Original Article

Interstitial lung disease and wedge resection are poor prognostic factors for non-small cell lung cancer

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Background: Although several prognostic factors in patients undergoing pulmonary resection with early-stage non-small cell lung cancer (NSCLC) have been reported, the risk factors are varied and have not been consistent among reports.

Methods: Clinical data of 540 patients with pathological stage IA NSCLC were analyzed. Patient factors, such as the sex, age, comorbidities, carcinoembryonic antigen (CEA) level, and smoking history, and surgical factors, such as the operative approach and procedure, were collected and analyzed.

Results: There were significant prognostic differences in the relapse-free survival (RFS) depending on the presence of interstitial lung disease (P<0.0001), CEA level (P=0.007), and wedge resection (P=0.002). There were significant prognostic differences in the overall survival (OS) depending on the presence of interstitial lung disease (P=0.0015), CEA level (P<0.0001), and smoking history (P=0.0003). Interstitial lung disease [hazard ratio (HR): 7.725, P=0.003], the CEA level (HR: 1.923, P=0.045), and operative procedure (HR: 2.086, P=0.025) were risk factors for the RFS in a multivariate analysis. The smoking history (HR: 2.539, P=0.002) and CEA level (HR: 2.464, P=0.002) were risk factors for the OS in a multivariate analysis.

Conclusions: Interstitial lung disease, the CEA level, and operative procedure were risk factors for the RFS, while the smoking history and CEA level were risk factors for the OS.

Keywords: Early stage; non-small cell lung cancer (NSCLC); interstitial lung disease; wedge resection

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for more than 80% of all cases (1). Although the standard treatment for early-stage NSCLC is lobectomy combined with systematic lymph node dissection, some reports showed that sublobar resection for early-stage NSCLC has a more favorable prognosis than lobectomy (2,3).

Video-assisted thoracic surgery (VATS) for patients with NSCLC has been widely adopted, and various studies have reported the advantages of this approach (4-7). These reports revealed that VATS is associated with minimal pain, a shorter hospital stay, less-marked reduction in the inflammatory immune response, and better maintenance of the postoperative respiratory function than thoracotomy. However, the relationship between the prognosis and

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operative approaches, such as VATS, in NSCLC patients undergo pulmonary resection has not been elucidated.

Several prognostic factors in patients with early-stage NSCLC have been reported (8-14). Although the prognosis of stage IA NSCLC is considered good compared with the advanced stage, the age, gender, carcinoembryonic antigen (CEA), tumor size, operative procedure, surgical margin, pleural invasion, lymphatic invasion, histological type, and presence of combined pulmonary fibrosis and emphysema (CPFE) have been reported as prognostic factors in patients with early-stage NSCLC. Furthermore, the risk factors are varied and not consistent among reports.

In the present study, we retrospectively evaluated the prognostic factors in pathological stage IA NCSLC patients who underwent pulmonary resection. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1757/rc).

Methods

Patients

Nine hundred and fifty-six NSCLC patients who underwent pulmonary resection at Kanazawa Medical University between January 2002 and March 2020 were identified. Among these, 8 patients were lost to follow-up and 5 patients had insufficient data, and then, 540 patients who had sufficient data with pathological stage IA were enrolled in this retrospective study.

Data, including clinicopathological factors, such as the gender, age, comorbidities, smoking history, respiratory function, CEA, lung cancer lobe involvement, histological type, lymphatic invasion, vascular invasion, and differentiation, were collected. Comorbidities were divided into three categories: interstitial lung disease, malignant disease, and angina pectoris. The smoking history was evaluated using the Brinkman index, which is calculated by multiplying the number of cigarettes smoked per day by the number of years the subject has been smoking. Respiratory function parameters, such as the percent-predicted vital capacity (%VC) and forced expiratory volume in 1 second as a percentage of forced vital capacity (FEV_1%), were collected.

Operative factors

The operative approach was divided into four categories: complete VATS (C-VATS, surgery performed only to provide a monitoring view), hybrid VATS (H-VATS, surgery combined with direct vision without rib spreading), robot-assisted thoracic surgery (RATS), and open thoracotomy. The operative procedure was stratified into three categories: wedge resection, segmentectomy, and lobectomy.

Postoperative complications

Postoperative complications were categorized into five grades according to the Clavien-Dindo classification system (15). The Clavien-Dindo classification was established in 1992. It is a simple and feasible grading system for all types of postoperative complications (16). In 2004, it was modified to allow grading of life-threatening complications and long-term disability caused by a complication (17). This revised version has defined five grades of severity with subgrades (grades I, II, IIIa, IIIb, IVa, IVb, and V), and the suffix "d" (for "disability") is used to denote any postoperative impairment. This modified version of the Clavien-Dindo classification has been widely used in clinical practice.

Statistical analyses

Pearson's chi-squared test of independence was used to compare the frequencies of the variables. The cumulative survival rates were calculated by the Kaplan-Meier method, and survival curves were compared using a log-rank test. The risk factors related to postoperative complications were analyzed using logistic regression analysis. All statistical analyses were two-sided and statistical significance was set at $P<0.05$. Statistical analyses were conducted using the JMP software program, version 13.2 (SAS Institute Inc., Cary, NC, USA).

Declaration and ethical statement

The present study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Kanazawa Medical University approved the protocol (No. I392) and written informed consent was obtained from all patients.

Results

Patient characteristics

The clinicopathological characteristics of the 540 NSCLC patients with pathological stage IA disease are listed in

Table 1 Patient characteristics (n=540)

Characteristics	Value
Gender (male/female), n	310/230
Age (years), median [range]	70.6 [22–92]
Comorbidity, n (%)	319 (59.1)
Interstitial lung disease	7 (1.3)
Malignant disease	107 (19.8)
Angina pectoris	35 (6.5)
Smoking index, median [range]	400 [0–3,250]
CEA (ng/mL), median [range]	3.0 [0.5–44.0]
%VC, median [range]	100.7 [53.4–177.7]
FEV_1%, median [range]	73.9 [30.5–99.4]
Lobe of lung cancer (RU/RM/RL/LU/LL), n	165/33/118/130/94
Operative approach (RATS/C-VATS/H-VATS/open), n	10/244/267/19
Operative procedure (Wedge/Seg/Lob), n	131/57/352
Histology (Ad/Sq/LCNEC/Pleo/AdSq/large/carcinoid), n	454/60/13/3/4/1/5
Lymphatic invasion (present/absent), n	92/448
Vascular invasion (present/absent), n	136/404
Differentiation (G1/2/3/4), n	240/243/45/12
Postoperative complication, n (%)	127 (23.5)
Clavien-Dindo grade (0/1/2/3a/3b), n	413/0/48/76/3
Thirty-day mortality, n (%)	1 (0.2)
Ninety-day mortality, n (%)	1 (0.2)
Postoperative hospital-stay (days), median [range]	10 [3–89]

CEA, carcinoembryonic antigen; %VC, percent-predicted vital capacity; FEV_1%, forced expiratory volume % in one second; RU, right upper; RM, right middle; RL, right lower; LU, left upper; LL, left lower; RATS, robot-assisted thoracic surgery; C, complete; VATS, video-assisted thoracic surgery; H, hybrid; Wedge, wedge resection; Seg, segmentectomy; Lob, lobectomy; Ad, adenocarcinoma; Sq, squamous cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; Pleo, pleomorphic carcinoma; AdSq, adenosquamous cell carcinoma; Large, large cell carcinoma; G, grade.

Table 1. Among these, 310 (57.4%) were men, and the median age was 70.6 years old. The median Brinkman index was 400. Altogether, 319 (59.1%) patients had comorbidities, including 7 (1.3%) with interstitial lung disease, 107 (19.8%) with malignant disease, and 35 (6.5%) with angina pectoris. The median CEA was 3.0 ng/mL, the median %VC was 100.7%, and the median FEV_1% was 73.9%. The pulmonary lobes resected for NSCLC included the right upper lobe in 165 (30.6%) patients, right middle lobe in 33 (6.1%), right lower lobe in 118 (21.9%), left upper lobe in 130 (24.1%), and left lower lobe in 94 (17.4%) patients.

Operative factors

C-VATS was performed in 244 (45.2%) patients, H-VATS in 267 (49.4%) patients, RATS in 10 (1.9%) patients, and open thoracotomy in 19 (3.5%) patients. Wedge resection was performed in 131 (24.3%) patients, segmentectomy in 57 (10.6%), and lobectomy in 352 (65.2%).

Pathological factors

Histological types were divided into 7 types as follows: 454 (84.1%) patients were diagnosed with adenocarcinoma, 60 (11.1%) patients with squamous cell carcinoma, 13 (2.4%) with large-cell neuroendocrine carcinoma, 3 (0.6%) with pleomorphic carcinoma, 4 (0.7%) with adenosquamous cell carcinoma, 1 (0.2%) with large cell carcinoma, and 5 (0.9%) with carcinoid. Lymphatic invasion was present in 92 (17.0%) patients, and vascular invasion was present in 136 (25.2%) patients. The differentiation grade was divided into 4 categories: G1 in 240 (44.4%) patients, G2 in 243 (45.0%) patients, G3 in 45 (8.3%) patients, and G4 in 12 (2.2%) patients.

Postoperative complications

Postoperative complications were observed in 127 (23.5%) patients. Clavien-Dindo grade II complications were noted in 48 (8.9%) patients, grade IIIa in 76 (14.1%), and grade IIIb in 3 (0.6%). Major postoperative complications included air leakage in 65 (12.0%) patients, arrhythmia in 21 (3.9%) [atrial fibrillation in 19 (3.5%) patients and paroxysmal supraventricular tachycardia in 2 (0.4%) patients], atelectasis in 16 (3.0%), pneumonia in 12 (22.2%), a fever in 4 (0.7%), chylothorax in 2 (0.4%), and cerebral infarction in 2 (0.4%). Serious postoperative complications included postoperative bleeding in one patient, postoperative respiratory failure in one patient, and right middle lobe congestion in one patient. Two patients improved with surgery, and one patient was ameliorated by a ventilator. The median duration of postoperative hospital

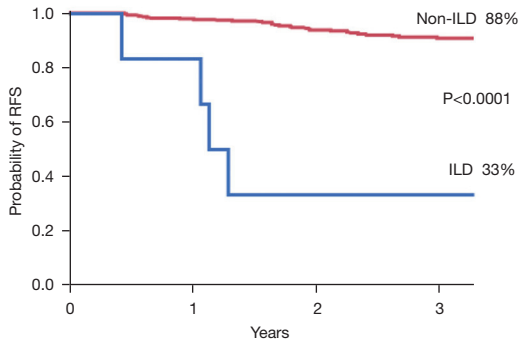

Figure 1 RFS for non-small cell lung cancer patients with pathological stage IA. Coexistence of ILD group was significantly worse than the absent of ILD group. RFS, relapse-free survival; ILD, interstitial lung disease.

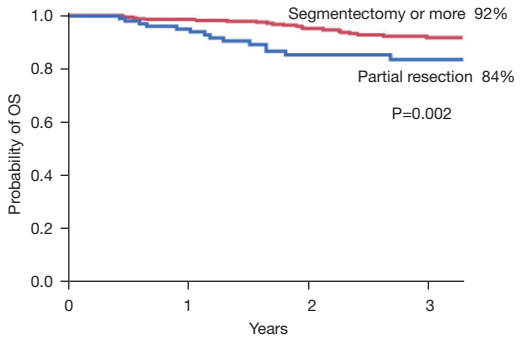

Figure 2 OS for non-small cell lung cancer patients with pathological stage IA. Coexistence of interstitial lung disease group was significantly worse than the absent of interstitial lung disease group. OS, overall survival.

stay was 10 days, and the 30- and 90-day mortality rates were 0.05% and 0.05%, respectively.

Survival analyses

The median relapse-free survival (RFS) time is 765 days (range, 5– 6,330 days) and the median overall survival (OS) time is 839 days (range, 5–6,330 days). The RFS is shown in *Figure 1*. There were significant prognostic differences depending on the presence of interstitial lung disease (P<0.0001), CEA level (P=0.007), and wedge resection (P=0.002). The OS is shown in *Figure 2*. There were significant prognostic differences depending on the presence interstitial lung disease (P=0.0015), CEA (P<0.0001) and the smoking history (P=0.0003).

Univariate and multivariate analyses

The relationship between clinicopathological patient characteristics or operative factors and the RFS was analyzed (*Table 2*). The presence of interstitial lung disease (P<0.0001), CEA level (P=0.006), and operative procedure (P=0.002) showed significant differences in the univariate analysis. Furthermore, the presence of interstitial lung disease [hazard ratio (HR): 7.725, 95% confidence interval (CI): 2.144–21.776, P=0.003], CEA level (HR: 1.923, 95% CI: 1.015–3.518, P=0.045), and operative procedure (HR: 2.086, 95% CI: 1.100–3.825, P=0.025) were considered risk factors for the RFS in the multivariate analysis.

The relationship between clinicopathological patient characteristics or operative factors and the OS was analyzed (*Table 3*). The presence of interstitial lung disease (P=0.0015), smoking history (P=0.0003), and CEA level (P<0.0001) showed significant differences in the univariate analysis. Furthermore, the smoking history (HR: 2.539, 95% CI: 1.372–5.002, P=0.002) and CEA level (HR: 2.464, 95% CI: 1.389–4.317, P=0.002) were considered risk factors for the OS in the multivariate analysis.

Discussion

In the present study, we analyzed the prognostic factors for inpatients who underwent pulmonary resection for pathological stage IA NSCLC. This study demonstrated that interstitial lung disease, CEA, and partial resection were significant prognostic factors for the RFS, whereas CEA and smoking history were significant prognostic factors for the OS. Although the survival rate has been similar between patients treated with limited resection and patients receiving lobectomy in some reports (18,19), wedge resection was reported to be a risk factor for locoregional recurrence in other reports (8, 20-22). Because these reports showed a trend toward a higher locoregional recurrence rate in patients who underwent wedge resection than in those receiving segmentectomy (8,20-22), segmentectomy appears to be the more suitable surgical procedure in patients being considered for sublobar resection.

We previously reported that the presence of CPFE was a statistically significant predictor of recurrence for patients with clinical stage I NSCLC (12). Furthermore, lung cancer patients with idiopathic pulmonary fibrosis (IPF) showed a significantly worse mortality rate than lung cancer patients without IPF (23). IPF is the most frequent and severe type of idiopathic interstitial pneumonia and has a median

Table 2 Univariate and multivariate analyses of clinicopathological factors in pathological stage IA NSCLC patients

Variables	5-year RFS (%)	Univariate P value	Multivariate analysis		
			HR	95% CI	P value
Gender		0.676	–	–	–
Male	86.3				
Female	88.9				
Age		0.175	–	–	–
≤75 years	85.7				
>75 years	90.8				
Comorbidity			–	–	–
Malignant disease		0.913			
Present	90.5				
Absent	86.8				
Interstitial lung disease		<0.0001	7.725	2.144–21.776	0.003
Present	33.3				
Absent	88.2				
Angina pectoris		0.651	–	–	–
Present	88.7				
Absent	87.3				
Smoking history		0.140	–	–	–
Present	86.3				
Absent	88.7				
%VC		0.611	–	–	–
<80	92.9				
≥80	87.0				
FEV^1%		0.209	–	–	–
<70	85.5				
≥70	88.2				
CEA		0.006	1.923	1.015–3.518	0.045
>5 ng/mL	79.0				
≤5 ng/mL	89.9				
Operative approach		0.331	–	–	–
C-VATS or RATS	82.4				
H-VATS or Open	88.7				
Operative procedure		0.002	2.086	1.100–3.825	0.025
Wedge resection	81.1				
Segmentectomy or more	89.2				

Table 2 (*continued*)

Table 2 (*continued*)

Variables	5-year RFS (%)	Univariate P value	Multivariate analysis		
			HR	95% CI	P value
Postoperative complication		0.641	–	–	–
Present	84.6				
Absent	88.1				
Lymphatic invasion		0.086	–	–	–
Present	81.9				
Absent	88.6				
Vascular invasion		0.120	–	–	–
Present	82.3				
Absent	89.2				
Differentiation		0.101	–	–	–
G1 or 2	85.4				
G3 or 4	82.6				

NSCLC, non-small cell lung cancer; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; %VC, percent-predicted vital capacity; FEV_1%, forced expiratory volume % in one second; CEA, carcinoembryonic antigen; C, complete; VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery; H, hybrid; G, grade.

Table 3 Univariate and multivariate analyses of clinicopathological factors in pathological stage IA NSCLC patients

Variables	5-year OS (%)	Univariate P value	Multivariate analysis		
			HR	95% CI	P value
Gender		0.344	–	–	–
Male	82.0				
Female	86.6				
Age		0.276	–	–	–
≤75 years	82.1				
>75 years	87.2				
Comorbidity					
Malignant disease		0.913	–	–	–
Present	83.1				
Absent	83.7				
Interstitial lung disease		0.0015	3.431	0.54–11.931	0.158
Present	62.5				
Absent	84.2				
Angina pectoris		0.575	–	–	–
Present	91.4				
Absent	83.4				

Table 3 (*continued*)

Table 3 (*continued*)

Variables	5-year OS (%)	Univariate P value	Multivariate analysis		
			HR	95% CI	P value
Smoking history		0.0003	2.539	1.372–5.002	0.002
Present	77.2				
Absent	91.6				
%VC		0.969	–	–	–
<80	89.6				
≥80	83.4				
FEV_1%		0.293	–	–	–
<70	81.6				
≥70	84.7				
CEA		<0.0001	2.464	1.389–4.317	0.002
>5 ng/mL	68.6				
≤5 ng/mL	88.5				
Operative approach		0.122	–	–	–
C-VATS or RATS	78.1				
H-VATS or Open	85.4				
Operative procedure		0.942	–	–	–
Wedge resection	90.0				
Segmentectomy or more	82.7				
Postoperative complication		0.098	–	–	–
Present	75.6				
Absent	86.3				
Lymphatic invasion		0.661	–	–	–
Present	76.8				
Absent	85.5				
Vascular invasion		0.499	–	–	–
Present	78.6				
Absent	85.6				
Differentiation		0.201	–	–	–
G1 or 2	84.5				
G3 or 4	78.0				

NSCLC, non-small cell lung cancer; OS, overall survival; HR, hazard ratio; CI, confidence interval; %VC, percent-predicted vital capacity; FEV_1%, forced expiratory volume % in one second; CEA, carcinoembryonic antigen; C, complete; H, hybrid; VATS, video-assisted thoracic surgery; G, grade; RATS, robot-assisted thoracic surgery.

survival of approximately 3 years after the diagnosis (24). In the treatment of lung cancer patients with IPF, physicians are reluctant to treat lung cancer because of the poor prognosis (25). The GAP [gender (G), age (A), and two lung physiology variables (P)] staging system has been used to predict the mortality and timing of lung transplantation in IPF patients (26). Although no beneficial treatment modalities were determined for GAP stage II/III, active therapies, such as surgery, for lung cancer patients with IPF in GAP stage I were recommended in a previous study (27). Therefore, the benefit of surgery for NSCLC patients with interstitial lung disease should be carefully evaluated using the GAP staging system.

Limitations

Several limitations associated with the present study warrant mention. First, the study was retrospective in nature and potentially involved unobserved cofounding and selection biases. Second, the present study was performed at a single institution, and the study population was relatively small.

In conclusion, our findings described the prognostic factors in pathological stage IA NCSLC patients who underwent pulmonary resection. This study revealed that the presence of interstitial lung disease, CEA level, and operative procedure were risk factors for the RFS, while the smoking history and CEA level were risk factors for the OS. These results suggest that segmentectomy is a more suitable surgical procedure than wedge resection for patients who are being considered for sublobar resection. Furthermore, the benefit of surgery for NSCLC patients with interstitial lung disease should be carefully evaluated.

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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-21-1757/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1757/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1757/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1757/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 present study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Kanazawa Medical University approved the protocol (No. I392) and written informed consent was obtained from all patients.

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