Prognostic factors in stage IB non-small cell lung cancer according to the 8th edition of the TNM staging system after curative resection

Youngkyu Moon[1], Si Young Choi[1], Jae Kil Park[2], Kyo Young Lee[3]

[1]Department of Thoracic & Cardiovascular Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Thoracic & Cardiovascular Surgery, [3]Department of Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Contributions: (I) Conception and design: Y Moon; (II) Administrative support: SY Choi, JK Park; (III) Provision of study materials or patients: JK Park, KY Lee; (IV) Collection and assembly of data: Y Moon, JK Park; (V) Data analysis and interpretation: Y Moon, SY Choi, KY Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Youngkyu Moon, MD, PhD. Department of Thoracic & Cardiovascular Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 1021, Tongil-ro, Eunpyeong-gu, Seoul 03312, Republic of Korea. Email: mykae@catholic.ac.kr.

Background: Patients with stage IB non-small cell lung cancer (NSCLC) with poor prognostic factors can be treated selectively with postoperative adjuvant chemotherapy. The aim of this study was to identify the prognostic factors of stage IB NSCLC according to the new 8th edition of the tumor, node, and metastasis (TNM) staging system.

Methods: From 2005 to 2016, 211 patients who were diagnosed with stage IB NSCLC according to the 8th edition of the TNM staging system underwent anatomical pulmonary resection (lobectomy or bilobectomy). We analyzed the outcomes of patients receiving adjuvant chemotherapy. The risk factors for prognosis after surgery were also analyzed for NSCLC stage IB.

Results: Differences between the 5-year recurrence-free-survival (RFS) rates (71.4% *vs.* 60.2%, P=0.173) and the 5-year disease-specific-survival (DSS) rates (88.0% *vs.* 81.4%, P=0.437) obtained by patients receiving surgical treatment only versus patients receiving both surgery and adjuvant chemotherapy, retrospectively, were not significant. Multivariate analysis was conducted to identify the risk factors for recurrence and cancer-related death. Lymphovascular invasion was an independent risk factor for both recurrence and cancer-related death [hazard ratio (HR) =2.045, P=0.020; HR =3.150, P=0.048, respectively).

Conclusions: Lymphovascular invasion was the only prognostic factor identified in patients with 8th edition stage IB NSCLC. Adjuvant chemotherapy was not an effective treatment for patients with stage IB NSCLC. The efficacy of adjuvant chemotherapy for stage IB patients with lymphovascular invasion should be evaluated in a future study.

Keywords: Prognostic factor; non-small cell lung cancer (NSCLC); 8th edition of tumor, node, and metastasis staging system (8th edition of TNM staging system)

Introduction

In 2015, the International Association for the Study of Lung cancer (IASLC) proposed the 8th edition of the tumor, node, and metastasis (TNM) classification of lung cancer, and the new staging system enacted in January 2017 (1). The new staging system contained modifications in stage groupings, but stage IB non-small cell lung cancer (NSCLC) had not been changed. According to the previous

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edition of the TNM staging system, only T2aN0M0 was considered stage IB disease. Stage IB of the 8th edition TNM classification also only includes T2aN0M0 (2,3). However, some criteria for T classifications were changed (1,4,5). First, the measurement of tumor size was changed. Previously, the tumor size was determined by the maximum size of the tumor including lepidic component. On the other hand, the T stage in the 8th edition is determined according to the maximum size of the invasive component, without the lepidic component. Second, the T2a category also changed. In the 7th edition, T2a was considered to be a tumor size ranging from 3 to 5 cm; whereas in the 8th edition, the T2a descriptor was changed to a size of the invasive component ranging from 3 to 4 cm. Therefore stage migration also occurred for stage IB NSCLC after adoption of the 8th edition of TNM staging system.

According to the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (Version 3.2019), adjuvant treatment after surgery may be considered for patients with several risk factors. In the NCCN guidelines, risk factors include poorly differentiated tumors, lymphovascular invasion, wedge resection, tumors >4 cm, visceral pleural invasion, and unknown lymph node status. These risk factors have been reported by several studies to be prognostic factors in patients with early-stage lung cancer (6-9). However, a re-evaluation on whether or not the prognostic factors for stage IB NSCLC remain the same for the new staging system is needed. In fact, no study has evaluated the prognostic factors of stage IB disease as classified by the new 8th edition of the TNM staging system. In addition, since stage classifications have changed, the efficacy of adjuvant chemotherapy for stage IB NSCLC also must be re-evaluated.

The aim of this study was to identify the prognostic risk factors in patients with stage IB NSCLC according to the 8th edition of TNM classification and to determine the outcomes of patients with stage IB NSCLC who received adjuvant chemotherapy.

Methods

Patients

From 2005 to 2016, 1,598 consecutive patients at a tertiary hospital in South Korea were diagnosed with NSCLC and underwent curative surgery. Of this population, 262 patients were diagnosed with 8th edition stage IB NSCLC. Finally, 211 patients satisfied the following study criteria: (I) anatomical lobectomy or bilobectomy; (II) complete

resection with clear resection margins; (III) no neoadjuvant treatment. The clinicopathological characteristics of all study patients were analyzed. We compared the clinicopathological characteristics and survival between the patients undergoing surgery only versus those who also received adjuvant chemotherapy. The risk factors for recurrence and cancer-related death were analyzed.

Surgical procedures

The operative procedures included lobectomy and bilobectomy. The surgery also included complete dissection of N1 lymph nodes. Most patients underwent mediastinal lymph node dissection. Systematic nodal dissection was defined as mediastinal lymph node dissection of more than 3 mediastinal lymph node stations and included the subcarinal lymph nodes. Selective mediastinal node dissection was defined as mediastinal lymph node dissection near the involved lobe.

Adjuvant chemotherapy

We defined adjuvant chemotherapy as postoperative chemotherapy involving the use of platinum-based agents. The selection of chemotherapy regimens depended on clinician preference. Most regimens included carboplatin or cisplatin combined with paclitaxel or vinorelbine. Chemotherapy was administered 1 month after surgery. Four cycles of chemotherapy were routinely recommended. There were no definite indications for adjuvant chemotherapy. When tumor size was larger than 4 cm or lymphovascular invasion was present, a clinician sometimes recommended adjuvant chemotherapy. The final decision was made by the patient.

Histological evaluation and restaging to the 8th-edition staging system

All clinical specimens and pathology reports were reviewed. Pathology report included tumor size, tumor location, nodal status, and pleural or lymphovascular invasion. Visceral pleural invasion was defined as tumor extending beyond the elastic layer. Lymphovascular invasion was defined as tumor cells present in lymphatic or vascular lumina. TNM staging was based on the 8th edition of the TNM staging system of lung cancer (2). To reclassify the T category according to the 8th edition, tumor size was remeasured by the pathologist at the greatest diameter of the invasive component on a histopathological preparation (5).

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Statistical analysis

The clinical and pathological characteristics of the surgery-only patients and adjuvant-chemotherapy patients were compared. The Student *t*-test or Wilcoxon rank-sum test was used for continuous variables, and the χ^2 test or Fisher exact test was applied for categorical variables.

The Kaplan-Meier method was used to analyse data collected from the interval between the time of operation and the time of the final follow-up visit. Recurrence-free-survival (RFS) rates and disease-specific-survival (DSS) rates were estimated by the Kaplan-Meier method using data collected from patients with confirmed recurrence and cancer-related death. The Cox proportional hazards model was used in a multivariate analysis to determine the risk factor of recurrence and cancer-related death for all the study patients. The variables with a P value <0.1 by the univariate analysis were entered into a multivariate analysis. A P value <0.05 was considered statistically significant.

Results

Table 1 shows the clinicopathological characteristics of patients with stage IB NSCLC. Lobectomy was performed for 200 patients (94.8%) and bilobectomy was performed for 11 patients (5.2%). Most patients (91.5%) underwent mediastinal lymph node dissection. Systematic nodal dissection was conducted in 134 patients (63.5%) and selective mediastinal node dissection in 59 patients (28.0%). Postoperative complications occurred in 33 patients (15.6%), and 3 patients (1.4%) died after surgery. Adjuvant chemotherapy was administered to 20 patients after surgery. Histopathological analysis revealed a mean total tumor size (including the lepidic component) of 3.0 cm. The mean invasive component size (excluding the lepidic component) was 2.6 cm. The most common histological tumor type was adenocarcinoma (70.1%). Visceral pleural invasion and lymphovascular invasion were present in 137 (64.9%) and 105 (49.8%) patients, respectively.

Comparisons of survival rates of surgery-only patients and adjuvant-chemotherapy patients

The median follow-up time of the study patients with stage IB NSCLC after surgery was 1,457 days (12–4,172 days). The wide range of the follow-up periods was accounted for by a single patient who died of a postoperative complication 12 days after surgery. Several patients had short follow-up periods, mostly because of cancer-related death or postoperative mortality. We compared the survival rates of patients undergoing surgery only (surgery-only patients, n=191) and of patients receiving adjuvant chemotherapy after undergoing surgery (adjuvant-chemotherapy patients, n=20). The differences between most clinicopathological characteristics in the two groups were not significant (*Table 2*). Only tumor size and invasive component size were larger in the adjuvant-chemotherapy patients. Recurrence was identified in 53 patients, and the differences between the sites of recurrence in the 2 groups were not significant (*Table 3*). The 5-year RFS rates of the surgery-only patients and adjuvant-chemotherapy patients were 71.4% and 60.2%, respectively (P=0.173, *Figure 1A*). The 5-year DSS rates of the surgery-only patients and adjuvant-chemotherapy patients were 88.0% and 81.4%, respectively (P=0.437, *Figure 1B*).

Prognostic factors in stage IB NSCLC according to the 8th edition of the TNM staging system

For all the study patients, the 5-year RFS and DSS rates were 70.3% and 87.3%, respectively. We analyzed risk factors for recurrence and cancer-related death. First, univariate and multivariate analyses were conducted to identify the risk factors for recurrence (*Table 4*). The specific variables identified as significant (P<0.1) by univariate analysis included smoking status, maximum standardized uptake value (SUVmax) on positron emission tomography (PET), tumor differentiation, and lymphovascular invasion. These variables were entered into the multivariate analysis. Multivariate analysis identified lymphovascular invasion as a significant independent risk factor [hazard ratio (HR) =2.045, P=0.020] for recurrence.

Univariate and multivariate analyses were also conducted to identify the risk factors for cancer-related death (*Table 5*). The specific variables identified as significant (P<0.1) by univariate analysis included age, smoking status, serum carcinoembryonic antigen (CEA) level, SUVmax, size of invasive component, and lymphovascular invasion. These variables were entered into the multivariate analysis. By multivariate analysis, lymphovascular invasion was the only significant independent risk factor (HR =3.150, P=0.048) for cancer-related death.

Since the 2 analyses identified lymphovascular invasion as a prognostic factor, we compared the 5-year RFS and DSS rates of patients with tumors that were with or without lymphovascular invasion. The 5-year RFS rates of patients

Table 1 Clinicopathological characteristics after curative surgery for patients with stage IB non-small cell lung cancer (N=211)

Variables	Mean (± SD) or n (%)
Age	66.5 (±9.8)
Gender	
Male	120 (56.9%)
Female	91 (43.1%)
Current or former smoker	88 (41.7%)
Serum CEA level (ng/mL)	3.4 (±4.0)
SUVmax	7.3 (±4.3)
Involved lobe	
Right upper lobe	64 (30.3%)
Right middle lobe	26 (12.3%)
Right lower lobe	51 (24.2%)
Left upper lobe	42 (19.9%)
Left lower lobe	28 (13.3%)
Pulmonary function	
FEV1 (%)	93.8 (±16.9)
DLCO (%)	87.9 (±19.6)
Surgical procedure	
Lobectomy	200 (94.8%)
Bilobectomy	11 (5.2%)
Intraoperative lymph node dissection	
No mediastinal lymph node evaluation	18 (8.5%)
Systematic nodal dissection	134 (63.5%)
Selective mediastinal node dissection	59 (28.0%)
Surgery	
VATS	154 (73.0%)
Open thoracotomy	57 (27.0%)
Postoperative complications	33 (15.6%)
Operative mortality	3 (1.4%)
Adjuvant chemotherapy	20 (9.5%)
Paclitaxel/carboplatin (4 cycles)	12
Paclitaxel/carboplatin (3 cycles)	2
Vinorelbine/cisplatin (4 cycles)	2
Vinorelbine/carboplatin (4 cycles)	2
Vinorelbine/cisplatin (3 cycles)	1

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Mean (± SD) or n (%)
Etoposide/cisplatin (4 cycles)	1
Total tumor size (cm)	3.0 (±0.9)
Invasive component size (cm)	2.6 (±1.0)
Location	
Central	34 (16.1%)
Peripheral	177 (83.9%)
Histology	
Adenocarcinoma	148 (70.1%)
Squamous cell carcinoma	45 (21.3%)
Others	18 (8.5%)
Differentiation	
Mild differentiation	50 (23.7%)
Moderate differentiation	111 (52.6%)
Poor differentiation	50 (23.7%)
Number of dissected lymph nodes	13.6 (±8.1)
Visceral pleural invasion	137 (64.9%)
Lymphovascular invasion	105 (49.8%)

SD, standard deviation; CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; VATS, video-assisted thoracoscopic surgery.

with tumors that were with or without lymphovascular invasion were 60.6% and 78.6%, respectively (*Figure 2A*, P=0.004). The 5-year DSS rates of patients with tumors that were with or without lymphovascular invasion were 83.0% and 91.7%, respectively (*Figure 2B*, P=0.015).

Discussion

After implementation of the 8th revision of the TNM classification of NSCLC, the composition of the tumors included in the stage IB classification was changed. Most importantly, the requirement for measuring tumor size was changed. Determination of the T stage in the 8th revision is based only on the maximum dimension of the invasive component and excludes the lepidic component (4,5). The size range of the T2a descriptor was also reduced from 3–5 to 3–4 cm. Therefore, the tumor characteristics for 7th

Table 2 Comparisons between the clinicopathological characteristics of patients with 8th edition stage IB non-small cell lung cancer grouped as those undergoing surgery only and those who also received adjuvant chemotherapy

Variables	Surgery only (n=191)	Adjuvant chemotherapy (n=20)	P value
Age	66.6 (±10.0)	64.7 (±7.7)	0.399
Gender			0.767
Male	108 (56.5%)	12 (60.0%)	
Female	83 (43.5%)	8 (40.0%)	
Current or former smoker	79 (41.4%)	9 (45.0%)	0.754
Serum CEA level (ng/mL)	3.3 (±3.5)	4.4 (±7.7)	0.540
SUVmax	7.2 (±4.3)	7.8 (±3.9)	0.633
Involved lobe			0.755
Right upper	56 (29.3%)	8 (40.0%)	
Right middle	23 (12.0%)	3 (15.0%)	
Right lower	48 (25.1%)	3 (15.0%)	
Left upper	39 (20.4%)	3 (15.0%)	
Left lower	25 (13.1%)	3 (15.0%)	
Pulmonary function			
FEV1 (%)	94.1 (±17.2)	90.9 (±14.0)	0.418
DLCO (%)	87.4 (±19.5)	93.4 (±20.0)	0.205
Surgical procedure			1.000
Lobectomy	181 (94.8%)	19 (95.0%)	
Bilobectomy	10 (5.2%)	1 (5.0%)	
Intraoperative lymph node dissection			0.083
No mediastinal lymph node evaluation	14 (7.3%)	4 (20.0%)	
Systematic nodal dissection	125 (65.4%)	9 (45.0%)	
Selective mediastinal node dissection	52 (27.2%)	7 (35.0%)	
Surgery			0.169
VATS	142 (74.3%)	12 (60.0%)	
Open thoracotomy	49 (25.7%)	8 (40.0%)	
Postoperative complications	31 (16.2%)	2 (10.0%)	0.746
Operative mortality	3 (1.6%)	0	1.000
Total tumor size (cm)	3.0 (±0.9)	3.5 (±1.1)	0.011
Invasive component size (cm)	2.6 (±1.0)	3.0 (±0.8)	0.036
Location			1.000
Central	31 (16.2%)	3 (15.0%)	
Peripheral	160 (83.8%)	17 (85.0%)	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Surgery only (n=191)	Adjuvant chemotherapy (n=20)	P value
Histology			0.812
Adenocarcinoma	133 (69.6%)	15 (75.0%)	
Squamous cell carcinoma	41 (21.5%)	4 (20.0%)	
Others	17 (8.9%)	1 (5.0%)	
Differentiation			0.458
Mild differentiation	46 (24.1%)	4 (20.0%)	
Moderate differentiation	102 (53.4%)	9 (45.0%)	
Poor differentiation	43 (22.5%)	7 (35.0%)	
Number of dissected lymph nodes	13.7 (±7.8)	12.4 (±10.4)	0.569
Visceral pleural invasion	125 (65.4%)	12 (60.0%)	0.627
Lymphovascular invasion	92 (48.2%)	13 (65.0%)	0.152

CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; VATS, video-assisted thoracoscopic surgery.

Table 3 Summary of recurrence

Overall recurrence	Surgery only	Adjuvant chemotherapy	P value
Locoregional recurrence	24 (52.2%)	3 (42.9%)	0.696
Distant recurrence	6 (13.0%)	1 (14.3%)	
Both	16 (34.8%)	3 (42.9%)	

Locoregional = recurrence within ipsilateral hemithorax, including pleura and mediastinal lymph nodes. Both = locoregional recurrence + distant recurrence.
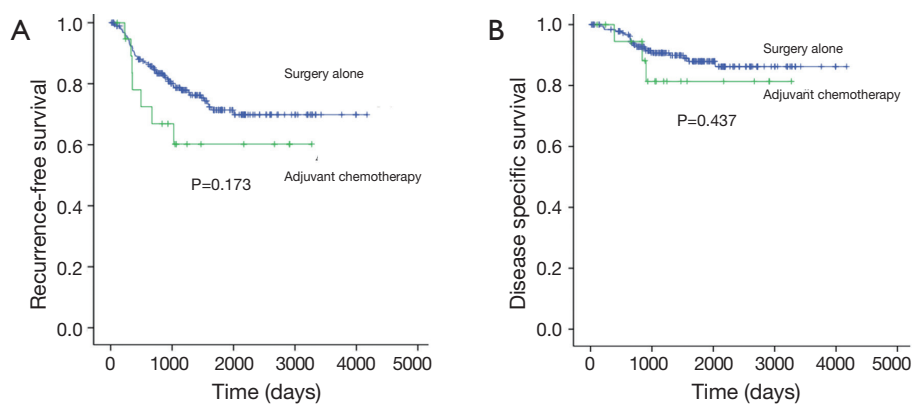

Figure 1 Comparisons between recurrence-free-survival (A) and disease-specific survival (B) of patients with 8th-edition stage IB non-small cell lung cancer grouped as those undergoing surgery only and those who also received adjuvant chemotherapy.

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Table 4 Univariate multivariate analysis of risk factors for recurrence in patients with 8th-edition stage IB non-small cell lung cancer

Variables	HR	95% CI	P value
Univariate analysis			
Age	1.003	0.975–1.031	0.851
Gender (male)	1.297	0.748–2.249	0.355
Smoker	1.728	1.006–2.970	0.048
Serum CEA level	1.046	0.986–1.109	0.134
SUVmax	1.052	0.991–1.116	0.096
Lobe			0.281
Right upper (reference)	1		
Right middle	1.229	0.543–2.783	0.621
Right lower	0.616	0.272–1.394	0.245
Left upper	1.374	0.670–2.818	0.386
Left lower	0.614	0.225–1.677	0.341
FEV1 (%)	0.995	0.979–1.011	0.525
DLCO (%)	1.003	0.989–1.017	0.667
Intraoperative lymph node dissection			0.842
No mediastinal lymph node evaluation (reference)	1		
Systematic nodal dissection	0.825	0.345–1.978	0.667
Selective mediastinal node dissection	0.751	0.288–1.957	0.558
Adjuvant chemotherapy	1.728	0.780–3.831	0.178
Tumor size	1.106	0.819–1.493	0.511
Invasive component size	1.051	0.799–1.384	0.721
Central location	0.702	0.317–1.556	0.384
Histology			0.796
Adenocarcinoma (reference)	1		
Squamous cell carcinoma	0.998	0.497–2.003	0.995
Others	1.373	0.540–3.489	0.506
Differentiation			0.055
Mild differentiation (reference)	1		
Moderate differentiation	1.752	0.800–3.833	0.161
Poor differentiation	2.792	1.192–6.541	0.018

Table 4 (*continued*)

Table 4 (*continued*)

Variables	HR	95% CI	P value
Number of dissected lymph nodes	1.003	0.970–1.037	0.858
Visceral pleural invasion	1.479	0.813–2.691	0.200
Lymphovascular invasion	2.227	1.274–3.892	0.005
Multivariate analysis			
Smoker	1.395	0.768–2.534	0.274
SUVmax	1.002	0.930–1.078	0.967
Differentiation			0.357
Mild differentiation (reference)	1		
Moderate differentiation	1.475	0.606–3.590	0.392
Poor differentiation	2.069	0.744–5.755	0.164
Lymphovascular invasion	2.045	1.117–3.742	0.020

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; VATS, video-assisted thoracoscopic surgery.

edition stage IB NSCLC were changed in the 8th edition. Because of these changes, we thought that prognostic factors should be re-evaluated for tumors staged IB according to the new staging system.

This study identified lymphovascular invasion in tumors considered to be stage IB NSCLC by the 8th edition of the TNM classification as the only significant prognostic factor. Tumor differentiation, visceral pleural invasion, and tumors measuring 4 cm, which had been considered to be prognostic factors, were not identified as prognostic factors in this study. With regard to tumor size, tumors larger than 4 cm were no longer a risk factor, because only the tumors 4 cm and smaller were considered to be stage IB disease by the 8th edition of the TNM staging system. Other factors warrant re-evaluation in a future larger study.

The surgical resections in this study included more than lobectomy only. When we performed anatomical lobectomies, the N1 lymph nodes were always completely dissected. However, mediastinal lymph node dissection was not performed in all patients, and a few patients did not undergo mediastinal lymph node dissection because of

Table 5 Univariate analysis and multivariate analysis of risk factors for cancer-related death in patients with 8th-edition stage IB non-small cell lung cancer

Variables	HR	95% CI	P value
Univariate analysis			
Age	1.046	0.998–1.096	0.061
Gender (male)	1.583	0.671–3.736	0.294
Smoker	2.270	0.991–5.202	0.053
CEA	1.072	1.009–1.138	0.025
SUVmax	1.093	1.000–1.194	0.050
Lobe			0.963
Right upper (reference)	1		
Right middle	1.466	0.413–5.200	0.553
Right lower	0.963	0.294–3.157	0.950
Left upper	1.266	0.386–4.152	0.697
Left lower	0.986	0.246–3.947	0.984
FEV1 (%)	0.994	0.970–1.019	0.645
DLCO (%)	1.001	0.980–1.023	0.911
Intraoperative mediastinal node evaluation			0.840
No mediastinal node evaluation (Reference)	1		
Systematic nodal dissection	0.685	0.194–2.420	0.557
Selective nodal dissection	0.753	0.194–2.920	0.681
Adjuvant chemotherapy	1.612	0.478–5.433	0.441
Tumor size	1.167	0.764–1.781	0.475
Invasive component size	1.517	0.947–2.427	0.083
Central location	0.700	0.208–2.360	0.565
Histology			0.190
Adenocarcinoma (reference)	1		
Squamous cell carcinoma	1.002	0.333–3.021	0.996
Others	2.729	0.905–8.227	0.075
Differentiation			0.195
Mild differentiation (reference)	1		
Moderate differentiation	1.324	0.421–4.160	0.631
Poor differentiation	2.643	0.793–8.807	0.114
Number of dissected lymph nodes	0.996	0.947–1.048	0.879
Visceral pleural invasion	0.873	0.378–2.020	0.751

Table 5 (*continued*)

Table 5 (*continued*)

Variables	HR	95% CI	P value
Lymphovascular invasion	2.873	1.178–7.010	0.020
Multivariate analysis			
Age	1.065	1.006–1.127	0.030
Smoker	2.190	0.792–6.054	0.131
CEA	1.095	1.019–1.177	0.014
SUVmax	1.050	0.928–1.188	0.440
Invasive component size	0.998	0.551–1.809	0.995
Lymphovascular invasion	3.150	1.013–9.800	0.048

CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; VATS, video-assisted thoracoscopic surgery.

technical difficulties (severe whole lung adhesion or unstable status of patient during operation). Systematic nodal dissection was conducted in 63.5% of the study patients. Indeed, systematic nodal dissection is recommended when lobectomies are performed for lung cancer (10,11), because occult lymph node metastasis can be present even in clinical stage N0 disease (12-14). Systematic nodal dissection is mandatory, especially for stage IB disease, because the possibility of occult lymph node metastasis is higher in stage IB than in stage IA disease (15). Nevertheless, intraoperative mediastinal lymph node dissection was not found to be a prognostic factor in this study. This result is accounted for by the fact that mediastinal lymph node dissection was performed for a large number of patients, and every patient underwent lobectomy to remove the N1 lymph nodes completely. In addition, because skip N2 metastasis rarely occurs without the presence of N1 metastasis, we decided that nodal staging was appropriate in this study.

Adjuvant treatment after surgery is not routinely recommended for stage IB NSCLC (9). However, the prognosis of these patients after undergoing surgical treatment for stage IB disease is not as satisfactory as the prognosis of IA patients after surgery. In this study, the 5-year RFS rate of patients with stage IB NSCLC was 70%. Therefore, additional treatment might be needed after surgery for some cases of stage IB NSCLC. In this study, however, adjuvant chemotherapy did not improve the prognosis of stage IB NSCLC. The differences between the RFS and DSS rates of the surgery-only patients versus
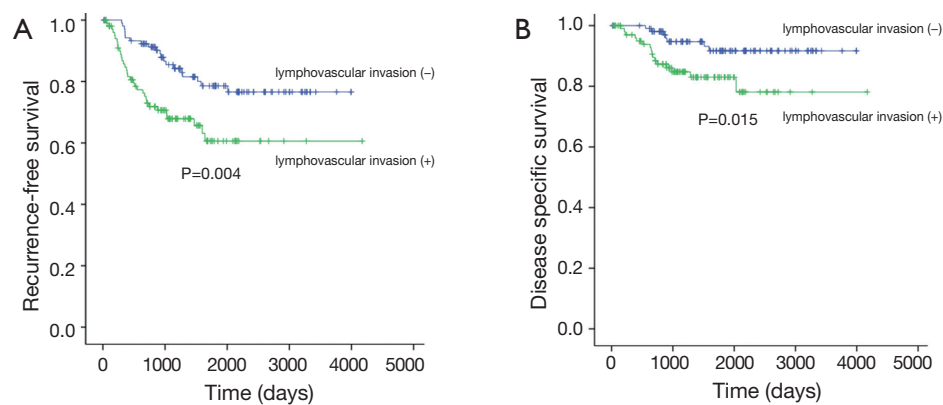
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Figure 2 Comparisons between recurrence-free-survival (A) and disease-specific survival (B) of patients with tumors that were with and without lymphovascular invasion.

adjuvant-chemotherapy patients were not significant. Adjuvant chemotherapy was also not a prognostic factor by multivariate analysis. Therefore, the administration of adjuvant chemotherapy to all patients with stage IB NSCLC is unreasonable, and the outcomes of high-risk patients with stage IB NSCLC who receive adjuvant chemotherapy must be further evaluated. We found that lymphovascular invasion was the independent risk factor for outcome in patients with IB NSCLC as staged by the new 8th edition staging system. We hope to perform prospective randomized controlled trials of adjuvant chemotherapy after surgery for patients with stage IB NSCLC showing lymphovascular invasion.

This study has several limitations. First, it was a retrospective study. Second, we obtained data from a single institution with a relatively small sample size, so generalizing our results is difficult. However, the study patients were treated by a standardized surgical protocol at single institution. Furthermore, a detailed analysis was possible because of detailed data that was stored in the electronic medical records. We also used detailed data from pathological specimens and pathological reports. We believe that our data can be used as the basis for future studies. Since there were only 20 patients undergoing adjuvant chemotherapy, comparing outcomes between the surgery-only and the adjuvant-chemotherapy patients is difficult. However, the main purpose of this study was not to compare the outcomes between patients with and without adjuvant chemotherapy, but to identify prognostic factors in the newly revised stage IB NSCLC. Finally, the follow-up period was relatively short. However, most patients

with NSCLC are known to have disease recurrence within a 2-year postoperative period (16), and early recurrence has been shown to be an accurate reflection of long-term outcome (17).

In conclusion, lymphovascular invasion was an independent prognostic factor for patients with stage IB NSCLC after surgical resection. Adjuvant chemotherapy was not an effective treatment for stage IB patients according to the new staging system. Additional studies that include prospective randomized controlled trials might provide more accurate results. Furthermore, the efficacy of adjuvant chemotherapy for stage IB NSCLC with lymphovascular disease should be evaluated.

Acknowledgments

None.

Footnote

References

1. Rami-Porta R, Asamura H, Travis WD, et al. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:138-55.

2. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.

3. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14.

4. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.

5. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2016;11:1204-23.

6. Yang HC, Kim HR, Jheon S, et al. Recurrence Risk-Scoring Model for Stage I Adenocarcinoma of the Lung. Ann Surg Oncol 2015;22:4089-97.

7. Park HJ, Park HS, Cha YJ, et al. Efficacy of adjuvant chemotherapy for completely resected stage IB non-small cell lung cancer: a retrospective study. J Thorac Dis 2018;10:2279-87.

8. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. Chest 2002;122:1037-57.

9. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.

10. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.

11. Watanabe S, Asamura H. Lymph node dissection for lung cancer: significance, strategy, and technique. J Thorac Oncol 2009;4:652-7.

12. Heineman DJ, Ten Berge MG, Daniels JM, et al. The Quality of Staging Non-Small Cell Lung Cancer in the Netherlands: Data From the Dutch Lung Surgery Audit. Ann Thorac Surg 2016;102:1622-9.

13. Moon Y, Kim KS, Lee KY, et al. Clinicopathologic Factors Associated With Occult Lymph Node Metastasis in Patients With Clinically Diagnosed N0 Lung Adenocarcinoma. Ann Thorac Surg 2016;101:1928-35.

14. Moon Y, Park JK, Lee KY, et al. Consolidation/Tumor Ratio on Chest Computed Tomography as Predictor of Postoperative Nodal Upstaging in Clinical T1N0 Lung Cancer. World J Surg 2018;42:2872-8.

15. Heineman DJ, Ten Berge MG, Daniels JM, et al. Clinical Staging of Stage I Non-Small Cell Lung Cancer in the Netherlands-Need for Improvement in an Era With Expanding Nonsurgical Treatment Options: Data From the Dutch Lung Surgery Audit. Ann Thorac Surg 2016;102:1615-21.

16. Tremblay L, Deslauriers J. What is the most practical, optimal, and cost effective method for performing follow-up after lung cancer surgery, and by whom should it be done? Thorac Surg Clin 2013;23:429-36.

17. Kiankhooy A, Taylor MD, LaPar DJ, et al. Predictors of early recurrence for node-negative t1 to t2b non-small cell lung cancer. Ann Thorac Surg 2014;98:1175-83.