Original Article

Impact of adjuvant chemotherapy on patients with stage IB non-small cell lung cancer with visceral pleural invasion

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Background: Adjuvant chemotherapy has reduced the risk of recurrence and death in stage IB non-small cell lung cancer (NSCLC) with high-risk factors; however, the impact of visceral pleural invasion (VPI) on outcomes in stage IB NSCLC treated with adjuvant chemotherapy remains controversial. The aim of this study was to explore the clinical and prognostic significance of adjuvant chemotherapy for stage IB (1–4 cm) NSCLC with VPI.

Methods: This retrospective study included 251 patients admitted between January 2008 and May 2018 from four hospitals who underwent complete resection for Tumor-Node-Metastasis (TNM) 8th edition stage IB NSCLC with VPI. The relationship between adjuvant chemotherapy and overall survival (OS) or recurrence-free survival (RFS) was analyzed using the Kaplan-Meier method and Cox proportional hazards model.

Results: Of 251 patients with stage IB NSCLC with VPI, 122 (48.6%) received adjuvant chemotherapy after surgical resection and 129 (51.4%) were placed under observation. Multivariable analysis showed that adjuvant chemotherapy was an independent predictor of RFS [adjusted hazard ratio (aHR), 0.57; 95% confidence interval (CI): 0.33–0.96; P=0.036]. A micropapillary pattern (aHR, 2.46; 95% CI: 1.33–4.55; P=0.004) and lymphovascular invasion (aHR, 2.86; 95% CI: 1.49–5.48; P=0.002) were associated with a higher risk of recurrence. Multivariable analysis also showed that adjuvant chemotherapy was an independent predictor of OS (aHR, 0.22; 95% CI: 0.09–0.58; P=0.002). In a subgroup analysis of patients with a tumor size of 1–3 cm, adjuvant chemotherapy was associated with improved RFS and OS, and this association was maintained even when patients with VPI had additional risk factors.

Conclusions: Our study shows that adjuvant chemotherapy is appropriate for patients with stage IB (1–4 cm) NSCLC with VPI, and even those with smaller tumors (1–3 cm).

Keywords: Adjuvant chemotherapy; non-small cell lung cancer (NSCLC); visceral pleural invasion (VPI)

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Introduction

The incidence of lung cancer is increasing and it is the leading cause of cancer-related death worldwide (1,2). The detection of early-stage lung cancer has increased with developments in computed tomography (CT) (3). Surgery is the primary treatment for early-stage lung cancer, especially stage I non-small cell lung cancer (NSCLC). However, previous studies have reported a recurrence rate of approximately 18–29% within 5 years after surgery for stage I NSCLC (4,5). Therefore, it is necessary to identify risk factors for poor prognosis after surgery. Current National Comprehensive Cancer Network (NCCN) guidelines (6) recommend adjuvant chemotherapy for patients with high-risk factors [poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural invasion (VPI), and incomplete lymph node sampling] who undergo surgery for stage IB NSCLC. However, the guidelines briefly describe these risk factors as considerations for adjuvant chemotherapy for stage IB NSCLC, and it is not enough to know what kind of prognosis each risk factor shows in stage IB patients classified as relatively low stage. Additionally, the effects when various factors are combined are not well known.

Among the high-risk factors, the presence of VPI is not only a tumor invasion pattern representing tumor aggressiveness in NSCLC, but also upgrades T1 (<3 cm) to T2 tumors, according to the Tumor-Node-Metastasis (TNM) staging system. The presence of VPI is associated with poor prognosis in early-stage NSCLC (7,8). However, the role of VPI in stage IB NSCLC treated with adjuvant chemotherapy remains controversial (9-12). We previously showed that adjuvant chemotherapy reduced the risk of recurrence and death in patients with stage IB NSCLC with high-risk factors (13). The aim of this study was to correlate adjuvant chemotherapy to recurrence-free survival (RFS) and overall survival (OS) in patients with stage IB (1–4 cm) NSCLC with VPI, and to investigate the effectiveness of adjuvant chemotherapy when other risk factors are added in those patients with VPI. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-936/rc).

Highlight box

Key findings

- Adjuvant chemotherapy improved recurrence-free survival (RFS) and overall survival (OS) in patients with stage IB non-small cell lung cancer (NSCLC) with visceral pleural invasion (VPI).

What is known and what is new?

- Adjuvant chemotherapy appeared to provide better RFS and OS in patients with stage IB NSCLC with VPI compared to the control group, and also provided better RFS and OS of patients with tumor size 1–3 cm and VPI compared to the control group.

What is the implication, and what should change now?

- We suggest that adjuvant chemotherapy be offered to patients with stage IB NSCLC with VPI regardless of tumor size (>1 cm).

Methods

Study design and participants

We retrospectively examined the medical records of patients with T2aN0M0 (stage IB) (≤4 cm) NSCLC with high-risk factors from four Korean hospitals. This study extends a previous study that demonstrated the clinical efficacy of adjuvant chemotherapy in patients with stage IB (≤4 cm) NSCLC with high-risk factors, which included patients admitted between January 2008 and May 2018 (13). The enrolled patients were observed until March 2023, and additional survival data were collected.

To analyze the individual contribution of VPI and evaluate the interaction of VPI with other risk factors, we selected patients with stage IB NSCLC with VPI from a previous study (13). Patients were divided into two groups according to the use of adjuvant chemotherapy: adjuvant chemotherapy and control.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of each hospital: Korea University Guro Hospital (No. k2023-1179), Korea University Anam Hospital (No. 2023AN0215), Catholic University Hospital (No. SC23RID10088), and Hanyang University Hospital (No. HYUH 2022-05-017). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Examination and treatment modalities

Our previously published study and this study included only patients who underwent lobectomy. Staging was performed according to the American Joint Committee on Cancer TNM classification (8th edition) (14). As in previous study (13), patients who received neoadjuvant chemotherapy, radiotherapy, or non-platinum-based adjuvant chemotherapy were excluded. Patients with unknown lymph node status (Nx) or who underwent wedge resection were excluded,

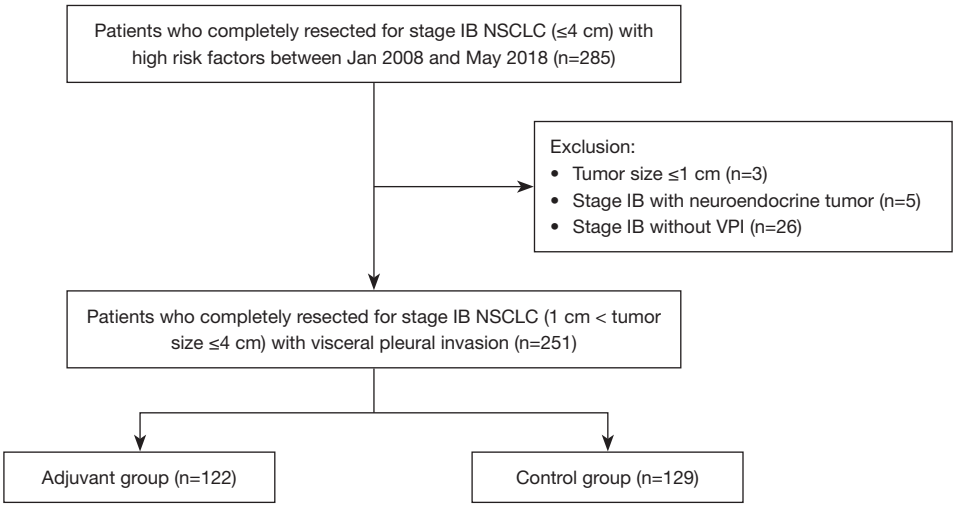

Figure 1 Flow chart of study population. NSCLC, non-small cell lung cancer; VPI, visceral pleural invasion.

because of the limited staging accuracy. Chest CT was performed every 3–6 months for the first 2 years after diagnosis, and then every 6 months for the following 5 years, or until death. When recurrence was suspected, chest CT or positron emission tomography (PET) was performed regardless of the timing. Recurrence was determined by chest CT or PET/CT. Comorbidities and smoking history were recorded at the time of surgery. Patients received adjuvant chemotherapy within 2 months of surgery. Five platinum-based regimens were used. Only patients who completed four cycles of adjuvant chemotherapy were enrolled. Chemotherapy cycles were administered every 3 weeks. The chemotherapy cycles and doses were adjusted according to the patient's general condition and side effects.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) and compared using Student's *t*-test. Categorical variables were expressed as numbers and percentages and compared using Chi-square or Fisher's exact tests. RFS was calculated from the date of surgery to the date of first recurrence, as evaluated by chest CT or PET/CT. OS was calculated from the date of surgery to the date of death from any cause. RFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) were calculated using a multivariable Cox proportional hazards model. Multivariable analysis was performed using backward elimination that included variables with P<0.2 in the univariable analysis. Subgroup analyses of patients with only VPI and at least two risk factors, including VPI in tumors of 1–4 cm, and patients with only VPI and at least two risk factors, including VPI in tumors of 1–3 cm, were performed in the same manner. A subgroup analysis of patients with adenocarcinoma with only VPI and at least two risk factors, including VPI, was also performed. A P value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC, USA). Graphs were generated using R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 285 patients were analyzed. Patients with T1a (≤1 cm) (n=3) or neuroendocrine tumors (n=5) were excluded. Additionally, patients with stage IB (1–4 cm) NSCLC with high-risk factors other than VPI (n=26) were excluded (*Figure 1*). All patients underwent lobectomy and complete lymph node dissection. None of the patients underwent pneumonectomy, bilobectomy, segmentectomy, or wedge resection. All patients underwent R0 resection. There was no evidence of cancer in the lymph nodes (N0).

One hundred and twenty-two patients (48.6%) were included in the adjuvant chemotherapy group and 129 patients (51.4%) were included in the control group. The mean and median follow-up duration was 50.7±16.7 and 60.8 months, respectively. There were no significant

Table 1 Baseline characteristics (n=251)

Variables	Adjuvant chemotherapy group (n=122)	Control group (n=129)	P value
Age (years)			
≥60 years	43 (35.2)	18 (14.0)	<0.001
Mean ± SD	63.2±8.3	68.6±9.0	<0.001
Median [IQR]	64 [58, 69]	71 [63, 75]	–
Sex, male	60 (49.18)	60 (46.51)	0.672
Smoking status			0.845
Never-smoker	79 (64.8)	82 (63.6)	
Ever-smoker	43 (35.2)	47 (36.4)	
Pulmonary function test			
FEV_1/FVC (%) (mean ± SD)	76±12	77±11	0.800
FEV_1/FVC <70%	30 (24.6)	24 (18.6)	0.249
Histology			0.821
Adenocarcinoma	108 (88.5)	113 (87.6)	
Non-adenocarcinoma	14 (11.5)	16 (12.4)	
Tumor diameter (cm) (mean ± SD)	2.42±0.73	2.39±0.74	0.933
Tumor diameter			0.835
1< size ≤2 cm	40 (32.8)	39 (30.2)	
2< size ≤3 cm	55 (45.1)	63 (48.9)	
3< size ≤4 cm	27 (22.1)	27 (20.9)	
Adjuvant chemotherapy regimen			
Paclitaxel + platinum	75 (61.5)	–	–
Vinorelbine + platinum	43 (35.2)	–	–
Pemetrexed + platinum	4 (3.3)	–	–
Micropapillary pattern	28 (23.0)	22 (17.1)	0.242
Lymphovascular invasion	29 (23.8)	16 (12.4)	0.019

Data are presented with n (%) except for the variables indicated separately. SD, standard deviation; IQR, interquartile range; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

differences between the groups, except for age and lymphovascular invasion (*Table 1*). Patients in the adjuvant chemotherapy group were younger than those in the control group (mean age: 63.2 *vs.* 68.6 years; P<0.001). The proportion of males was similar between the two groups (P=0.672). Of the 251 patients, approximately 64% were never smokers. There was no significant difference in smoking status between the two groups. Adenocarcinoma was the most common histological subtype in all patients (n=221; 88%). Fifty-four patients (approximately 22%) had tumors >3 cm in diameter. The frequency of lymphovascular invasion was significantly higher in the adjuvant chemotherapy group than in the control group (23.8% *vs.* 12.4%; P=0.019). The adjuvant chemotherapy regimens were as follows: paclitaxel-platinum (n=75; 61.5%), vinorelbine-platinum (n=43; 35.2%), and pemetrexed-platinum (n=4; 3.3%).

RFS and OS in total patients

Recurrence was observed in 24 (19.7%) of 122 patients in

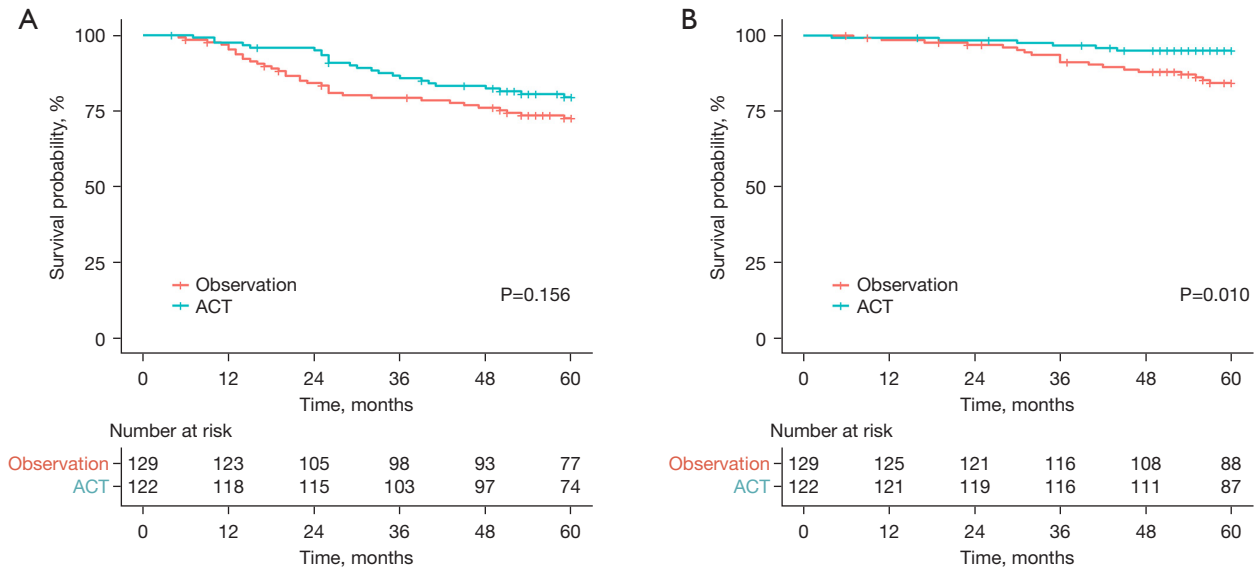

Figure 2 Kaplan-Meier curve for recurrence-free survival (A) and overall survival (B) for all population. ACT, adjuvant chemotherapy.

the chemotherapy group, and in 34 (26.4%) of 129 patients in the control group (P=0.209). In the adjuvant chemotherapy group, 6 (4.9%) of 122 patients died and, in the control group, 19 (14.7%) of 129 patients died (P=0.010). The 5-year RFS rates were 79.6% and 72.6% in the adjuvant chemotherapy and control groups, respectively (log-rank test, P=0.156) (*Figure 2A*). The 5-year OS rates were 95.0% and 84.4% in the adjuvant chemotherapy and control groups, respectively (log-rank test, P=0.010) (*Figure 2B*). Among patients with only VPI, those who received adjuvant chemotherapy had longer OS than controls (log-rank test, P=0.018) (Figure S1). Among patients with at least two risk factors, including VPI, those who received adjuvant chemotherapy also had longer OS than controls (log-rank test, P=0.024) (Figure S2).

Risk factors for RFS and OS in patients with stage IB NSCLC with VPI are shown in *Table 2*. In the multivariable analysis, the adjuvant chemotherapy group had a lower risk of recurrence than the control group [adjusted HR (aHR), 0.57; 95% confidence interval (CI): 0.33–0.96; P=0.036]. A micropapillary pattern (aHR, 2.46; 95% CI: 1.33–4.55; P=0.004) and lymphovascular invasion (aHR, 2.86; 95% CI: 1.49–5.48; P=0.002) were associated with a higher risk of recurrence. The adjuvant chemotherapy group also had a lower risk of death than the control group (aHR, 0.22; 95% CI: 0.09–0.58; P=0.002). The risk of death was higher among ever-smokers (aHR, 4.16; 95% CI: 1.21–14.38; P=0.024) and patients with lymphovascular invasion (aHR, 7.24; 95% CI: 3.10–16.90; P<0.001).

Subgroup analysis

The results of the subgroup analysis are shown in *Table 3*. In patients with a tumor size of 1–3 cm, adjuvant chemotherapy was associated with improved RFS (aHR, 0.45; 95% CI: 0.24–0.84; P=0.013) and OS (aHR, 0.27; 95% CI: 0.09–0.79; P=0.017), and this association was maintained even when patients with VPI had additional risk factors (OS: aHR, 0.28; 95% CI: 0.09–0.87; P=0.027). In patients with adenocarcinoma with VPI, adjuvant chemotherapy was also associated with improved RFS (aHR, 0.56; 95% CI: 0.32–0.99; P=0.048) and OS (aHR, 0.14; 95% CI: 0.04–0.46; P=0.001).

Discussion

We conducted a multicenter study to investigate the efficacy of adjuvant chemotherapy in patients with TNM 8th edition stage IB NSCLC with VPI. We showed that adjuvant chemotherapy improved RFS and OS in patients with stage IB NSCLC with VPI. In the multivariable analysis, adjuvant chemotherapy had a beneficial effect on recurrence and survival compared to the control group. In the subgroup analysis, adjuvant chemotherapy improved RFS and OS, even in patients with a tumor size of 1–3 cm.

According to the NCCN guidelines (6), there are several

Table 2 Risk factors for recurrence-free survival and overall survival of patients with IB NSCLC with visceral pleural invasion (n=251)

Variables	RFS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	aHR (95% CI)	P value	HR (95% CI)	P value	aHR (95% CI)	P value
Age ≥60 years	1.06 (0.58–1.94)	0.845	–	–	2.64 (0.79–8.81)	0.115	2.38 (0.69–8.23)	0.170
Sex, male	1.26 (0.75–2.11)	0.382	–	–	2.53 (1.09–5.86)	0.031	0.72 (0.20–2.53)	0.605
Smoking status, ever-smoker	1.19 (0.70–2.02)	0.520	–	–	3.63 (1.60–8.21)	0.002	4.16 (1.21–14.38)	0.024
Histology, adenocarcinoma	0.74 (0.35–1.56)	0.432	–	–	0.48 (0.18–1.27)	0.139	1.44 (0.48–4.25)	0.515
Tumor diameter, cm								
1< size ≤2	Reference		–		Reference		–	
2< size ≤3	1.34 (0.72–2.50)	0.359	–	–	1.90 (0.68–5.26)	0.220	–	–
3< size ≤4	1.41 (0.68–2.92)	0.354	–	–	1.77 (0.54–5.81)	0.345	–	–
Micropapillary pattern, yes	1.77 (1.003–3.11)	0.049	2.46 (1.33–4.55)	0.004	0.53 (0.16–1.77)	0.302	–	–
Lymphovascular invasion, yes	1.92 (1.07–3.46)	0.029	2.86 (1.49–5.48)	0.002	5.24 (2.39–11.48)	<0.001	7.24 (3.10–16.90)	<0.001
Adjuvant chemotherapy, yes	0.69 (0.41–1.16)	0.159	0.57 (0.33–0.96)	0.036	0.32 (0.13–0.80)	0.015	0.22 (0.09–0.58)	0.002

NSCLC, non-small cell lung cancer; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

Table 3 Subgroup analysis through multivariable analysis

Subgroups	Adjuvant chemotherapy group (n=122)	Control group (n=129)	RFS		OS	
			aHR (95% CI)	P value	aHR (95% CI)	P value
1< size ≤4 cm						
≥1 risk factor including VPI (overall)	122	129	0.52 (0.30–0.89)	0.017	0.22 (0.08–0.58)	0.003
≥2 risk factors including VPI*	66	46	0.57 (0.29–1.13)	0.105	0.29 (0.10–0.80)	0.017
1< size ≤3 cm						
≥1 risk factor including VPI (overall)	95	102	0.45 (0.24–0.84)	0.013	0.27 (0.09–0.79)	0.017
≥2 risk factors including VPI*	50	39	0.48 (0.22–1.05)	0.065	0.28 (0.09–0.87)	0.027
Adenocarcinoma						
≥1 risk factor including VPI (overall)	108	113	0.56 (0.32–0.99)	0.048	0.14 (0.04–0.46)	0.001
≥2 risk factors including VPI*	60	41	0.58 (0.27–1.22)	0.149	0.19 (0.06–0.63)	0.007

The multivariable analysis was conducted for variables with P<0.2 in the univariable analysis among adjuvant chemotherapy, age, sex, smoking status, histology, tumor diameter, micropapillary pattern, and lymphovascular invasion. *, this means the population with at least two risk factors including VPI + micropapillary pattern or VPI + lymphovascular invasion, or all three risk factors. RFS, recurrence-free survival; OS, overall survival; aHR, adjusted hazard ratio; CI, confidence interval; VPI, visceral pleura invasion.

high-risk factors for stage IB NSCLC, including lung neuroendocrine tumors, vascular invasion, wedge resection, tumor size >4 cm, and VPI. In particular, VPI has been shown to be associated with an unfavorable prognosis in NSCLC (7,8). VPI is diagnosed using elastic staining and affects tumor staging in approximately 25% of cases of early-stage NSCLC (15,16). A systematic review and meta-analysis (7) reported that VPI is an adverse factor in NSCLC with negative nodes and no metastasis. Patients with tumor size 3–5 cm and VPI had worse OS than those

with tumor size <3 cm and VPI. The authors concluded that the larger the tumor size the greater the impact of VPI on OS.

Although it is well known that VPI is associated with a worse prognosis, several studies (8-12) have reported conflicting results regarding the effect of adjuvant chemotherapy in resected NSCLC with VPI. The stages and sample sizes in each study were different, and this may have affected the reporting of results. Park *et al.* (9) and Zhang *et al.* (17) suggested that patients with stage IB NSCLC with VPI did not benefit from adjuvant chemotherapy. However, these single-center retrospective studies had relatively small sample sizes, with 27 and 22 patients with stage IB NSCLC with VPI receiving adjuvant chemotherapy (9,17). Xie *et al.* (11) reported using the SEER database that patients with stage IB NSCLC with VPI, who received adjuvant chemotherapy between 2010 and 2015, showed an upward trend in OS compared with the control group, although the difference was not statistically significant (P=0.216). After removing age, adjuvant chemotherapy was found to be an independent prognostic factor for OS in patients with stage IB NSCLC with VPI (11). The differences in 1-, 3-, and 5-year OS rates between the adjuvant chemotherapy and control groups tended to increase with follow-up time.

A Chinese study (12) of 648 patients with stage IB–IIA NSCLC (stage IB: n=566; 87%) showed that patients with VPI may benefit from adjuvant chemotherapy, because they have a lower risk of recurrence after adjuvant chemotherapy. However, adjuvant chemotherapy did not improve the OS of these patients. Patients with VPI in the 3–5 cm subgroup may have benefited from adjuvant chemotherapy in terms of recurrence and survival (12). This study did not only include patients with stage IB NSCLC. However, the rate of stage IB NSCLC was as high as 87%, and some effects of adjuvant chemotherapy were observed in patients with resected NSCLC with VPI. A United States study using the National Cancer Database (10) showed that, for all tumor sizes combined, patients with VPI who received adjuvant chemotherapy had a significantly better 5-year OS rate than those who did not receive adjuvant chemotherapy (65.5% *vs.* 58.8%; P<0.001). In the multivariable analysis, adjuvant chemotherapy was associated with significantly longer 5-year OS for tumor size 3–4 cm (aHR, 0.62; 95% CI: 0.46–0.83; P=0.001) (10).

Our multicenter study showed that the effect of adjuvant chemotherapy in resected NSCLC was similar to that reported in previous large-scale studies. However, we only included patients with stage IB (1–4 cm) NSCLC, and showed that adjuvant chemotherapy improved recurrence and survival outcomes. A previous study (7) has shown a synergistic effect between VPI and tumor size on prognosis. Several studies (8,10,12,18) have shown that the effect of adjuvant chemotherapy is more pronounced in tumors >3 cm in diameter. However, in this study, adjuvant chemotherapy had beneficial effects on recurrence and survival in patients with NSCLC and VPI, even in those with a tumor size of 1–3 cm. Some studies (7,19) have suggested a potential benefit of adjuvant chemotherapy in patients with small tumors of <3 cm in diameter. In this study, adjuvant chemotherapy was effective in patients with small tumors and multiple risk factors, including VPI. Patients with stage IB NSCLC with small tumors, who may benefit from adjuvant chemotherapy, may be further stratified by other clinical factors, such as performance status and pulmonary function, which have not yet been studied. Larger prospective studies are needed to identify populations of patients with resected stage IB NSCLC with small tumors (1–3 cm) that would benefit from adjuvant chemotherapy.

Our study has several limitations. First, given its retrospective nature, the study is subject to selection bias. Because the study was conducted in South Korea, the data cannot be generalized to other regions. Second, we did not classify VPI as PL1 or PL2. Pleural invasion can be classified into four groups: PL0, PL1, PL2, and PL3 (20). Among them, PL1 and PL2 are considered VPI in the current TNM staging system. Previous studies (21,22) have shown that among patients with VPI, there may be differences in survival depending on whether patients have PL1 or PL2. A meta-analysis (21) showed that patients with PL2 had a significantly lower 5-year survival rate than those with PL1. In this study, we could not evaluate RFS and OS according to PL1 or PL2. Third, performance status and cause of death was not analyzed in all patients (13). Eastern Cooperative Oncology Group performance status was only assessed in the adjuvant chemotherapy group. Fourth, the toxicity and dose intensity of adjuvant chemotherapy were not evaluated. No chemotherapy-related deaths occurred during this study. The dose intensity could not be accurately determined in some patients, because of the long enrollment period [2008–2018]. Additionally, our study did not investigate information on the mutation status of cancer-related genes, such as epidermal growth factor receptor and anaplastic lymphoma kinase. Therefore, we were unable to provide additional information on this aspect. Lastly, clinicians decided to administer adjuvant

chemotherapy based on several factors, which may have introduced bias. Despite these limitations, we included patients with stage IB NSCLC with VPI from multiple centers, which has the advantage of evaluating the effects of adjuvant chemotherapy specifically in patients with TNM 8th edition stage IB NSCLC with VPI. These effects were not previously observed due to the heterogeneity of previous studies.

Conclusions

Adjuvant chemotherapy appeared to provide better RFS and OS in patients with stage IB NSCLC with VPI compared to the control group. Adjuvant chemotherapy also provided better RFS and OS of patients with tumor size 1–3 cm and VPI compared to the control group. We suggest that adjuvant chemotherapy be offered to patients with stage IB NSCLC with VPI regardless of tumor size (>1 cm). To support our findings, additional prospective studies, including information on toxicity and PL1-PL2 status, should be conducted in the future.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-936/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-936/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of each hospital: Korea University Guro Hospital (No. k2023-1179), Korea University Anam Hospital (No. 2023AN0215), Catholic University Hospital (No. SC23RID10088), and Hanyang University Hospital (No. HYUH 2022-05-017). The requirement for written informed consent was waived owing to the retrospective nature of the study.

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Supplementary

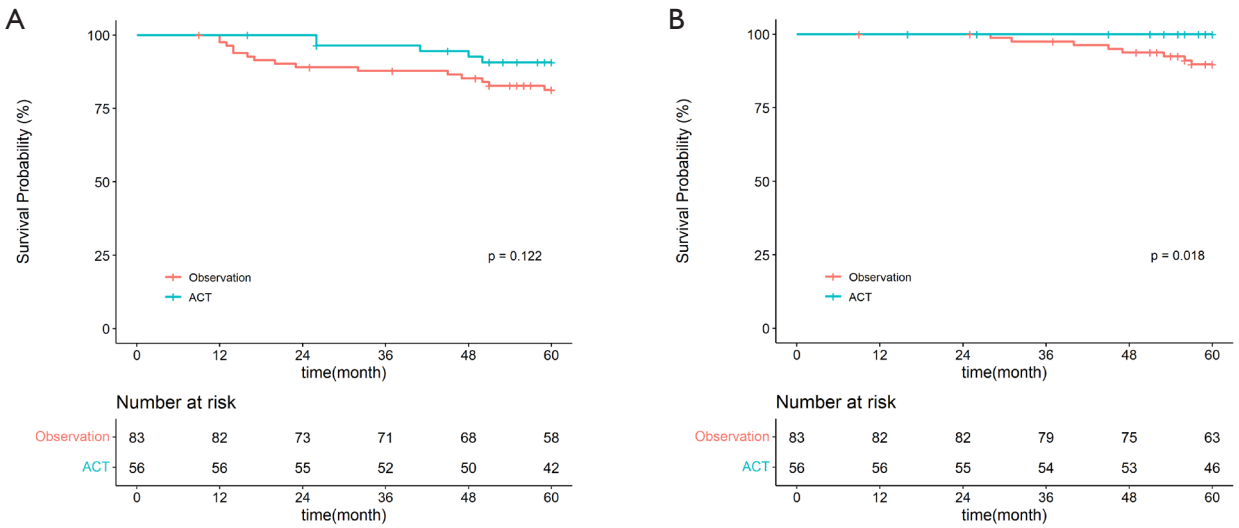

Figure S1 Kaplan-Meier curves of recurrence-free survival (A) and overall survival (B) for patients with stage IB NSCLC only visceral pleural invasion. NSCLC, non-small cell lung cancer.

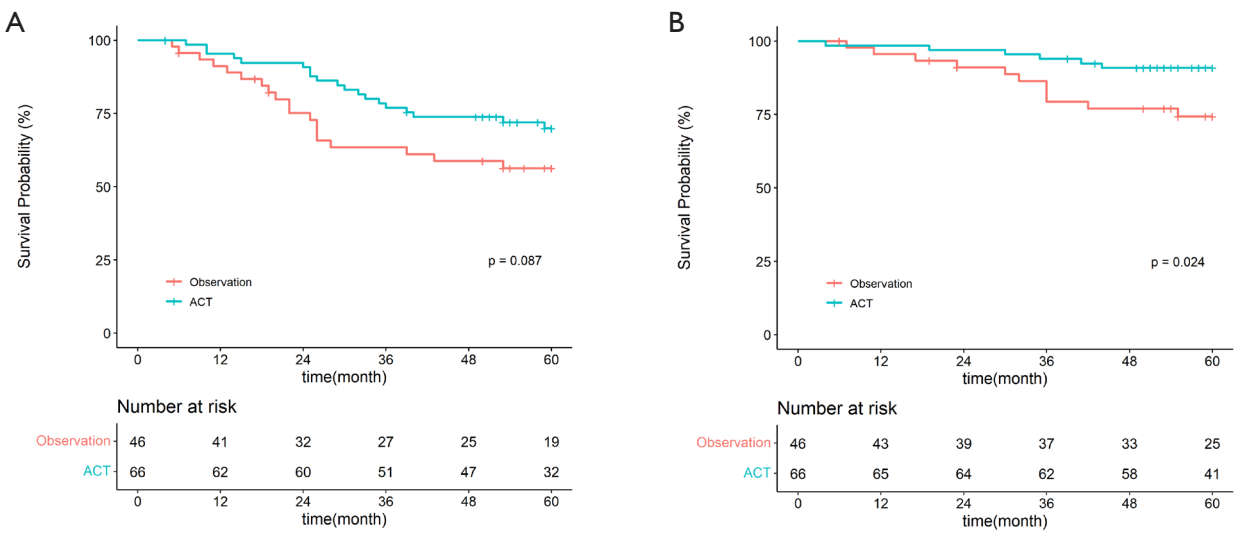

Figure S2 Kaplan-Meier curves of recurrence-free survival (A) and overall survival (B) for patients with stage IB NSCLC with at least two risk factors including visceral pleural invasion. NSCLC, non-small cell lung cancer.

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