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ORIGINAL ARTICLE

Extent of visceral pleural invasion and the prognosis of surgically resected node-negative non-small cell lung cancer

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Abstract

Background: Visceral pleural invasion (VPI) is generally considered a poor prognostic factor in non-small cell lung cancer (NSCLC). VPI is defined as penetration beyond the elastic layer of visceral pleura (PL1), including the visceral pleural surface without the involvement of adjacent structures (PL2) by cancer cells. The aim of this study was to evaluate the influence of the extent of VPI on NSCLC prognosis.

Methods: This was a retrospective study of 90 patients with resected node-negative NSCLC with VPI. The overall survival (OS) and disease-free survival (DFS) rates were estimated using the Kaplan–Meier method. Multivariate analysis for prognostic factors was performed using a Cox proportional hazards regression model. The pattern of recurrence was also compared between PL1 and PL2 groups.

Results: Seventy-three patients had PL1. The three-year OS rates for the PL1 and PL2 groups were 97.4% and 82.4%, respectively ($P = 0.004$). The two-year DFS rates for PL1 and PL2 groups were 81.0% and 76.5%, respectively ($P = 0.419$). According to the multivariate analysis, PL2 was not a significant prognostic factor for survival outcome in node-negative NSCLC with VPI compared to PL1 (hazard ratio for DFS 1.753, 95% confidence interval 0.582–5.284; $P = 0.319$). In this study, six patients in the PL1 and one in PL2 group developed ipsilateral pleural recurrence ($P = 1.000$).

Conclusion: VPI extent may not influence survival outcomes in patients with surgically resected node-negative NSCLC with VPI.

Introduction

Visceral pleural invasion (VPI) has been recognized as an adverse prognostic factor in non-small cell lung cancer (NSCLC) patients, and is included in the tumor node metastasis (TNM) staging system.[1] For NSCLC tumors sized 3 cm or less, the presence of VPI increases the T stage from T1 to T2.[1,2]

Pleural invasion is classified into the following: PL0, tumor with no pleural involvement beyond its elastic layer; PL1, tumor that invades beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface; PL2, tumor that invades to the pleural surface; and PL3, tumor that invades to the parietal pleura.[2] Therefore, PL0 is not classified as VPI, while PL3 is classified as chest wall invasion as is associated with parietal pleural invasion. Although classified separately, PL1 and PL2 are both interpreted as VPI in the TNM staging system. Previous studies have reported that patients with PL2 have significantly poorer postoperative survival outcomes than those with PL1.[3,4] It has also been reported that the percentage of pleural recurrence in PL2 groups is significantly higher than in PL1 groups.[3]

Therefore, the aim of this study was to compare the prognostic value of the extent of VPI in patients with resected node-negative NSCLC. We also focused on patterns of recurrence, particularly the presence of ipsilateral pleural recurrence.

Methods

Patients

This study was a retrospective review and analysis of the lung cancer database. All enrolled patients had undergone curative surgical resection at Kyungpook National University Medical Center between January 2012 and May 2015 and were pathologically diagnosed with node-negative NSCLC. Patients with lymph node metastases were excluded from the analysis in order to focus on the relationship between the extent of VPI and survival outcomes. Patients with no VPI (PL0) or parietal pleural invasion (PL3) were also excluded. None of the patients in this study had received neoadjuvant therapy.

Pathology

Visceral pleural invasion was examined in tumor sections with hematoxylin and eosin staining. Van Gieson staining was performed if the VPI status (PL1 or PL2) was unclear with hematoxylin and eosin staining alone. VPI was classified according to the revised International Union Against Cancer and American Joint Committee on Cancer TNM classification.[2] Lymphatic and vascular involvement were also examined.

Statistical analysis

The patients were divided into two groups based on the extent of VPI (PL1 and PL2). Fisher's exact and χ^2 tests were used to assess the differences in the categorical variables between the two groups. Shapiro–Wilk and Mann–Whitney tests were used for discrete and continuous variables. Overall survival (OS) was defined as the interval between the date of surgical resection and the date of either death or the last follow-up. Disease-free survival (DFS) was calculated from the date of surgical resection to the date of diagnosis of first recurrence. The OS and DFS rates were calculated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model. VPI extent and variables that showed statistical significance on univariate analysis were included in multivariate analysis. Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Chicago, IL, United States). All *P* values less than 0.05 were defined as statistically significant.

Results

This study included 90 patients with surgically resected NSCLC with VPI (PL1 or PL2). All patients were pathologically diagnosed with node-negative NSCLC and were divided into two groups based on the extent of VPI (PL1 vs. PL2). PL1 was identified in 73 patients. No significant differences were found between PL1 and PL2 groups in age, gender, smoking history, type of surgery, and comorbidities. The mean follow-up periods for both groups were around 23 months (Table 1).

Of the 73 patients in the PL1 group, adenocarcinoma was the most common histologic type (48 cases, 65.8%). According to tumor size, there were 22 cases ≤20 mm (30.1%), 21 cases >20 to ≤30 mm (28.8%), 24 cases >30 to ≤50 mm (32.9%), and six cases >50 to ≤70 mm (8.2%). Lymphatic invasion was identified in 12 patients (16.4%), and vascular invasion was identified in eight (11.0%). Of the 17 patients in the PL2 group, there was no significant difference in the pathologic findings including the histologic type, tumor size, lymphatic invasion, and vascular invasion compared to the PL1 group ($P = 0.719$, 0.818, 0.448, and 0.344, respectively; Table 2).

Among the 90 patients, two cancer-related deaths occurred (1 patient in each group). The three-year OS rates for the PL1 and PL2 groups were 97.4% and 82.4%, respectively ($P = 0.004$, Fig 1). Nineteen recurrences occurred; the recurrence rates were 19.2% (14 of 73 patients) in the PL1 and 29.4% (5 of 17 patients) in the PL2 group. The two-year DFS rates for the PL1 and PL2 groups were 81.0% and 76.5%, respectively ($P = 0.419$, Fig 2). Two local recurrences, six distant recurrences, and six both local and distant recurrences developed in the PL1 group. Two local recurrences and three distant recurrences developed in the PL2 group (Table 3). There was no significant difference in the patterns of recurrence between the groups ($P = 0.113$). Seven ipsilateral pleural recurrences developed (6 patients in the PL1, 1 in the PL2 group; $P = 1.000$; Table 3). Although the patients with PL2 had poorer survival outcomes, univariate analysis indicated that there was no significant difference between the groups based on the extent of VPI (hazard ratio [HR] 1.941; 95% confidence interval [CI], 0.681–5.528; $P = 0.214$; Table 4). Multivariate analysis also revealed that DFS was not significantly associated with the extent of VPI (HR 1.753, 95% CI 0.582–5.284; $P = 0.319$; Table 4).

Discussion

Although the TNM staging system is the most powerful predictor of NSCLC, survival and recurrence rates in NSCLC patients with the same pathologic TNM stage were variable.[5] Therefore, many researchers are currently working on developing a more accurate TNM staging system.

Visceral pleural invasion is one of the important prognostic factors in patients with surgically resected NSCLC,[6–8] and it is included in the TNM staging system as a factor that upstages the T factor from T1 to T2.[2] VPI is

Table 1 Patient characteristics

Variables	PL1 group (n = 73) N (%)	PL2 group (n = 17) N (%)	P
Mean age (years)	68.3 ± 9.0	64.4 ± 8.4	0.093
Gender			0.430
Male	44 (60.3)	12 (70.6)	
Female	29 (39.7)	5 (29.4)	
Smoking			0.832
Never	36 (49.3)	7 (41.2)	
Ex	22 (30.1)	6 (35.3)	
Current	15 (20.5)	4 (23.5)	
Pack-year index			0.704
≤20	11	4	
>20	26	6	
CEA, ng/mL†			0.881
<3	40 (64.5)	10 (62.5)	
≥3	22 (35.5)	6 (37.5)	
Operation			0.255
Lobectomy	68 (93.2)	15 (88.2)	
Bilobectomy	0	1 (5.9)	
Limited resection	5 (6.8)	1 (5.9)	
Hypertension			0.224
Absence	50 (68.5)	9 (52.9)	
Presence	23 (31.5)	8 (47.1)	
Diabetes mellitus			0.518
Absence	58 (79.5)	12 (70.6)	
Presence	15 (20.5)	5 (29.4)	
Tuberculosis			0.471
Absence	71 (97.3)	16 (94.1)	
Presence	2 (2.7)	1 (5.9)	
CAD			0.579
Absence	68 (93.2)	17 (100)	
Presence	5 (6.8)	0	
CVA			1.000
Absence	65 (89)	16 (94.1)	
Presence	8 (11)	1 (5.9)	
Mean follow-up period (months)	23.8 ± 11.8	22.4 ± 11.0	0.620

†Data are lacking in some patients for this variable. CAD, coronary artery disease; CEA, carcinoembryonic antigen; CVA, cerebral vascular accident.

defined as tumor extension beyond the elastic layer of the visceral pleura, regardless of invasion of the pleural surface.[2] If a tumor extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface, it is classified as PL1. If a tumor is exposed on the pleural surface but does not involve adjacent anatomic structures, it is classified as PL2. VPI is shown to be associated with extensive mediastinal lymph node metastases, and, thus, poor surgical outcomes.[6,9] The higher frequency of mediastinal lymph node metastasis is probably a result of the drainage of cancer cells through the subpleural lymphatics into the mediastinal lymph nodes.[10] Some studies have also demonstrated that VPI is a significant prognostic factor regardless of N status.[7,11] Brewer speculated that VPI may lead to diffuse dissemination of cancer cells throughout the pleural cavity by pleural effusion.[12] Previous studies have also reported a close correlation between VPI and malignant pleural effusion.[13,14]

The microscopic anatomy of the visceral pleura consists of five layers, although there is some variation in the number and composition.[10] An important anatomical landmark is the elastic layer, consisting of a broader and stronger layer and a thinner inner layer.[10] The visceral pleura contains many lymphatic and blood vessels sandwiched in between these elastic layers.[10,15] Therefore, the closer the cancer cells are to the pleural surface, the more likely that they are drained through the subpleural lymphatics, and, hence, the more likely they are to be associated with malignant pleural effusion. Hung *et al.* reported that the overall recurrence rate in patients with PL2 was significantly higher than those with PL1.[3] They also reported that the percentage of pleural recurrence in the PL2 group was

Table 2 Pathologic findings

Variables	PL1 group (n = 73)	PL2 group (n = 17)	P
Histologic type			0.719
Squamous cell carcinoma	22	6	
Adenocarcinoma	48	10	
Others	3	1	
Tumor size			0.818
≤20 mm	22	4	
>20 to ≤30 mm	21	4	
>30 to ≤50 mm	24	7	
>50 to ≤70 mm	6	2	
Lymphatic invasion			0.448
Absence	61	16	
Presence	12	1	
Vascular invasion			0.344
Absence	65	17	
Presence	8	0	

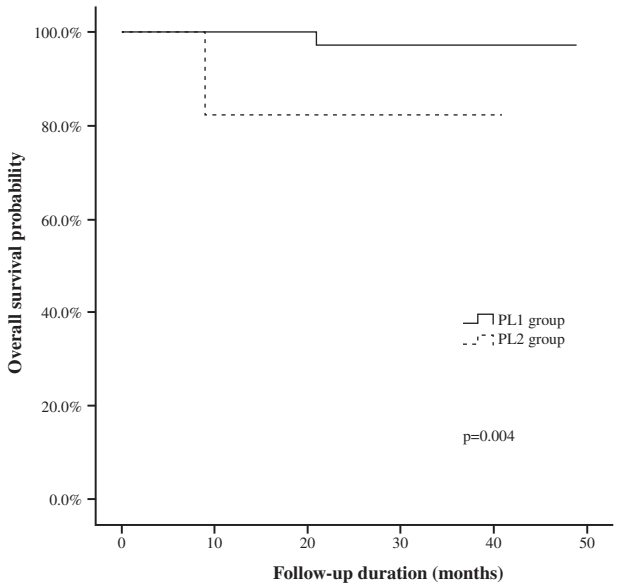

Figure 1 Overall survival curve of patients according to the extent of visceral pleural invasion.

significantly higher than in the PL1 group.[3] In their study, all patients had been diagnosed with pathologic node-negative NSCLC. Kudo *et al.* also reported that the five-year OS rate in patients with PL2 was significantly poorer than in those with PL1 (P = 0.03).[4] On the other hand, Osaki *et al.* reported that no significant survival difference was found between PL1 and PL2 groups (P = 0.61).[16] In actual fact, the five-year OS rate in the PL1 group in Osaki *et al.*'s study was 43.9%, which was lower than that in their PL2 group (54.9%). Shimizu *et al.* reported that the five-year OS rates for patients with PL1 or PL2 tumors of 3 cm or less were not significantly different (P = 0.20).[17] In their

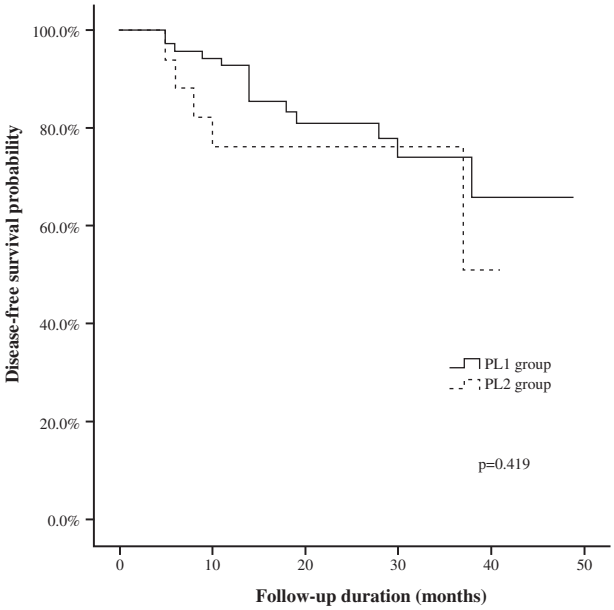

Figure 2 Disease-free survival curve of patients according to the extent of visceral pleural invasion.

Table 3 Characteristics of recurrence

Variables	PL1 (n = 73)	PL2 (n = 17)	P
Recurrence			0.342
No	59	12	
Yes	14	5	
Patterns of recurrence			0.113
Local recurrence only	2	2	
Distant recurrence only	6	3	
Both recurrence	6	0	
Ipsilateral pleural recurrence			1.000
Absence	67	16	
Presence	6	1	
Disease-free interval (months)	22.1 ± 11.7	21.8 ± 11.9	0.893

study, the five-year OS rates for patients with PL1 or PL2 tumors larger than 3 cm were also not significantly different (P = 0.47).[17] Adachi *et al.* also found no evidence of a significant survival difference between PL1 and PL2 groups, regardless of the status of lymph node metastasis.[8] In our study, the three-year OS rate for the PL1 group (97.4%) was significantly higher than that of the PL2 (82.5%) (P = 0.004). Although the two-year DFS rate in the PL1 group (81.0%) was better than that in the PL2 group (76.5%), there was no significant difference between these groups (P = 0.419). Considering the anatomy of the visceral pleura, it was thought that lymphatic and vascular invasion would be more common in the PL2 group. However, we found no significant difference between the groups and, in actual fact, lymphatic and vascular invasion was more frequently found in the PL1 group (P = 0.448, and 0.344, respectively). Regarding patterns of recurrence, it

Table 4 Univariate and multivariate analyses for disease-free survival

	Univariate			Multivariate		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Gender						
Male	1			1		
Female	0.212	0.048–0.931	0.040	0.385	0.067–2.198	0.283
Age	0.986	0.939–1.036	0.584	0.980	0.929–1.033	0.449
CEA						
<3	1					
≥3	0.371	0.105	1.315			
Smoking						
Never	1			1		
Ex	4.740	1.534–14.644	0.007	4.740	1.534–14.644	0.007
Current	1.652	0.390–6.993	0.496	1.652	0.390–6.993	0.496
Pack-year index						
≤20	1					
>20	1.152	0.301–4.399	0.836			
Operation						
Major resection	1					
Limited resection	0.833	0.110–6.316	0.860			
Tumor size						
≤20 mm	1			1		
>20 to ≤30 mm	2.782	0.636–12.165	0.174	2.542	0.548–11.783	0.233
>30 to ≤50 mm	3.338	0.837–13.302	0.088	2.860	0.607–13.469	0.184
>50 to ≤70 mm	7.347	1.549–34.844	0.012	3.232	0.531–19.681	0.203
Pathology						
SQCC	1					
AD	0.424	0.156–1.151	0.092			
Other	0.966	0.118–7.898	0.974			
Visceral pleural invasion						
PL1	1			1		
PL2	1.941	0.681–5.528	0.214	1.753	0.582–5.284	0.319
Lymphatic invasion						
Absence	1					
Presence	1.821	0.592–5.603	0.296			
Vascular invasion						
Absence	1					
Presence	0.605	0.080–4.577	0.626			

AD, adenocarcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; SQCC, squamous cell carcinoma.

was hypothesized that ipsilateral pleural recurrence would be more common in the PL2 group. However, there was no significant difference in the ipsilateral pleural recurrence rate between the PL1 and PL2 groups (8.2%, and 5.9%, respectively; $P = 1.000$).

We found that the extent of VPI (PL1 or PL2) was not a significant poor predictor of surgical outcome in node-negative NSCLC patients after curative resection in both univariate and multivariate analyses. According to our findings, it is valid to use the current TNM classification to assess VPI, even though they do not distinguish between PL1 and PL2.

This study has some limitations. The sample size was small and the follow-up period was relatively short. Future studies with a larger patient population and longer follow-up period may allow more precise analysis of cancer-related death and recurrence.

In conclusion, in patients with pathologic node-negative NSCLC with VPI, the extent of VPI (PL1 or PL2) was not a significant or independent prognostic factor. Therefore, VPI extent may not influence survival outcomes in patients with node-negative NSCLC with VPI. The current TNM staging system, which defines both PL1 and PL2 status as VPI, is valid for the assessment of VPI. Our results revealed higher OS and DFS rates in the PL1 than in the PL2 group. Further studies with a larger sample size and longer follow-up period are required for more precise analysis.

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Disclosure

No authors report any conflict of interest.

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