

ORIGINAL ARTICLE

Effect of visceral pleural invasion on the prognosis of patients with lymph node negative non-small cell lung cancer

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Keywords

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Abstract

Background: Visceral pleural invasion (VPI) is an adverse prognostic factor in non-small cell lung cancer (NSCLC); however, its effect in relation to tumor size remains under debate. To better understand the prognostic impact and potential consequences for staging, we examined correlations between VPI and clinicopathologic characteristics in patients with NSCLC, particularly those with lymph node negative NSCLC.

Methods: We retrospectively analyzed 813 cases of radically resected NSCLC treated in our institution between December 2005 and December 2011. Patients were divided into two groups according to VPI status to compare their clinicopathologic characteristics. Survival analysis was performed in 521 cases with pN0 NSCLC.

Results: VPI was diagnosed in 379 (46.6%) cases. It was more common in women, patients with non-squamous cell carcinoma, elevated preoperative serum carcinoembryonic antigen levels, moderately or poorly differentiated tumors, and larger-sized tumors. The incidence of mediastinal lymph node metastasis, particularly multi-station metastasis, was higher in patients with VPI. Patients with pN0 NSCLC, 2–3 cm tumors, and VPI had a significantly poorer prognosis (VPI vs. -non-VPI: five-year overall survival 78.3% vs. 84.5%, $P = 0.039$; five-year disease-free survival 69.2% vs. 80.0%, $P = 0.046$, respectively); however, no significant effect was observed for tumors ≤ 2 , 3–5, and 5–7 cm. P-N0 patients with VPI had a significantly higher incidence of postoperative local recurrence and distant metastasis than those without VPI ($P = 0.01$), especially ipsilateral pleural recurrence.

Conclusion: VPI was an adverse prognostic factor in radically resected pN0 NSCLC, especially for tumors 2–3 cm in size.

Introduction

Visceral pleural invasion (VPI) is an adverse factor affecting the prognosis of patients with non-small cell lung cancer (NSCLC). In the 1970s, Brewer *et al.* observed that patients with a tumor growing under the pleura had a significantly poorer prognosis than those with a tumor in the lung parenchyma.¹ The authors suggested that these tumors were more likely to break through the visceral pleura, causing

pleural intraluminal metastasis. Shimizu *et al.* found that cases involving the elastic layer of the visceral pleura had a poorer prognosis, and that these tumors exhibited strong growth and invasive capabilities.^{2,3} They termed these cases visceral pleural invasion. Manac'h *et al.* reported that a higher proportion of patients with VPI developed widespread mediastinal lymph node metastasis.⁴ Their findings confirmed that VPI was an independent factor for poor

prognosis in patients with NSCLC. Consequently, VPI was used to upstage T1 tumors to T2 in the seventh edition of the tumor node metastasis (TNM) classification system.^{5–7} However, reports on the prognostic significance and staging of VPI in relation to tumor size have been contradictory, covering a spectrum from T1a to T3 for tumors ≤ 2 , 2–3 and >3 cm.^{8–10} A large-scale meta-analysis on patients with lymph node-negative NSCLC subdivided cases by tumor size (≤ 3 , 3–5, and 5–7 cm) and found that VPI had an adverse effect on the prognosis of each group.¹¹ The aim of this study was to gain a better understanding of the prognostic impact of VPI in patients with NSCLC, in particular, the effect of tumor size in patients with lymph node negative (pN0) NSCLC. To achieve this, we carried out a retrospective analysis of 813 cases of radically resected NSCLC, including 521 cases with pN0 NSCLC, and compared their survival outcomes against a range of clinicopathologic features, including VPI status and tumor size.

Methods

Patient selection and treatment

We retrospectively analyzed the clinical and pathological data of 813 patients with NSCLC who underwent primary lung tumor resection and systematic lymph node dissection in our institution between December 2005 and December 2011. Gender, age, smoking history, surgical procedure, histological type, degree of differentiation, tumor location, tumor size, vessel carcinoma embolus, lymph node metastasis, preoperative serum carcinoembryonic antigen (CEA) level (where available), and VPI status were recorded. Tumors were staged according to the criteria of the seventh edition of the TNM classification system.¹² The exclusion criteria were as follows: (i) routine preoperative examination revealing N3 lymph node metastasis or distant metastasis (M1); (ii) administration of preoperative adjuvant therapy, including neoadjuvant chemotherapy and targeted therapy; (iii) intraoperative examination showing intrathoracic dissemination of the tumor and only a biopsy was taken; (iv) incomplete resection of a tumor because of a positive surgical margin, including positive macroscopic (R2) and positive microscopic (R1) margins; and (v) primary tumor resection was performed without lymph node dissection. The institution's ethics committee approved the study, and all participating patients provided written informed consent.

Pathology and follow-up

Surgical resection specimens were collected from all patients and fixed in formalin and embedded in paraffin

before being sliced for pathological examination. A diagnosis of NSCLC was confirmed by conventional hematoxylin and eosin staining. Two independent experienced pathologists performed pathological examination to determine the presence of VPI (defined as tumor invasion into the visceral pleura elastic layer but not the parietal pleura).¹³ All of the patients received regular follow-up in our hospital, with a median follow-up time of 41.4 months. Overall survival (OS) was defined as the time between surgery and death from any cause or the last follow-up; disease-free survival (DFS) was defined as the time between surgery and tumor recurrence or the last follow-up.

Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and STATA 12.0 (Stata Corp, College Station, TX, USA) software were used for statistical analyzes. Pearson's chi-squared test (χ^2) test was used to identify differences in clinicopathologic features between the two groups, the Kaplan–Meier method and log-rank test were used to estimate differences in survival between the groups, and multivariate analysis was performed using a Cox regression model to identify significant independent factors for survival between groups. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics

The 813 patients included in this study comprised 473 men (58.2%) and 340 women (41.8%), with a median age of 61 years (range 38–81). There were 549 (67.5%) cases of adenocarcinoma and 194 (23.9%) cases of squamous cell carcinoma. All patients received surgical resection. Most of the patients also received lobectomy (91.3%). Sub-lobectomy, bi-lobectomy, and pneumonectomy were performed in 2.2%, 5.4%, and 1.1% of the patients, respectively. The clinicopathologic data are summarized in Table 1. All patients underwent mediastinal lymph node dissection and 76.5% of patients had ≥ 3 stations sampled. The average number of dissected mediastinal lymph node stations was 3.96 and the average number of lymph nodes was 12.71. Postoperative pathology confirmed 522 (64.2%) cases without lymph node metastasis (N0), 118 (14.5%) with N1 lymph node metastasis, and 173 (21.3%) with N2 lymph node metastasis.

There were 379 (46.6%) patients with VPI compared with 434 (53.4%) without VPI. The clinicopathologic data comparing these groups are shown in Table 2. A higher proportion of VPI was observed in women, in cases of

Table 1 Clinicopathological characteristics of 813 patients with radically resected NSCLC

Characteristic	Description	No. of cases (%)
Age (years)	61 (16–81)	813 (100%)
Gender	Male	473 (58.2%)
	Female	340 (41.8%)
Smoking history	Yes	397 (48.8%)
	No	416 (51.2%)
Surgical procedure	Open	613 (75.4%)
	VATS	200 (24.6%)
Surgical extension	Sub-lobectomy	18 (2.2%)
	Lobectomy	742 (91.3%)
	Bilobectomy	44 (5.4%)
	Pneumonectomy	9 (1.1%)
Pathological pattern	Adenocarcinoma	549 (67.5%)
	Squamous carcinoma	194 (23.9%)
	Other	70 (8.6%)
Degrees of differentiation	Low differentiation	332 (40.8%)
	Moderate differentiation	337 (41.5%)
	High differentiation	144 (17.7%)
Vessel carcinoma embolus	No	715 (87.9%)
	Yes	98 (12.1%)
Tumor size (cm)	≤2	257 (31.6%)
	2–3	267 (32.8%)
	3–5	216 (26.6%)
	>5	73 (9.0%)
Lymph node metastasis	N0	522 (64.2%)
	N1	118 (14.5%)
	N2	173 (21.3%)
Preoperative CEA level (ng/ml)†	≤5	488 (74.5%)
	>5	167 (25.5%)
Visceral pleural invasion	No	434 (53.4%)
	Yes	379 (46.6%)

†A total of 655 patients underwent preoperative serum carcinoembryonic antigen (CEA) examination. NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery.

non-squamous cell carcinoma, with moderately and poorly differentiated tumors, and in patients with vessel carcinoma embolus. In addition, the proportion of patients with abnormally elevated levels of preoperative serum CEA was higher in those with VPI compared with those without VPI. The probability of VPI increased with tumor size, from 41.2% for tumors with a long diameter ≤3 cm to 51.4% for tumors between 3 and 5 cm, and 71.2% for tumors >5 cm ($P < 0.001$).

Patients with N2 lymph node metastasis had higher rates of VPI compared with those with N1 or N0 NSCLC (60.1%, 42.4%, and 43.1% for N2, N1, and N0, respectively; $P < 0.001$). Patients with multi-station mediastinal lymph nodes also had higher rates of VPI compared with those without multi-station mediastinal lymph node metastasis (64.4% vs. 44.5%; $P < 0.001$).

Table 2 Analysis of clinicopathologic characteristics of patients with radically resected NSCLC according to VPI status

Characteristic	Non-VPI (n = 434)	VPI (n = 379)	P
Age (years)			0.164
<60	202 (56.1%)	158 (43.9%)	
≥60	232 (51.2%)	221 (48.8%)	
Gender			0.039
Male	267 (56.4%)	206 (43.6%)	
Female	167 (49.1%)	173 (50.9%)	
Pathological pattern			<0.001
Adenocarcinoma	263 (47.9%)	286 (52.1%)	
Squamous carcinoma	131 (67.5%)	63 (32.5%)	
Other	40 (57.1%)	30 (42.9%)	
Degrees of differentiation			0.032
Low differentiation	168 (50.6%)	164 (49.4%)	
Moderate differentiation	175 (51.9%)	162 (48.1%)	
High differentiation	91 (63.2%)	53 (36.8%)	
Vessel carcinoma embolus			0.015
No	393 (55.0%)	322 (45.0%)	
Yes	41 (41.8%)	57 (58.2%)	
Tumor size (cm)			<0.001
≤3	308 (58.8%)	216 (41.2%)	
3–5	105 (48.6%)	111 (51.4%)	
>5	21 (28.8%)	52 (71.2%)	
Lymphatic metastasis			<0.001
N0	297 (56.9%)	225 (43.1%)	
N1	68 (57.6%)	50 (42.4%)	
N2	69 (39.9%)	104 (60.1%)	
Multi-station N2 metastasis			<0.001
No	403 (55.5%)	323 (44.5%)	
Yes	31 (35.6%)	56 (64.4%)	
Preoperative CEA†			<0.001
<5	289 (59.2%)	199 (40.8%)	
≥5	64 (38.3%)	103 (61.7%)	

†A total of 655 patients underwent preoperative serum carcinoembryonic antigen (CEA) examination. NSCLC, non-small cell lung cancer; VPI, visceral pleural invasion.

Survival rates in patients with lymph node negative non-small cell lung cancer (NSCLC)

A total of 522 patients pathologically confirmed as lymph node negative were initially identified. One patient died in the perioperative period as a result of postoperative pulmonary embolism, while the remaining 521 patients completed follow-up and were included in the survival analyses. The five-year OS rates were significantly poorer in patients with VPI compared with those without VPI (five-year OS: 79.9% vs. 86.7%, respectively; $P = 0.04$; Fig. 1). Similarly, the five-year DFS was significantly lower in patients with VPI compared with those without VPI (70.8% vs. 83.2%, respectively; $P < 0.001$; Fig. 1). The following clinicopathologic features were included in multivariable analysis: gender, age, smoking history, surgical

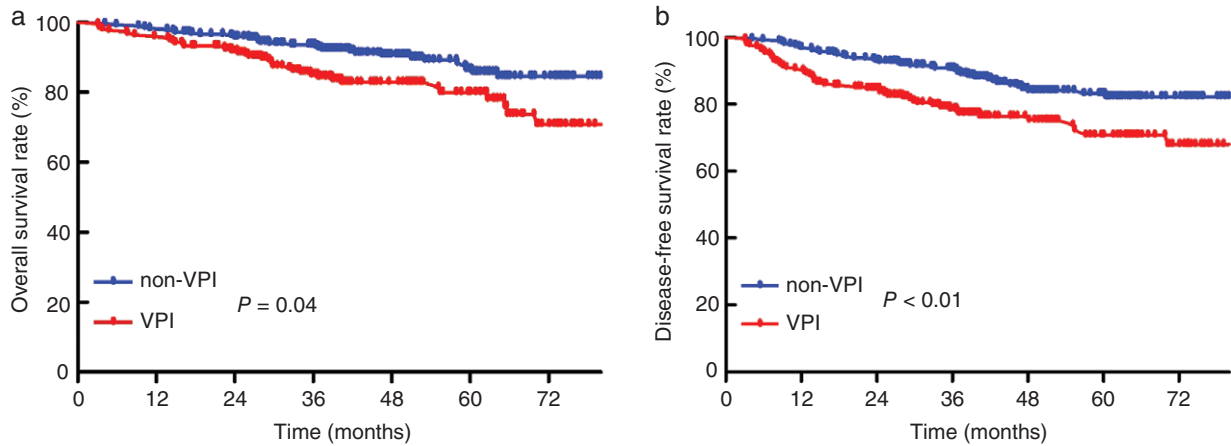


Figure 1 Survival curves showing (a) overall survival and (b) disease-free survival rates in patients with radically resected non-small cell lung cancer without lymphatic metastasis. Blue indicates non-visceral pleural invasion (VPI); red indicates VPI.

procedure, pathological type, tumor size, degree of differentiation, vessel carcinoma embolus, and VPI. The results showed that tumor size, degree of differentiation (moderate and low vs. high), and VPI (with vs. without) were independent risk factors of OS and DFS in patients with radically resected N0 NSCLC (Table 3).

In order to investigate the effect of VPI on the prognosis of patients in relation to tumor size, the 521 patients were subdivided into four groups according to tumor size (≤ 2 , 2–3, 3–5, and 5–7 cm). The analyses showed that VPI had no significant effect on prognosis in patients with tumors ≤ 2 cm: the five-year OS rates were 93.1% and 96.6% ($P = 0.78$), and the five-year DFS rates were 89.4% and 86.1% ($P = 0.898$) for the non-VPI and VPI groups, respectively. Similarly, VPI had no significant effect on prognosis in patients with 3–5 or 5–7 cm tumors: in the 3–5 cm group, the five-year OS rates were 81.5% and 78.6% ($P = 0.759$), and the five-year DFS rates were 78.2% and 67.3% ($P = 0.215$) for the non-VPI and VPI cases, respectively; for the 5–7 cm group, the five-year OS rates were 61% and 64.9% ($P = 0.549$), and the five-year DFS rates were 64.8% and 55.7% ($P = 0.503$), respectively. In contrast, VPI had a significant adverse effect on the

survival outcome of patients with 2–3 cm tumors: the five-year OS rates were 84.5% and 78.3% ($P = 0.039$), and the five-year DFS rates were 80.0% and 9.2% ($P = 0.046$) for non-VPI vs. VPI cases, respectively. The survival curves are shown in Figure 2, and the results are summarized in Table 4.

Recurrence rates in patients with lymph node negative NSCLC

Among the 521 patients with pN0 NSCLC who completed follow-up, 94 (17.3%) suffered recurrence, consisting of 12 cases of regional recurrence (including stump, ipsilateral hilar or mediastinal lymph node, and ipsilateral pleural recurrence), 43 cases of distant metastasis (including contralateral lung, supraclavicular lymph node, and other extrathoracic organ metastasis), and 39 cases of unknown sites. The proportion of patients with regional or distant metastasis was significantly higher in those with VPI compared with those without VPI ($P = 0.01$; Table 5). Three of the patients with regional metastasis developed postoperative ipsilateral pleural metastasis; all three had been diagnosed with VPI, suggesting that the onset of VPI might

Table 3 Multiple factor analysis of five-year overall and disease-free survival rates in 521 patients with radically resected pN0 NSCLC

Risk factors	OS			DFS		
	HR	95% CI	P	HR	95% CI	P
Tumor size	1.173	1.033–1.331	0.014	1.198	1.078–1.331	0.0001
Degrees of differentiation						
High	Reference			Reference		
Moderate/low	3.893	1.391–10.894	0.01	2.596	1.234–5.460	0.012
Visceral pleural invasion						
No	Reference			Reference		
Yes	1.647	1.019–2.661	0.041	1.701	1.125–2.572	0.012

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival.

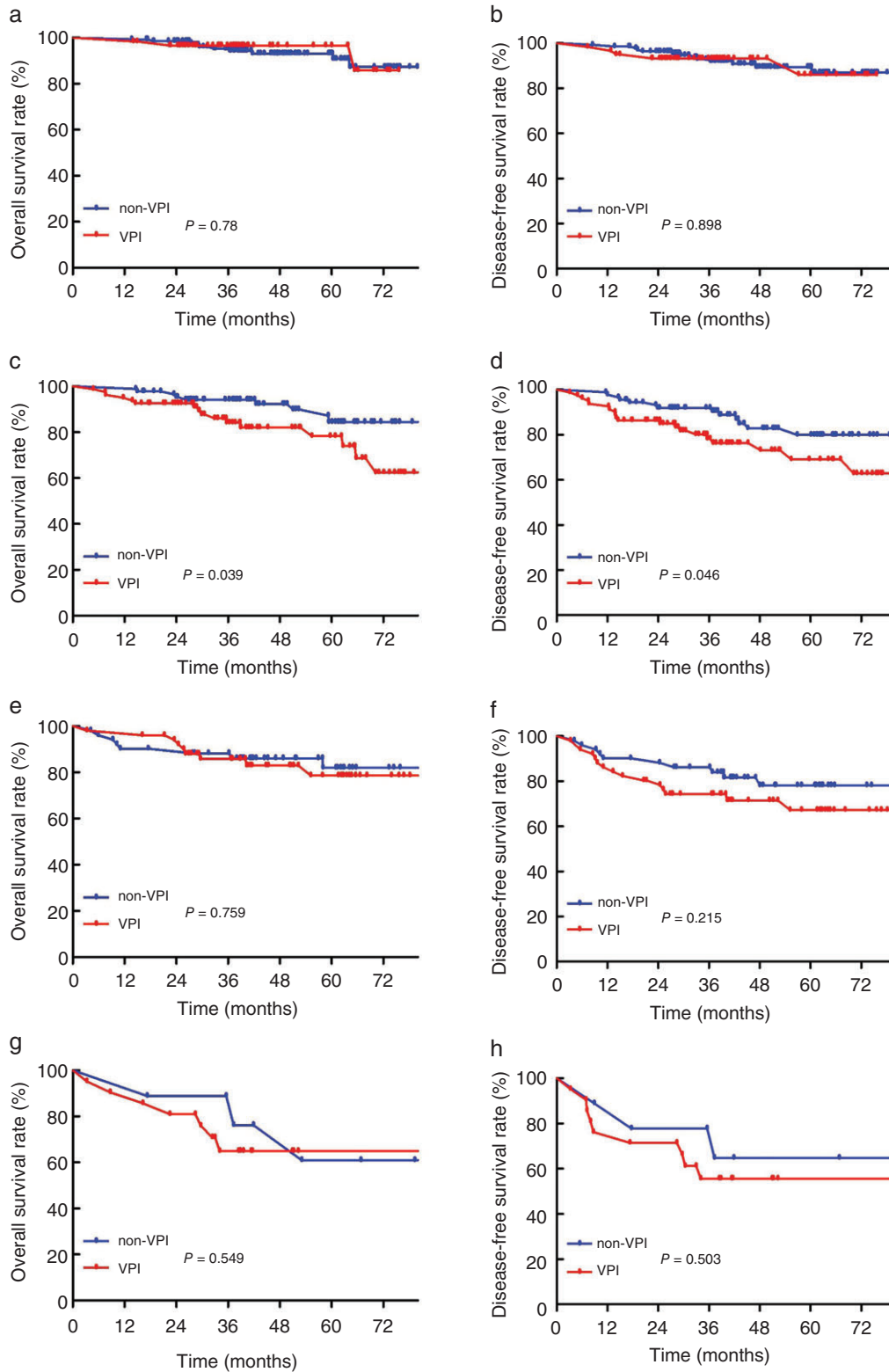


Figure 2 Overall and disease-free survival curves for patients with radically resected pN0 non-small cell lung cancer for different sized tumors: (a,b): ≤ 2 cm; (c,d): 2–3 cm; (e,f): 3–5 cm, and (g,h): 5–7 cm. Blue indicates non-visceral pleural invasion (VPI); red indicates VPI.

Table 4 Effect of VPI on the prognosis of patients with radically resected pN0 NSCLC according to tumor size

Tumor size (cm)	VPI	Number	Five-year OS (%)	<i>P</i>	Five-year DFS (%)	<i>P</i>
≤2	–	139	93.1	0.78	89.4	0.898
≤2	+	60	96.6		86.1	
2–3	–	89	84.5	0.039	80.0	0.046
2–3	+	81	78.3		69.2	
3–5	–	51	81.9	0.759	78.2	0.215
3–5	+	51	78.6		67.3	
5–7	–	9	61	0.549	64.8	0.503
5–7	+	21	64.9		55.7	
T3		20	69.3		65.2	

DFS, disease-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; VPI, visceral pleural invasion.

Table 5 Recurrence and metastasis patterns in 521 patients with radically resected pN0 NSCLC

	Non-VPI (<i>n</i> = 297)	VPI (<i>n</i> = 224)	<i>P</i>
Recurrence and metastasis			
No recurrence or metastasis	256 (86.2%)	171 (76.3%)	0.01
Regional recurrence	4 (1.3%)	8 (3.6%)	
Distant metastasis	16 (5.4%)	27 (12.1%)	
Unknown recurrence and metastasis sites	21 (7.1%)	18 (8.0%)	

NSCLC, non-small cell lung cancer; VPI, visceral pleural invasion.

have prompted the formation of ipsilateral pleural metastasis.

Discussion

Visceral pleural invasion was recognized as a separate category of stage T2 NSCLC in the seventh edition of the TNM staging system; however, the specific details have not yet been defined because of a lack of comprehensive data.⁵ The impact of VPI on the prognosis and staging of patients with NSCLC remains under debate.^{9,14–17} This study focused on patients with lymph node-negative NSCLC following radical resection to mitigate potential confounding factors. Analysis of clinicopathologic characteristics confirmed that VPI was an independent adverse factor for prognosis. Fractional analysis by tumor size revealed that VPI only significantly affected prognosis in patients with 2–3 cm tumors. In combination with previous reports, we proposed that these tumors should be upstaged, whereas the staging of tumors ≤2, 3–5, and 5–7 cm should remain unchanged.^{9,16} The association between VPI and prognosis in patients with NSCLC has been the subject of numerous studies.^{9,14–17} Shimizu *et al.* analyzed data from 1653 patients with NSCLC who had undergone surgery and found that VPI had a significant effect on the prognosis of patients with tumors ≤3 or >3 cm.² As a result, they suggested the staging of tumors ≤3 cm + VPI be increased to T2 while the staging of tumors >3 cm + VPI was increased to T3. However, their study included patients with lymph

node metastasis, which may have been a confounding factor. Ou *et al.* analyzed 9157 cases of stage IA and 10 545 cases of stage IB NSCLC, and found that the prognosis of patients with tumors ≤3 cm in size was not influenced by VPI, and suggested these cases should be classed as stage IA.⁸ However, their study combined VPI, atelectasis, or obstructive pneumonia as a single group. Kawase *et al.* analyzed 4995 cases of stage T1a–T3 N0 NSCLC and proposed that staging should be raised to T2b for 3–5 cm tumors if VPI was present, but should remain at T2b for 5–7 cm tumors.¹⁶ Conversely, Yoshida *et al.* found that the prognosis of patients with NSCLC with tumors ≤2 cm and VPI was worse than that at stage T1a but better than that at T2a, regardless of the presence or absence of lymph node metastasis, and suggested that staging for these cases should be adjusted to T1b. Similarly, patients with 2–3, 3–5, and 5–7 cm tumors had a poorer prognosis if VPI was present, suggesting that the staging of these cases should be increased to T2a, T2b, and T3, respectively.⁹ Fibla *et al.* used the American College of Surgeons Oncology Group Z0030 database to analyze the prognostic effect of VPI in patients with stage IB NSCLC.¹⁰ They found that patients with VPI and tumors >3 cm had significantly poorer prognosis compared with patients with smaller tumors, and proposed that the staging of these cases be increased to IIA. The development of imaging techniques and an increase in the clinical application of low-dose computed tomography for screening has enabled more patients with lung cancer to be diagnosed at early stage.¹⁸

Hattori *et al.* analyzed the imaging data of 446 patients with early stage lung cancer, and showed that for tumors ≤ 3 cm, VPI only affected the prognosis of patients with completely solid nodules, and had no significant effect on those with part-solid (ground-glass) nodules.¹⁹

By analyzing the prognostic impact of VPI in relation to tumor size in patients with surgically resected pN0 NSCLC, we found that VPI had no significant influence on five-year OS or postoperative recurrence and metastasis in cases with tumors ≤ 2 cm; therefore, these cases should continue to be classed as stage T1a NSCLC. These patients only require regular follow-up and postoperative monitoring, thereby avoiding additional damage from unnecessary chemotherapy. Detailed fractional analysis showed that patients with pN0 NSCLC with VPI and 2–3 cm tumors had a poorer prognosis compared with non-VPI patients and should be considered for postoperative adjuvant therapy to reduce the risk of postoperative recurrence and metastasis. We found that patients with tumor size ≤ 3 cm were more heterogeneous. Hattori *et al.* reported that for tumors sized ≤ 3 cm, VPI did not affect the prognosis of patients with a part-solid nodule.¹⁹ In their study, part-solid nodules were more common in the tumor size ≤ 2 cm group than in the 2–3 cm group. Our results indicated that tumors sized ≤ 2 cm were less aggressive and invasive than tumors sized 2–3 cm. Patients with tumors sized ≤ 2 cm had good prognosis even though the tumor invaded the visceral pleura. However, VPI can significantly influence the prognosis of a patient with a tumor sized 2–3 cm. Although there was a separate trend in the DFS survival curves between patients with 3–5 and 5–7 cm tumors, the presence of VPI did not significantly affect the prognosis of these patients. VPI was not a critical prognostic factor among patients with tumors sized >3 cm. This result was consistent with the current TNM staging system but differed from Kawase *et al.*'s findings, which suggested that cases of NSCLC with VPI and 3–5 cm tumors should be re-classed as stage T2b.¹⁶ The number of cases in our study with tumors 5–7 cm was relatively small compared to previous reports and our findings will need to be verified using a larger study sample. In our opinion, the prognostic influence of VPI could change along with tumor size.

We investigated the effect of VPI on postoperative recurrence in patients with early stage NSCLC. Our results showed that VPI was strongly associated with an increased incidence of regional and distant metastasis, suggesting that VPI might be involved in promoting the development of postoperative ipsilateral pleural metastasis in patients with radically resected NSCLC. These findings were consistent with several previous studies. Hung *et al.* reported that an increase in the degree of VPI was associated with an increase in the proportion of patients with postoperative

malignant pleural effusion.²⁰ Kameyama *et al.* observed a higher proportion of pleural lavage cytology positive patients with VPI compared with that in patients without VPI, and showed that these patients had a poorer prognosis.²¹ Based on these findings, we hypothesized that as the tumor invaded the visceral pleura, there was a greater likelihood of tumor cells detaching during surgery to form micrometastases in the pleural cavity. We recommend that intraoperative pleural lavage cytology be performed in patients with suspected pleural invasion, and that adjuvant therapy should be administered to cases with a positive cytologic examination to reduce the risk of recurrence.

Lymphatic metastasis is an important prognostic factor in NSCLC.^{6,22} Patients with multi-station mediastinal lymph node metastasis (≥ 2 stations) have a significantly poorer prognosis compared with those with single-station mediastinal lymph node metastasis.^{23–25} Manac'h *et al.* proposed that as the tumor invaded the visceral pleura, tumor cells were more susceptible to dispersing throughout the lymphatic system.⁴ In support of these studies, our data showed that the probability of mediastinal lymph node metastasis in patients with resected NSCLC was significantly higher in patients with VPI compared with those without VPI, and that these patients were more vulnerable to multi-station mediastinal lymph node metastasis. In addition, we found that patients with moderately and poorly differentiated tumors, vessel carcinoma embolus, abnormal elevation of preoperative serum CEA level, or larger tumors had a higher incidence of VPI than those without these risk factors. This suggested that the probability of VPI might not only depend on the site of tumor, but may be closely related to the inherent growth and invasive capacity of the tumor.³

Our study had several limitations. As this was a retrospective study, there may have been selection bias and data on clinical and pathologic staging, co-morbidities, and pulmonary function testing results were not available. The degree of VPI was not known in detail, and therefore should be the subject of further investigation. Our study size was small, therefore our findings need to be verified in a larger study sample.

In conclusion, we determined that VPI is an adverse prognostic factor in patients with radically resected pN0 NSCLC, particularly in those with 2–3 cm tumors. In line with others, we propose that these cases should be upstaged, whereas the prognosis of cases involving tumors sized ≤ 2 , 3–5, or 5–7 cm was not significantly affected by VPI and their staging should remain unchanged. Consistent with the results of previous studies, our findings indicated that VPI interacts with tumor size, which influenced prognosis. Our findings may have clinical significance for screening high-risk patients for postoperative adjuvant therapy and improving postoperative survival.

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Disclosure

No authors report any conflict of interest.

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