcinoma vs others)
Other	5	81	
Pathologic pleural involvement			
p0	26	732	
p1–3	28	396	0.019
Pathologic N status			
N0	10	776	
N1–3	44	352	<0.001
Lymphatic invasion			
Positive	43	463	
Negative	11	665	<0.001
Vascular invasion			
Positive	41	614	
Negative	13	514	0.002
Resection completeness			
Complete	25	1,001	
Incomplete	29	127	<0.001
Scar grade			
1–2	3	186	
3–4	47	821	0.022
NA	4	121	
Nuclear atypia			
1–2	18	423	
3	32	588	0.465
NA	4	117	
Mitotic index			
1–2	42	790	
3	8	221	0.382
NA	4	117	

NA = data not available.

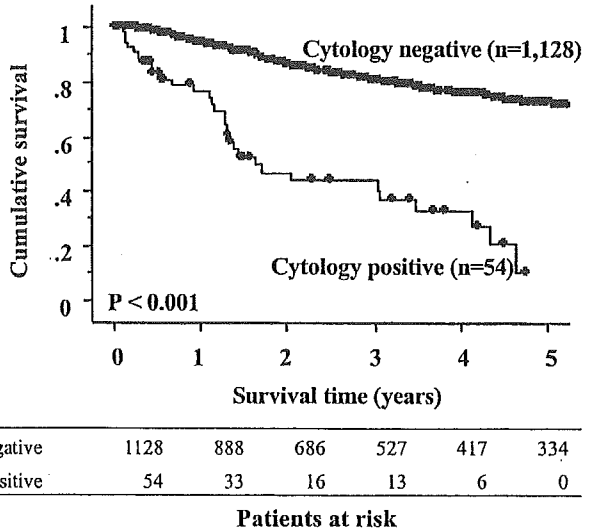
any cause or the last follow-up. An observation was censored at the last follow-up when the patient was alive or lost to follow-up. The survival rates were calculated by the Kaplan-Meier method [8] and univariate analyses were performed by means of the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model [9]. Forward and backward stepwise procedures were used to determine the combination of prognostic factors (StatView: version 5.0; SAS Institute, Inc, Cary, NC). A *p*



Negative	1156	903	692	528	369	238
Positive	38	21	10	7	5	5

Patients at risk

Fig 1. Survival curves of patients according to pre-PLC results. The 5-year survival rate was 27% for positive pre-PLC patients and was significantly worse (71%) for negative pre-PLC patients. The crosses indicate censored cases at the respective points. (PLC = pleural lavage cytology.)



Negative	1128	888	686	527	417	334
Positive	54	33	16	13	6	0

Patients at risk

Fig 2. Survival curves of patients according to post-PLC results. The 5-year survival rate was 10% for positive post-PLC patients and was significantly worse (73%) for negative post-PLC patients. The crosses indicate censored cases at the respective points. (PLC = pleural lavage cytology.)

value less than 0.05 was taken to indicate a statistical significance.

Results

Patient clinicopathologic characteristics are shown in Table 1. There were 781 men and 433 women. Their ages ranged from 22 to 89, with a median of 65 years. Clinicopathologic characteristics for pre-PLC and post-PLC are shown in Tables 2 and 3, respectively. For pre-PLC, definitive cytologic results were obtained in 1,194 patients, with a positive result in 38 (3.2%). Univariate analyses revealed significant differences between pre-PLC positive and negative patients in pathologic pleural involvement, pathologic N status, lymphatic permeation, vascular invasion, resection completeness, and scar grade. For post-PLC, definitive cytologic result was obtained in 1,182 patients, 54 (4.6%) of which showed a positive result. Significant differences were observed in pathologic stage, pathologic pleural involvement, pathologic N status, lymphatic permeation, vascular invasion, resection completeness, and scar grade between post-PLC positive and negative patients. The 5-year survival rate was 27% for positive pre-PLC patients, which was significantly worse than 71% for negative pre-PLC patients (Fig 1). The 10% 5-year survival rate for positive post-PLC patients was significantly worse 73% for negative post-PLC patients (Fig. 2).

Five-year survival rates for patients with negative pre-PLC and post-PLC (n = 1,094), positive pre-PLC and negative post-PLC (n = 21), negative pre-PLC and positive post-PLC (n = 37), and positive pre-PLC and positive post-PLC (n = 13) were 81, 50, 12, and 0%, respectively. Multivariate analyses revealed 6 independent prognostic factors when only factors available before lung resection were analyzed (Table 4): age, CEA level, cT factor, cN factor, sP factor, and pre-PLC result. When factors available after postoperative pathologic evaluation were included in multivariate analyses, however, 10 independent prognostic factors were recognized, but pre-PLC result was not (Table 5): Age, CEA level, cT factor, pT factor, pN factor, p factor, lymphatic invasion, vascular invasion, resection completeness, and post-PLC result.

Comment

The first report on PLC was in 1958 by Spjut and associates [10]. They reported the results of post-PLC in 49 patients with lung cancer undergoing surgical resection. The cytologic results were positive for malignant cells in 16 (33%) of them, but outcomes were not analyzed. In 1984, Eagan and colleagues [11] reported positive post-PLC in 12 (8.9%) of 135 patients. Lung cancer recurred in nine of the 12 patients, with only two in the

Table 4. Multivariate Analysis Results for Prognostic Factors Available Before Lung Resection

Variable	Hazard Ratio (95% CI)	*p* Value
Age	1.020 (1.006–1.035)	0.005
Gender	0.958 (0.638–1.436)	0.833
Smoking (S.I > 400)	0.963 (0.648–1.433)	0.853
CEA	1.732 (1.320–2.272)	<0.001
cT factor (2–4 vs 1)	0.624 (0.475–0.814)	0.002
cN factor (1–3 vs 0)	0.512 (0.379–0.691)	<0.001
sP factor (2–3 vs 1–2)	0.621 (0.475–0.814)	<0.001
Pre-PLC	2.980 (1.683–5.277)	<0.001

CEA = serum carcinoembryonic antigen; CI = confidence interval; PLC = pleural lavage cytology; S.I = smoking index.

Table 5. Multivariate Analysis Results Including Factors Available After Lung Resection

Variable	Hazard Ratio (95% CI)	*p* Value
Age	1.021 (1.006–1.037)	0.006
CEA	1.301 (0.970–1.744)	0.079
cT factor (2–4 vs 1)	0.971 (1.411–2.051)	0.071
cN factor (1–3 vs 0)	0.951 (0.652–1.388)	0.796
sP factor (1–3 vs 0)	1.244 (0.834–1.856)	0.284
pT factor (2–4 vs 1)	1.285 (1.181–1.399)	<0.001
pN factor (1–3 vs 0)	0.446 (0.316–0.629)	<0.001
p factor (1–3 vs 0)	0.726 (0.527–1.001)	0.050
Histology (Ad.[a] vs others)	1.100 (0.769–1.573)	0.602
Lymphatic invasion	1.495 (1.058–2.114)	0.023
Vascular invasion	2.161 (1.410–3.311)	<0.001
Scar grade (3–4 vs 1–2)	0.792 (0.453–1.383)	0.412
Nuclear atypia (3 vs 1–2)	0.634 (0.447–0.898)	0.010
Mitotic index (3 vs 1–2)	0.875 (0.617–1.239)	0.452
Resection completeness	0.676 (0.472–0.968)	0.033
Pre-PLC	1.833 (0.949–3.541)	0.071
Post-PLC	1.803 (1.077–3.018)	0.024

Ad.[a] = adenocarcinoma; CEA = serum carcinoembryonic antigen; PLC = pleural lavage cytology.

ipsilateral pleural space. Eight patients died of lung cancer, one recurring locally and seven having distant metastases. They concluded the prognostic role of PLC needed further study. The first report on pre-PLC was by Kondo and associates in 1989 [12], followed by their expanded result analyses in 1993 [13]. They reported that 42 (9.0%) of 467 lung cancer patients undergoing surgery with little or no pleural effusion had a positive pre-PLC result. The 3-year survival rates of the patients with negative and positive cytology results were 68.7% and 22.9%, respectively. The prognosis of the positive cytology group was as poor as that of stage IIIB or IV patients. They concluded that pre-PLC was an important prognostic factor, indicating microscopic cancer cell exfoliation into the pleural cavity and subclinical malignant pleural effusion. Okada and associates [14] reported, based on 1,000 patients in 2003, that 45 (4.5%) patients had positive pre-PLC findings. Positive cytologic findings were observed more frequently in patients with adenocarcinoma, advanced stage, extended lymph node involvement, pleural involvement, lymphatic invasion, vascular invasion, high serum CEA level, and male gender. The survival rate at 5 years was 28% in patients with a positive result and 67% in negative patients ($p < 0.001$). Multivariate analysis demonstrated that pre-PLC was an independent prognostic determinant ($p = 0.0290$). Higashiyama and associates [1] performed pre-PLC and post-PLC in 325 lung cancer patients without malignant pleurisy. Positive post-PLC patients especially with adenocarcinoma resulted in a poor outcome. The survival rate at 5 years was 71% in 250 patients with negative pre-PLC and post-PLC results, while it was 33% in 19 patients with positive results. However, in multivariate analyses, neither pre-PLC nor post-PLC result was an independent prognostic factor in their study. Dresler and associates [3] reported the pre-PLC and post-PLC analysis in 137 patients in 1999. The 3-year survival rates of the patients with negative and positive pre-PLC results were 55% and 0%, respectively ($p = 0.088$). The 3-year survival rates of the patients with negative and positive post-PLC results were 50% and 0%, respectively ($p < 0.04$). In the present study, we analyzed both pre-PLC and post-PLC in almost 1,200 patients, the largest cohort ever studied with regard to PLC. Both pre-PLC and post PLC were analyzed in a multivariable setting, together with conventional significant clinicopathologic prognostic factors we reported previously [15]. Although our study yielded results similar to previous studies and post-PLC proved to be an important prognostic predictor, we found no difference in PLC results in relation to histologic characteristics. There have been a considerable number of reports concluding positive pre-PLC to be a poor prognosis predictor since pre-PLC was first reported by Kondo and associates in 1989 [12]. However, positive pre-PLC is currently not recognized as equivalent to T4 or a factor indicating incomplete resection [16–18]. In our study, pre-PLC was an independent prognostic factor when analyzed with prognostic factors available before lung resection, but not when postoperative pathologic factors and post-PLC results were combined in analyses. Positive pre-PLC patient outcome, when post-PLC was negative, was not very poor, with the 5-year survival rate reaching almost 60%. Therefore, positive pre-PLC result alone does not contraindicate surgical resection. In contrast, post-PLC proved to be an independent prognostic factor as significant as other established prognostic factors, including pathologic TNM status. No positive post-PLC patients survived beyond 4 years. As the patient outcome was extremely poor when pre-PLC was also positive, adjuvant therapy may be needed in these patients. We conclude PLC should be recognized as an essential prognostic factor and should be performed in NSCLC patients without pleural effusion and dissemination. And post-PLC, compared with pre-PLC, had a greater and independent impact on survival and needs to be incorporated in the pathologic staging of NSCLC in the future. As Vicidomini and associates referred to in their recent article on PLC [19], the results of the American College of Surgeons Oncology Group's Z0040 trial, which has completed a 1,200 patient accrual, will further define the potential implications of PLC in the management of lung cancer.

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