Adjuvant chemotherapy may improve prognosis after resection of stage I lung cancer with lymphovascular invasion

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ABSTRACT

Objectives: This study explored the prognostic significance and adjuvant chemotherapy benefits in resected patients with stage I non–small cell lung cancer with lymphovascular invasion.

Methods: A total of 2633 patients who received complete resection with pathologic stage I non–small cell lung cancer in the Shanghai Chest Hospital (2008–2012) were enrolled in the study, of whom 222 were diagnosed with lymphovascular invasion. By using the Kaplan–Meier method and Cox proportional hazard regression model, we explored the impact of lymphovascular invasion on prognosis and determined if the use of adjuvant chemotherapy is associated with improved outcomes in patients with lymphovascular invasion. A propensity score–matched analysis was implemented to reduce the selection bias.

Results: Patients with lymphovascular invasion had an unfavorable overall survival and recurrence-free survival in stage I non–small cell lung cancer. Multivariate Cox analysis indicated that lymphovascular invasion was an independent poor prognostic factor for recurrence-free survival (hazard ratio [HR], 2.06; 95% confidence interval [CI], 1.58–2.71; $P < .001$) and overall survival (HR, 2.04; 95% CI, 1.45–2.87; $P < .001$) in patients with stage I. After using propensity score–matched pairs, analysis of 65 pairs of patients with lymphovascular invasion indicated a beneficial recurrence-free survival (HR, 0.33; 95% CI, 0.16–0.67; $P = .002$) and overall survival (HR, 0.30; 95% CI, 0.12–0.74; $P = .009$) from adjuvant chemotherapy.

Conclusions: Lymphovascular invasion was correlated with poor prognosis in patients with stage I non–small cell lung cancer. For such patients, adjuvant chemotherapy was associated with improved survival. Our study suggests that adjuvant chemotherapy might be an appropriate option for patients with stage I non–small cell lung cancer with lymphovascular invasion. (*J Thorac Cardiovasc Surg* 2018;156:2006–15)

The RFS curves (ACT vs observation) in stage I NSCLC with lymphovascular invasion.

Central Message

For patients with stage I lung cancer, LVI has been reported to be a strong risk factor. ACT may improve the poor prognosis in patients with stage I lung cancer with LVI.

Perspective

This study investigated the influence of LVI in patients with stage I NSCLC based on the 8th edition of the TNM classification and whether ACT may improve the poor prognosis in patients with stage I with LVI.

See Editorial Commentary page 2016.

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Lung cancer is one of the most common cancers and a major cause of cancer-related deaths worldwide.¹ Today, with the prevalence of low-dose computed tomography (CT) for screening, patients are being diagnosed at earlier stages.² For these patients with early-stage disease, operation is the optimal treatment. Patients with stage IA and IB non–

Scanning this QR code will take you to a supplemental figures and video for this article.

Abbreviations and Acronyms	
ACT	= adjuvant chemotherapy
CI	= confidence interval
CT	= computed tomography
HR	= hazard ratio
LVI	= lymphovascular invasion
LVI-N	= lymphovascular invasion negative
LVI-P	= lymphovascular invasion positive
NCCN	= National Comprehensive Cancer Network
NSCLC	= non-small cell lung cancer
OS	= overall survival
PET	= positron emission tomography
PSM	= propensity score matching
RFS	= recurrence-free survival
VPI	= visceral pleural invasion

small cell lung cancer (NSCLC) have 82% and 66% 5-year survival, respectively, according to the 7th TNM stage.³ When compared with other malignant tumors, stage I NSCLC has a good prognosis; however, a few patients eventually die of lung cancer, potentially indicating the existence of a poor prognostic group.^{4,5}

Previous studies have reported clinicopathologic parameters, including sex, age, smoking history, serum carcinoembryonic antigen level, extent of operation, tumor

VIDEO 1. Lobectomy and lymph node dissection of left upper lobe of lung. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31779-3/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31779-3/fulltext).

differentiation, tumor size, visceral pleural invasion (VPI), and lymphovascular invasion (LVI), that may be related to prognosis.⁶⁻¹¹ Of these parameters, LVI was demonstrated to be an important prognostic factor in NSCLC.¹² LVI was defined as tumor growth around the vessel, destruction of vascular walls, or intravascular tumor thrombi formation that can be divided into blood vessel invasion and lymphatic vessel invasion.¹³ Because of the poor prognosis of LVI, some scholars suggested cataloging LVI into T stage.¹⁴

For patients with stage II to IIIA NSCLC, platinum-based adjuvant chemotherapy (ACT) is routinely recommended.

FIGURE 1. Diagram of study cohort selection step. *Mia*, Minimally invasive adenocarcinoma; *LVI*, lymphovascular invasion; *ACT*, adjuvant chemotherapy.

But the benefit from ACT for those with stage I NSCLC is still lacking evidence. Several clinical trials have drawn different conclusions. ANITA showed no benefits from ACT in patients with stage IB.¹⁵ JBR.10 showed no survival benefit from ACT for patients with stage IB, although patients with tumors larger than 4 cm appeared to benefit from chemotherapy.¹⁶ However, Cancer and Leukemia Group B 9633 recommended ACT for patients with stage IB who have tumors more than 4 cm in diameter.¹⁷ National Comprehensive Cancer Network (NCCN) guidelines recognized that chemotherapy may be considered for patients with stage IB with high-risk factors, including poorly differentiated tumors, vascular invasions, wedge resection, tumors greater than 4 cm, visceral pleural involvement, and unknown lymph node status. There was no conclusion in the use of ACT in patients with stage IA. Studies from Japan showed that tegafur-uracil significantly improved survival in patients with stage I NSCLC, particularly those with lung adenocarcinomas greater than 2 cm, which was revealed by randomized phase 3 trials and meta-analysis.¹⁸⁻²⁰

We explored the benefits of ACT for patients with stage I NSCLC, especially those with LVI. Therefore, the aim of our study was to investigate the impact of LVI on prognosis and to determine if the use of ACT is associated with improved outcomes in patients with LVI.

PATIENTS AND METHODS

Patients

This study was approved by the Institutional Review Board of Shanghai Chest Hospital (Shanghai, China). We reviewed the medical records of patients who had undergone pulmonary surgery between January 2008 and December 2012 in the Shanghai Chest Hospital and restaged these patients on the basis of the 8th edition of the TNM Classification for Lung and Pleural Tumors of the Union for International Cancer Control and postoperative pathology.³ According to the 8th TNM classification, stage IA (T1a-cN0M0) is divided into 3 groups: IA1, IA2, and IA3, defined as 1 cm or less, greater than 1 cm but 2 cm or less, greater than 2 cm but 3 cm or less in greatest dimension without lymph node involvement and distant metastasis, respectively. Stage IB (T2aN0M0) is defined as tumor greater than 3 cm but 4 cm or less in greatest dimension, or tumor with any of the following features (if ≤ 4 cm in greatest dimension): involves main bronchus regardless of distance from the carina of the carina but without involvement; invades visceral pleura without lymph node involvement and distant metastasis.

All patients underwent complete resection, including wedge resection, lobectomy (Video 1), and more extensive lung resection with systematic ipsilateral hilar and mediastinal lymph node dissection, and there was no evidence of residual cancer macroscopically or microscopically. There were also no positive lymph nodes or distant metastasis observed. In addition, all patients underwent preoperative examination, including contrast-enhanced CT, brain magnetic resonance imaging or CT, and abdominal CT or ultrasonography, and had good Eastern Cooperative Oncology Group performance status (0-1). Most patients underwent a radionuclide bone scan, and the remainder underwent positron emission tomography (PET) and CT. Patients were excluded if they were diagnosed with other malignant tumors or multiple primary lung cancer, received neo-ACT/radiotherapy, or were lost to follow-up. Finally, we included 2633 patients in the statistical analysis (Figure 1).

TABLE 1. Clinicopathologic characteristics of all patients with stage I stratified by lymphovascular invasion

	LVI negative (n = 2411) (%)	LVI positive (n = 222) (%)	P value
Age, y, (range)	60 (31-83)	60 (25-81)	.493*
Sex			.789†
Female	1163 (48.2)	105 (47.3)	
Male	1248 (51.8)	117 (52.7)	
Smoking history			.123†
Yes	693 (28.7)	53 (23.9)	
No	1718 (71.3)	169 (76.1)	
Cancer-related comorbidity			.652†
Yes	818 (33.9)	72 (32.4)	
No	1593 (66.1)	150 (67.6)	
Pulmonary function FEV1/FVC $\geq 70\%$	2249 (93.3)	209 (94.1)	.621†
PET-CT, n			.191†
Yes	296 (12.3)	34 (15.3)	
No	2115 (87.7)	188 (84.7)	
Procedure 1			.180†
Lobectomy	2195 (91.0)	208 (93.7)	
Sub-lobectomy	216 (9.0)	14 (6.3)	
Procedure 2			<.001†
VATS	2292 (95.1)	188 (84.7)	
Open	119 (4.9)	34 (15.3)	
P or C			.052†
P	2242 (93.0)	214 (96.4)	
C	169 (7.0)	8 (3.6)	
Postoperative complication			1.000‡
Yes	43 (1.8)	4 (1.8)	
No	2368 (98.2)	218 (98.2)	
TNM stage			.002†
Stage IA1-3	1482 (61.5)	113 (50.9)	
Stage IB	929 (38.5)	109 (49.1)	
Total tumor size, cm $\pm$ SD	2.6 $\pm$ 0.8	2.7 $\pm$ 0.8	.317*
Histology			.003†
Adenocarcinoma	2009 (83.3)	202 (91.0)	
Nonadenocarcinoma	402 (16.7)	20 (9.0)	
VPI			.042†
Yes	752 (31.2)	84 (37.8)	
No	1659 (68.8)	138 (62.2)	
Recurrence	420 (17.4)	67 (30.2)	<.001†
Mortality	304 (12.6)	42 (18.9)	.008†
Lung cancer mortality	272 (11.3)	41 (18.5)	
Other causes mortality	32 (1.3)	1 (0.5)	
ACT	706 (29.3)	148 (66.7)	<.001†

Nonadenocarcinoma includes squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma. LVI, Lymphovascular invasion; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PET-CT, positron emission tomography-computed tomography; VATS, video-assisted thoracoscopic surgery; P, peripheral lung cancer; C, central lung cancer; TNM stage, tumor-node-metastasis stage; SD, standard deviation; VPI, visceral pleura invasion; ACT, Adjuvant chemotherapy.

*Mann-Whitney U test. †Chi-square test. ‡Fisher exact test.

TABLE 2. Multivariate analyses of prognostic factors of patients with stage I non-small cell lung cancer

	Multivariate analysis of RFS		Multivariate analysis of OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.00 (0.99-1.02)	.658	1.01 (0.99-1.02)	.527
Sex				
Female	0.81 (0.64-1.01)	.065	0.65 (0.50-0.86)	.002
Smoking history				
Yes	1.09 (0.85-1.38)	.500	1.10 (0.83-1.44)	.516
Cancer-related comorbidity				
Yes	1.71 (1.37-2.13)	<.001	1.95 (1.50-2.55)	<.001
Pulmonary function				
FEV1/FVC ≥70%	3.00 (2.20-3.97)	<.001	3.35 (2.45-4.58)	<.001
PET-CT				
Yes	0.72 (0.57-0.92)	.008	0.77 (0.58-1.03)	.079
Procedure 1				
Lobectomy	0.65 (0.49-0.86)	.003	0.59 (0.43-0.82)	.002
Procedure 2				
VATS	0.57 (0.35-0.92)	.022	0.72 (0.41-1.27)	.254
P or C				
P	0.69 (0.43-1.12)	.133	0.86 (0.49-1.54)	.628
Postoperative complication				
Yes	1.79 (1.04-3.12)	.036	1.59 (0.88-2.86)	.127
Total tumor size	1.34 (1.16-1.54)	<.001	1.59 (1.35-1.89)	<.001
Histology				
Adenocarcinoma	0.90 (0.69-1.18)	.450	0.85 (0.63-1.15)	.290
VPI				
Yes	1.80 (1.28-2.53)	.001	2.08 (1.39-3.10)	<.001
LVI				
Yes	2.06 (1.58-2.71)	<.001	2.04 (1.45-2.87)	<.001
TNM stage				
IB	1.18 (0.81-1.74)	.390	1.30 (0.83-2.04)	.256
ACT				
Yes	0.94 (0.77-1.16)	.588	1.22 (0.95-1.55)	.119

Nonadenocarcinoma includes squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma. *RFS*, Recurrence-free survival; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *PET-CT*, positron emission tomography-computed tomography; *VATS*, video-assisted thoracoscopic surgery; *P*, peripheral lung cancer; *C*, central lung cancer; *VPI*, visceral pleura invasion; *LVI*, lymphovascular invasion; *TNM stage*, tumor-node-metastasis stage; *ACT*, adjuvant chemotherapy.

Histopathologic Studies

Histopathologic studies were performed according to the World Health Organization criteria. Detailed examinations of LVI were routinely performed by senior pathologists at our institution. LVI was defined as the obvious presence of tumor emboli in vessels under the microscope, regardless of whether they were blood or lymphatic vessels. If there were any doubts about diagnosis, specimens were stained with anti-D2-40 monoclonal antibody (DAKO, Carpinteria, Calif) to evaluate lymphatic vessels and Elastica van Gieson stain to confirm blood vessel invasion.

Follow-up

Follow-up was mainly conducted by patients visit and telephone. All of the patients were informed to visit our hospital or other institutions every 3 months for the first 3 years after surgery and every 6 months thereafter. Examination items, including thoracic CT, blood carcinoma embryonic antigen test, abdominal CT scan, or ultrasonography, were conducted every

visit. Bone scan and cranial CT scan or magnetic resonance imaging were performed annually if there were no symptoms. PET-CT was also recognized if permitted.

We collected the clinicopathologic parameters, including sex, age, smoking history, tumor location, operative procedures, operation date, histology type, tumor size, LVI, VPI, and cancer-related comorbidities and postoperative complication. Comorbidities included hypertension, diabetes mellitus, ischemic heart disease, abnormal pulmonary function, or other diseases proved to be related to the mortality of cancer by previous studies.²¹⁻²³ Normal pulmonary function was defined as forced expiratory volume in 1 second/forced vital capacity 70% or greater.

Criteria for Adjuvant Chemotherapy Treatment

In this study, cisplatin/carboplatin-based ACT was recommended for patients. Regimen dose and cycles followed NCCN guidelines.²⁴ At least 3 cycles of chemotherapy were considered as effective chemotherapy.

FIGURE 2. RFS (A) and OS (B) curves of patients with stage I NSCLC stratified by LVI. *LVI-N*, Lymphovascular invasion negative; *LVI-P*, lymphovascular invasion positive; *HR*, hazard ratio; *CI*, confidence interval.

Statistical Analysis

Data are presented as follows: Continuous variables are reported as median (range), and dichotomous variables are reported as number (percent). The chi-square test was used to compare frequencies for categorical variables, and the Fisher exact test was used for small samples. In the LVI positive (LVI-P) group, patients who received chemotherapy were younger than those in the observation group. To correct the bias of the ACT group and surgery alone group, propensity score matching (PSM) was used to balance clinical characteristics, including age, sex, smoking history, comorbidities, pulmonary function, PET-CT examination, surgery procedures, postoperative complications, histology, VPI, and tumor size. For PSM, nearest neighbor matching was selected with a caliper width of 0.2 of standard deviation. Patients in the observation group were randomly matched to those in the ACT group with 1:1 matching methods. The PSM was conducted using the package “MatchIt” of R (version 3.4.3; R Development Core Team). After PSM, McNemar’s test and paired-samples *t* test were used to analyze the propensity score–matched pairs.

Recurrence-free survival (RFS) was defined as the time from surgery to the date of the earliest recurrence or death due to any cause or the last follow-up. Overall survival (OS) was defined as the time from the day of surgery to death from any cause or the last follow-up.

The Kaplan–Meier method was applied to graphically describe the distribution of OS and RFS. The Cox proportional hazard model was used to assess the potential effects of LVI and ACT on OS and RFS after adjustment for other clinical variables.

The relative hazards and the relative 95% confidence intervals (CIs) were calculated. SPSS statistical software, version 22 (SPSS Inc, Chicago, Ill), was used for all statistical analyses.

RESULTS

Patient Characteristics

The median follow-up after surgery was 61.0 months, ranging from 0.3 to 106.3 months. The demographic and clinicopathologic characteristics of 2633 patients are summarized in Table 1. A total of 1595 patients had stage IA, and 1038 patients had stage IB. The median patient age was 60 years (range, 18–85 years). Approximately half (48.2%) of the patients were female, 84.0% were diagnosed with adenocarcinoma, and 28.3% had a history of smoking.

LVI was observed in 222 patients (8.4%); 113 (50.9%) had stage IA, and 109 (49.1%) had stage IB. With increasing tumor size, the presence of LVI increases: The presence of LVI in diameter from 0 to 1 cm, 1 to 2 cm, 2 to 3 cm, and 3 to 4 cm was 2.3%, 5.4%, 10.5%, and 13.3%, respectively. The 2 groups, LVI-P and lymphovascular invasion negative (LVI-N), showed a significant difference in histology ($P = .003$) and VPI ($P = .042$), indicating that LVI may be correlated with VPI and adenocarcinoma. The survival outcomes are summarized in Table 1.

Lymphovascular Invasion Was a Poor Prognostic Factor for Recurrence-Free Survival and Overall Survival in Patients With Stage I Non–Small Cell Lung Cancer

Univariate survival analysis was used to determine that LVI was a significantly poor prognostic factor for OS (LVI-P vs LVI-N: $P = .008$) and RFS (LVI-P vs LVI-N: $P < .001$). Multivariate Cox proportional hazard regression models were performed to identify whether LVI was an independent risk factor for OS and RFS after adjusting for other clinical covariates, including sex, age, smoking history, comorbidities, pulmonary function, PET-CT examination, extent of surgery, histology, VPI, locations, postoperative complication, and TNM stage. The results are shown in Table 2. The Kaplan–Meier curves are shown in Figure 2. For all patients with stage I, the LVI-P group also had a greater risk of recurrence (hazard ratio [HR], 2.06; 95% CI, 1.58–2.71; $P < .001$) (Figure 2, A), and LVI was associated with poor OS (HR, 2.04; 95% CI, 1.45–2.87; $P < .001$) (Figure 2, B). In the subgroup of patients with stage IA1–3 NSCLC, there were significant differences in RFS (HR, 2.91; 95% CI, 1.89–4.50; $P < .001$) and OS

TABLE 3. Clinicopathologic characteristics of patients with stage I non–small cell lung cancer with lymphovascular invasion before and after propensity score matching

	Before PSM			After PSM		
	ACT (n = 148, %)	Observation (n = 74, %)	P value	ACT (n = 65, %)	Observation (n = 65, %)	P value
Age, y, (range)	59 (25-78)	64 (40-81)	.001*	62 (38-78)	62 (40-80)	.882†
Sex, n (%)			.776‡			1.000§
Female	71 (48.0)	34 (45.9)		30 (46.2)	30 (46.2)	
Male	77 (52.0)	40 (54.1)		35 (53.8)	35 (53.8)	
Smoking history, n (%)			.578‡			.793§
Yes	37 (25.0)	16 (21.6)		16 (24.6)	14 (21.5)	
No	111 (75.0)	58 (78.4)		49 (75.4)	51 (78.5)	
Cancer-related comorbidity, n (%)			.068‡			.430§
Yes	42 (28.4)	30 (40.5)		20 (30.8)	25 (37.5)	
No	106 (71.6)	44 (59.5)		45 (69.2)	40 (61.5)	
Pulmonary function FEV1/FVC ≥70%	138 (93.2)	71 (95.9)	.419‡	59 (90.8)	62 (95.4)	.661§
PET-CT, n (%)			.356‡			.793§
Yes	25 (16.9)	9 (12.2)		9 (13.8)	7 (10.8)	
No	123 (83.1)	65 (87.8)		56 (86.2)	58 (89.2)	
Procedure 1			.051‡			.727§
Lobectomy	142 (95.9)	66 (89.2)		60 (92.3)	63 (96.9)	
Sub-lobectomy	6 (4.1)	8 (10.8)		5 (7.7)	2 (3.1)	
Procedure 2			.792‡			.661§
VATS	126 (85.1)	62 (83.8)		57 (87.7)	54 (83.1)	
Open	22 (14.9)	12 (16.2)		8 (12.3)	11 (16.9)	
P or C			.722			.727§
P	142 (95.9)	72 (97.3)		60 (92.3)	63 (96.9)	
C	6 (4.1)	2 (2.7)		5 (7.7)	2 (3.1)	
Postoperative complication, n (%)			.602			1.000§
Yes	2 (1.4)	2 (2.7)		1 (1.5)	1 (1.5)	
No	146 (98.6)	72 (97.3)		64 (98.5)	64 (98.5)	
T size, cm ± SD	2.60 ± 0.87	2.71 ± 0.87	.282*	2.56 ± 0.82	2.60 ± 0.78	.726†
Histology, n (%)			.407‡			.930§
Adenocarcinoma	133 (89.9)	69 (93.2)		61 (93.8)	60 (92.3)	
Nonadenocarcinoma	15 (10.1)	5 (6.8)		4 (6.2)	5 (7.7)	
Pleural invasion			.240‡			.661§
Yes	60 (40.5)	24 (32.4)		26 (40.0)	23 (36.9)	
No	88 (59.5)	50 (67.6)		39 (60.0)	42 (63.1)	

Nonadenocarcinoma includes squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma. PSM, Propensity score matched; ACT, adjuvant chemotherapy; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PET-CT, position emission tomography computed tomography; VATS, video-assisted thoracic surgery; P, peripheral lung cancer; C, central lung cancer; SD, standard deviation. *Mann–Whitney U test. †Paired-samples t test. ‡Chi-square test. §McNemar’s test. ||Fisher exact test.

(HR, 2.01; 95% CI, 1.13-3.60; $P = .018$). In patients with stage IB, there were significant differences in RFS (HR, 1.68; 95% CI, 1.16-2.41; $P = .006$) and OS (HR, 1.87; 95% CI, 1.19-2.94; $P = .007$) (Figures E1 and E2).

Adjuvant Chemotherapy Was Associated With Improved Survival of Patients With Stage I Non–Small Cell Lung Cancer With Lymphovascular Invasion

Among all patients with stage I, 854 patients received at least 3-cycle cisplatin/carboplatin–based ACT. A total of 87

patients received vinorelbine, 48 patients received gemcitabine, 598 patients received docetaxel, and 121 patients received pemetrexed. Table 2 shows that ACT was not correlated with improved survival for all patients with stage I NSCLC (RFS: HR, 0.94; 95% CI, 0.77-1.16; $P = .588$; OS: HR, 1.22; 95% CI, 0.95-1.55; $P = .119$).

To identify whether ACT could improve the survival of patients with stage I NSCLC with LVI, we further divided the LVI-P group into 2 subgroups: the surgery alone group (observation group) and the ACT group. A total of 148 patients received ACT after surgery, of whom 67 had stage

TABLE 4. Multivariate analyses of prognostic factors of patients with stage I non-small cell lung cancer with lymphovascular invasion after propensity score matching

	Multivariate analysis of RFS		Multivariate analysis of OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y(range)	1.04 (0.99-1.09)	.073	1.06 (1.00-1.12)	.046
Sex				
Female	0.76 (0.35-1.64)	.484	0.88 (0.43-2.99)	.793
Smoking history				
Yes	2.15 (0.95-4.88)	.067	1.79 (0.66-4.85)	.067
Cancer-related comorbidity				
Yes	1.25 (0.59-2.68)	.561	1.12 (0.43-2.88)	.820
Pulmonary function				
FEV1/FVC $\geq 70\%$	0.34 (0.04-2.67)	.306	0.64 (0.08-5.46)	.683
PET-CT				
Yes	0.96 (0.37-2.48)	.936	1.94 (0.53-7.02)	.315
Procedure 1				
Lobectomy	0.44 (0.10-1.92)	.276	0.53 (0.09-3.01)	.475
Procedure 2				
VATS	0.65 (0.24-1.79)	.402	1.06 (0.34-3.28)	.921
P or C				
P	0.60 (0.06-5.68)	.656	0.74 (0.07-7.63)	.799
Postoperative complication				
Yes	1.29 (0.15-11.43)	.820	0.73 (0.07-7.29)	.790
T size	1.35 (0.86-2.13)	.197	1.34 (0.76-2.36)	.311
Histology				
Adenocarcinoma	0.52 (0.16-1.72)	.282	0.37 (0.10-1.34)	.130
Pleural invasion				
Yes	7.32 (0.98-54.42)	.052	5.90 (0.77-45.19)	.087
TNM stage				
IB	8.47 (0.91-78.69)	.060	8.06 (0.75-86.56)	.085
ACT				
Yes	0.33 (0.16-0.67)	.002	0.30 (0.12-0.74)	.009

Nonadenocarcinoma includes squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma. RFS, Recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PET-CT, position emission tomography computed tomography; VATS, video-assisted thorascopic surgery; P, peripheral lung cancer; C, central lung cancer; TNM stage, tumor-node-metastasis stage; ACT, adjuvant chemotherapy.

IA disease and 81 had stage IB disease. The patients who accepted chemotherapy tended to be younger. The basic patient characteristics of both groups are shown in Table 3. There was no significance in the distribution in other clinical characteristics. A PSM analysis was implemented to reduce the selection bias. Finally, 65 pairs of patients were included in the analysis. The results of multivariate analysis for all matched patients are summarized in Table 4.

For all patients with stage I with LVI, after adjustment for other clinical variables, including sex, age, smoking history, comorbidities, pulmonary function, PET-CT examination, extent of surgery, histology, VPI, locations, postoperative complication, and TNM stage, multivariable analysis indicated that ACT was associated with increased RFS (HR, 0.33; 95% CI, 0.16-0.67; $P = .002$) and OS (HR, 0.30; 95% CI, 0.12-0.74; $P = .009$) (Figure 3, A and B). To identify

the ACT benefits in patients with stage IA1-3 and patients with stage IB with LVI, we also conducted a subgroup analysis. ACT was associated with statistically improved RFS (HR, 0.21; 95% CI, 0.06-0.69; $P = .011$) and OS (HR, 0.09; 95% CI, 0.01-0.67; $P = .018$) for those with stage IA1-3 and improved RFS (HR, 0.37; 95% CI, 0.14-0.94; $P = .037$) and OS (HR, 0.26; 95% CI, 0.09-0.78; $P = .018$) for those with stage IB with LVI (Figures E3 and E4).

DISCUSSION

This study investigated the prognostic effect of LVI in stage I NSCLC using the 8th edition of the TNM classification and explored the survival benefits from ACT in such patients. Our primary results suggested that LVI was an independent negative prognostic factor in patients with stage I NSCLC. We also found that ACT was associated

FIGURE 3. RFS (A) and OS (B) curves (ACT vs observation) of all patients with stage I NSCLC with LVI. ACT, Adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.

with improved outcomes in patients with stage I NSCLC with LVI.

In previous studies, LVI has been demonstrated to be an unfavorable significant prognostic factor in patients with stage I NSCLC. LVI can be divided into blood vessel invasion and lymphatic vessel invasion. Both of them were reported to be significant prognostic factors in the studies by Gabor and colleagues²⁵ and Brechot and colleagues.²⁶ In recent years, several relatively large-scale studies demonstrated that the OS of patients with stage IA with LVI overlapped that of those with stage IB without LVI. The study by Tsuchiya and colleagues²⁷ in Japan directly demonstrated that the prognosis of patients with stage IA NSCLC with LVI was similar to that of patients with stage IB NSCLC without LVI.²⁷ This was confirmed in a larger study from Naito and colleagues.¹² The study included 826 patients with stage I with NSCLC, of whom 279 had LVI. Because of the poor OS of patients with stage I with LVI, several studies suggest including LVI in the T grade.^{14,28} However, this was not included in the newest 8th TNM staging. It is possible that more evidence is needed for LVI to be a factor in upstaging.

Although there is no definite consensus on the use of ACT for stage I NSCLC, several clinical trials and meta-analysis recommend ACT for patients with resected stage II and IIIA NSCLC. The use of ACT is still controversial in patients with stage IB. Cancer and Leukemia Group B 9633 recommended ACT for patients with stage IB whose tumor size was 4 cm or greater. The other 2 studies, JBR.10 and ANITA, showed no beneficial survival from ACT in patients with stage IB. Meanwhile, the use of ACT in patients with stage IA NSCLC is not clear yet. The most famous study was from Japan,¹⁸ demonstrating that oral uracil-tegafur was effective for patients with stage

I NSCLC, particularly when the tumor was 2 cm or larger. A meta-analysis also showed a proven benefit of ACT, but failed to find an advantage in patients with stage IA.²⁹ However, a study from Tsuchiya and colleagues²⁷ demonstrated that oral uracil-tegafur chemotherapy significantly increased the 5-year survival of the stage IA vascular invasion group by more than 25% and was the first study to show a benefit from ACT. In 2014, another study from Tsutani and colleagues³⁰ found that ACT was effective in patients with stage I NSCLC, particularly those with an invasive component larger than 2 cm or with lymphatic invasion.³⁰ The benefit from ACT in patients with stage IA is still unclear. Because of the heterogeneity of stage I NSCLC, finding optimal candidates for ACT should be the appropriate strategy. In our center, ACT was recommended for patients with stage IB with high-risk factors according to NCCN guidelines. For the patients with stage IA, some specialists suggested ACT for patients with risk factors, such as LVI based on the previous studies.^{18,30} When the pathologic findings were reported, a case-based learning was held in the medical team and the decision was made. In our study, a relatively large-scale study, we compared OS and RFS between LVI-P patients who received ACT and surgery alone and found that adjuvant therapy could be beneficial in this subset. Especially for patients with stage I with LVI, ACT was associated with improved survival.

Study Limitations

There were some limitations in our study. First, the study had an insufficient patient cohort; therefore, a homogeneous cohort and selection bias are inevitable because it is a retrospective study. Although we performed PSM to eliminate the selection bias as much as possible, there are some

unrecognized confounders, such as the economic capability of patients and the cultural education of patients and disposition from the hospital. Second, in our study, we excluded micro-invasive carcinoma; such patients have a good prognosis but this might have influenced our results. Third, we did not distinguish blood vessels from lymphatic vessels, because several studies determined both were unfavorable significant prognostic factors, whereas the others did not.^{10,13,26} Fourth, the mechanism of benefit from ACT is still uncertain. In our study, we defined 3- to 4-cycle treatment as effective chemotherapy, but we did not explore the relationship among regimens, dosage and toxicity, and survival. Last but not least, the gene status and postrecurrence treatment are unclear in our study. Further prospective studies are needed to validate the results.

CONCLUSIONS

Our study indicated that LVI was a strong prognostic factor in patients with stage I NSCLC, and ACT was associated with improved OS in patients with stage I with LVI. For pathologic LVI-P patients, either stage IA or stage IB, the application of ACT might be a more appropriate choice.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: adjuvant chemotherapy, lymphovascular invasion, non-small cell lung cancer, Stage I, visceral pleura invasion

FIGURE E1. RFS (A) and OS (B) curves of patients with stage IA1-3 stratified by LVI. *LVI-N*, Lymphovascular invasion negative; *LVI-P*, lymphovascular invasion positive; *HR*, hazard ratio; *CI*, confidence interval.

FIGURE E2. RFS (A) and OS (B) curves of patients with stage IB stratified by LVI. *LVI-N*, Lymphovascular invasion negative; *LVI-P*, lymphovascular invasion positive; *HR*, hazard ratio; *CI*, confidence interval.

FIGURE E3. RFS (A) and OS (B) curves (ACT vs observation) of patients with stage IA1-3 with LVI. ACT, Adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.

FIGURE E4. RFS (A) and OS (B) curves (ACT vs observation) of patients with stage IB with LVI. ACT, Adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.