

# Interstitial Lung Disease and Partial Resection are Poor Prognostic Factors for pStage IA NSCLC: A Retrospective Study

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## Research Article

**Keywords:** early stage, non-small cell lung cancer, interstitial lung disease, partial resection

**Posted Date:** September 22nd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-793480/v2>

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# Abstract

**Introduction:** The prognostic factors in patients who underwent pulmonary resection with early stage non-small cell lung cancer (NSCLC) have not been elucidated.

**Materials and methods:** Clinical data of 540 patients with pathological stage IA NSCLC were analyzed. Patient factors such as sex, age, comorbidities, carcinoembryonic antigen (CEA), smoking history, and operative aspects such as operative approach and operative procedures were collected and analyzed.

**Results:** There were significant prognostic differences according to the interstitial lung disease ( $p < 0.0001$ ), CEA ( $p = 0.007$ ), and partial resection ( $p = 0.002$ ) in the relapse-free survival (RFS). There were significant prognostic differences according to the interstitial lung disease ( $p = 0.0015$ ), CEA ( $p < 0.0001$ ), and smoking history ( $p = 0.0003$ ) in the overall survival (OS). Interstitial lung disease (hazard ratio [HR]: 7.725,  $p = 0.003$ ), CEA (HR: 1.923,  $p = 0.045$ ), and operative procedure (HR: 2.086,  $p = 0.025$ ) were risk factors for RFS in a multivariate analysis. Smoking history (HR: 2.539,  $p = 0.002$ ) and CEA (HR: 2.464,  $p = 0.002$ ) were risk factors for OS in a multivariate analysis.

**Conclusion:** Interstitial lung disease, CEA, and operative procedure were risk factors for RFS, while smoking history and CEA were risk factors for OS.

## 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<sup>1</sup>. Although the standard treatment for early stage NSCLC is lobectomy combined with systematic lymph node dissection, sublobar resection for early stage NSCLC leads toward a more favorable prognosis than lobectomy<sup>2,3</sup>.

Video-assisted thoracic surgery (VATS) for patients with NSCLC has been widely adopted, and various studies have reported the advantages of this approach<sup>4-7</sup>. These reports revealed that VATS is associated with minimal pain, shorter hospital stay, less reduction in the inflammatory immune response, and maintenance of postoperative respiratory function when compared with thoracotomy. However, the relationship between the prognosis and operative approaches such as VATS in NSCLC patients who underwent pulmonary resection has not been elucidated.

Several prognostic factors in patients with early stage NSCLC have been reported<sup>8-17</sup>. Although the prognosis of stage IA NSCLC is considered good compared with the advanced stage, 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.

In the present study, we retrospectively evaluated the prognostic factors in pathological stage IA NSCLC patients who underwent pulmonary resection.

## Results

### Patient characteristics

The clinicopathological characteristics of the 540 NSCLC patients with pathological stage IA are listed in Table 1. Among these, 310 were men and the median age was 70.6 years. The median Brinkman index was 400. Altogether, 310 patients had comorbidities including 7 with interstitial lung disease, 107 with malignant disease, and 35 with angina pectoris. The median CEA was 3.0 ng/mL. The median %VC was 100.7% and the median FEV<sub>1</sub>% was 73.9%. The pulmonary lobes resected for NSCLC included the right upper lobe in 169 patients, right middle lobe in 33, right lower lobe in 118, left upper lobe in 130, and left lower lobe in 94 patients.

Table 1  
Patient characteristics (n = 540)

<b>Gender (Male / Female)</b>	<b>310 / 230</b>
<b>Age (year), median (range)</b>	70.6 (22–92)
<b>Comorbidity</b>	319 (59.1%)
<b>Interstitial lung disease (%)</b>	7 (1.3%)
<b>Malignant disease (%)</b>	107 (19.8%)
<b>Angina pectoris (%)</b>	35 (6.5%)
<b>Smoking index, median (range)</b>	400 (0–3250)
<b>CEA (ng/ml), median (range)</b>	3.0 (0.5–44)
<b>%VC, median (range)</b>	100.7 (53.4–177.7)
<b>FEV<sub>1</sub>%, median (range)</b>	73.9 (30.5–99.4)
<b>Lobe of lung cancer</b>	
<b>RU / RM / RL / LU / LL</b>	165 / 33 / 118 / 130 / 94
<b>Operative approach</b>	
<b>RATS / C-VATS / H-VATS / Open</b>	10 / 244 / 267 / 19
<b>Operative procedure</b>	
<b>Part / Seg / Lob</b>	131 / 57 / 352
<b>Histology (Ad / Sq / LCNEC / Pleo / AdSq / Large / Carcinoid)</b>	454 / 60 / 13 / 3 / 4 / 1 / 5
<b>Lymphatic invasion (present/absent)</b>	92 / 448
<b>Vascular invasion (present/absent)</b>	136 / 404
<b>Differentiation (G1 / 2 / 3 / 4)</b>	240 / 243 / 45 / 12
<b>Postoperative complication</b>	127 (23.5%)
<b>Clavien-Dindo grade (0 / 1 / 2 / 3a / 3b)</b>	413 / 0 / 48 / 76 / 3
<b>Thirty-day mortality (%)</b>	1 (0.05%)
<b>Ninety-day mortality (%)</b>	1 (0.05%)

CEA; carcinoembryonic antigen, %VC; vital capacity, FEV<sub>1</sub>%; 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, Part; partial 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

<b>Gender (Male / Female)</b>	<b>310 / 230</b>
<b>Postoperative hospital-stay (day), median (range)</b>	<b>10 (3–89)</b>
CEA; carcinoembryonic antigen, %VC; vital capacity, FEV1%; 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, Part; partial 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	

## Operative factors

C-VATS was performed in 244 patients, H-VATS in 267 patients, RATS in 10 patients, and open thoracotomy in 19 patients. Partial resection was performed in 131 patients, segmentectomy in 57, and lobectomy in 352.

## Pathological factors

Histological types were divided into 7 types as follows: 454 patients were diagnosed as adenocarcinoma, 60 patients as squamous cell carcinoma, 13 as large cell neuroendocrine carcinoma, 3 as pleomorphic carcinoma, 4 as adenosquamous cell carcinoma, 1 as large cell carcinoma, and 5 as carcinoid.

Lymphatic invasion was present in 92 patients and vascular invasion was present in 136 patients. Grade of differentiation was divided into 4 categories: G1 in 240 patients, G2 in 243 patients, G3 in 45 patients, and G4 in 12 patients.

## Postoperative complications

Postoperative complications were observed in 127 patients (23.5%). Clavien–Dindo grade II complications were noted in 48 patients, grade IIIa in 76, and grade IIIb in 3. Major postoperative complications included air leakage in 65 patients, arrhythmia in 21 (atrial fibrillation in 19 patients and paroxysmal supraventricular tachycardia in 2 patients), atelectasis in 16, pneumonia in 12, fever in 4, chylothorax in 2, and cerebral infarction in 2. Serious postoperative complications included postoperative bleeding in 1 patient, postoperative respiratory failure in 1 patient, and right middle lobe congestion in 1 patient. Two patients improved with surgery and 1 patient was ameliorated by a ventilator. The median duration of postoperative hospital stay was 10 days, and thirty-day and ninety-day mortality was 0.05% and 0.05%, respectively.

## Survival analyses

Relapse free survival (RFS) is shown in Fig. 1. There were significant prognostic differences according to the interstitial lung disease ( $p < 0.0001$ ), CEA ( $p = 0.007$ ), and partial resection ( $p = 0.002$ ). Overall survival (OS) is shown in Fig. 2. There were significant prognostic differences according to the interstitial lung disease ( $p = 0.0015$ ), CEA ( $p < 0.0001$ ) and smoking history ( $p = 0.0003$ ).

## Univariate and multivariate analysis

The relationship between clinicopathological patient characteristics or operative factors and RFS was analyzed (Table 2). Interstitial lung disease ( $p < 0.0001$ ), CEA ( $p = 0.006$ ), and operative procedure ( $p = 0.002$ ) were significant differences in the univariate analysis. Furthermore, interstitial lung disease (hazard ratio [HR]: 7.725, 95% confidence interval [CI]: 2.144–21.776,  $p = 0.003$ ), CEA (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 risk factors for RFS in the multivariate analysis.

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

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

RFS; relapse free survival, HR; hazard ratio, CI; confidence interval, %VC; vital capacity, FEV<sub>1</sub>%; 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

Variables		5-year RFS (%)	Univariate <i>p</i> value	Multivariate analysis		
<b>Operative procedure</b>	Partial resection	81.1	0.002	2.086	1.100–3.825	0.025
	Segmentectomy or more	89.2				
<b>Postoperative complication</b>	Present	84.6	0.641			
	Absent	88.1				
<b>Lymphatic invasion</b>	Present	81.9	0.086			
	Absent	88.6				
<b>Vascular invasion</b>	Present	82.3	0.120			
	Absent	89.2				
<b>Differentiation</b>	G1 or 2	85.4	0.101			
	G3 or 4	82.6				

RFS; relapse free survival, HR; hazard ratio, CI; confidence interval, %VC; vital capacity, FEV1%; 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

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

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

Variables		5-year OS (%)	Univariate <i>p</i> value	Multivariate analysis		
				HR	95%CI	<i>p</i> value
<b>Gender</b>	Male	82.0	0.344			
	Female	86.6				
<b>Age</b>	≤ 75 year	82.1	0.276			
	> 75 year	87.2				
<b>Comorbidity</b>						
<b>Malignant disease</b>	Present	83.1	0.913			
	Absent	83.7				
<b>Interstitial lung disease</b>	Present	62.5	0.0015	3.431	0.54–11.931	0.158
	Absent	84.2				
<b>Angina pectoris</b>	Present	91.4	0.575			
	Absent	83.4				
<b>Smoking history</b>	Present	77.2	0.0003	2.539	1.372–5.002	0.002
	Absent	91.6				
<b>%VC</b>	< 80	89.6	0.969			
	≥ 80	83.4				
<b>FEV<sub>1</sub>%</b>	< 70	81.6	0.293			
	≥ 70	84.7				
<b>CEA</b>	> 5 ng/ml	68.6	< 0.0001	2.464	1.389–4.317	0.002
	≤ 5 ng/ml	88.5				
<b>Operative approach</b>	C-VATS or RATS	78.1	0.122			
	H-VATS or Open	85.4				
OS; overall survival, HR; hazard ratio, CI; confidence interval, %VC; vital capacity, FEV <sub>1</sub> %; 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						

Variables		5-year OS (%)	Univariate <i>p</i> value	Multivariate analysis
<b>Operative procedure</b>	Partial resection	90.0	0.942	
	Segmentectomy or more	82.7		
<b>Postoperative complication</b>	Present	75.6	0.098	
	Absent	86.3		
<b>Lymphatic invasion</b>	Present	76.8	0.661	
	Absent	85.5		
<b>Vascular invasion</b>	Present	78.6	0.499	
	Absent	85.6		
<b>Differentiation</b>	G1 or 2	84.5	0.201	
	G3 or 4	78.0		

OS; overall survival, HR; hazard ratio, CI; confidence interval, %VC; vital capacity, FEV1%; 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

## 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 RFS, whereas CEA and smoking history were significant prognostic factors for OS. Although survival was similar for patients treated with limited resection to that of patients receiving lobectomy in some reports<sup>18–19</sup>, partial resection was reported as the risk factor for locoregional recurrence in other reports<sup>8,20–22</sup>. Because these reports showed a trend toward a higher locoregional recurrence rate in patients who underwent wedge resection compared with segmentectomy<sup>8,20–22</sup>, segmentectomy should 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<sup>12</sup>. Furthermore, lung cancer patients with idiopathic pulmonary fibrosis (IPF) showed a statistically significant worse mortality rate compared to lung cancer patients without IPF<sup>23</sup>. IPF is the most frequent and severe type of idiopathic interstitial pneumonia and has a median survival of approximately 3 years after diagnosis<sup>24</sup>. In the treatment of lung cancer patients with IPF, physicians are reluctant to treat lung cancer because of the poor prognosis<sup>25</sup>. GAP (gender [G], age [A], and two lung physiology variables [P]) staging system has been used to predict the mortality and the

timing of lung transplantation in IPF patients<sup>26</sup>. Although beneficial treatment modalities were not found at GAP stage II/III, active therapies such as surgery for lung cancer patients with IPF in GAP stage I are recommended in the previous study<sup>27</sup>. Therefore, the benefit of surgery for NSCLC patients with interstitial lung disease should be carefully evaluated by using the GAP staging system.

Reportedly, VATS is associated with minimal pain, less reduction in the inflammatory immune response, and maintenance of postoperative respiratory function when compared with thoracotomy. Therefore, VATS is considered as a less invasive procedure<sup>4-7</sup>. However, the relationship between prognosis and operative approaches such as VATS or RATS in NSCLC patients who have undergone pulmonary resection has not been elucidated. Our previous study revealed that operative invasiveness does not affect the prognosis of patients with NSCLC<sup>28</sup>. Because VATS and RATS were not prognostic factors in the present study, the operative approach therefore does not influence the prognosis of NSCLC patients.

The present study has several limitations. First, the study was retrospective in nature and potentially involved unobserved confounding and selection biases. Second, the present study was performed at a single institution, and the study population was relatively small.

## Conclusion

Our findings described the prognostic factors in pathological stage IA NSCLC patients who underwent pulmonary resection. This study revealed that interstitial lung disease, CEA, and operative procedure were risk factors for RFS while smoking history and CEA were risk factors for OS. These results thereby postulate that segmentectomy is a more suitable surgical procedure 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.

## Materials And Methods

### Patients

Nine hundred fifty-six NSCLC patients who underwent pulmonary resection at Kanazawa Medical University between January 2002 and March 2020 and 540 patients with pathological stage IA were enrolled in this retrospective study.

Data including clinicopathological factors such as 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. Smoking history was assessed 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<sup>29</sup>. Respiratory function parameters such as percent-predicted vital capacity (%VC) and forced expiratory volume in 1 second as a percentage of forced vital capacity (FEV<sub>1</sub>%) 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: partial resection, segmentectomy, and lobectomy.

## Postoperative complications

Postoperative complications were categorized into five grades according to the Clavien–Dindo classification system<sup>15</sup>. The Clavien–Dindo classification was established in 1992. It is a simple and feasible grading system for all types of postoperative complications<sup>16</sup>. In 2004, it was modified to allow grading of life-threatening complications and long-term disability caused by a complication<sup>17</sup>. 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

We used Pearson's chi-square test of independence to compare the frequencies of the variables. Cumulative survival was calculated by the Kaplan-Meier method and survival curves were compared using the Logrank test. Risk factors associated with postoperative complications were analyzed using logistic regression analysis. All statistical analyzes were performed on both sides and the statistical significance was set to  $p < 0.05$ . Statistical analysis was performed using JMP software program version 13.2 (SAS Institute Inc., Cary, NC, USA).

This study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review committee of Kanazawa Medical University approved the protocol (approval number: 1392), and all patients gave written informed consent

## Abbreviations

NSCLC

non-small cell lung cancer, VATS:video-assisted thoracic surgery, CEA:carcinoembryonic antigen, CPFE:combined pulmonary fibrosis and emphysema, %VC:percent-predicted vital capacity, FEV<sub>1</sub> %:forced expiratory volume in 1 second as a percentage of forced vital capacity, RATS:robot-assisted thoracic surgery, RFS:relapse free survival, OS:overall survival, HR:hazard ratio, CI:confidence interval.

## Declarations

**Ethics approval and consent to participate**

The present study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Boards of Kanazawa Medical University approved the protocol (approval number: I392), and written informed consent was obtained from all of the patients.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available due to [our institutional restrictions e.g. them containing information that could compromise research participant privacy/consent], but are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

This study has not been funded.

### **Author's contributions**

N. M. performed the research, collected and analyzed the data and wrote the paper. M.I., S. I., A.Y., and Y.I. contributed to sample collection. H. U. contributed to supervision of this study and revision of the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

### **Acknowledgements**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

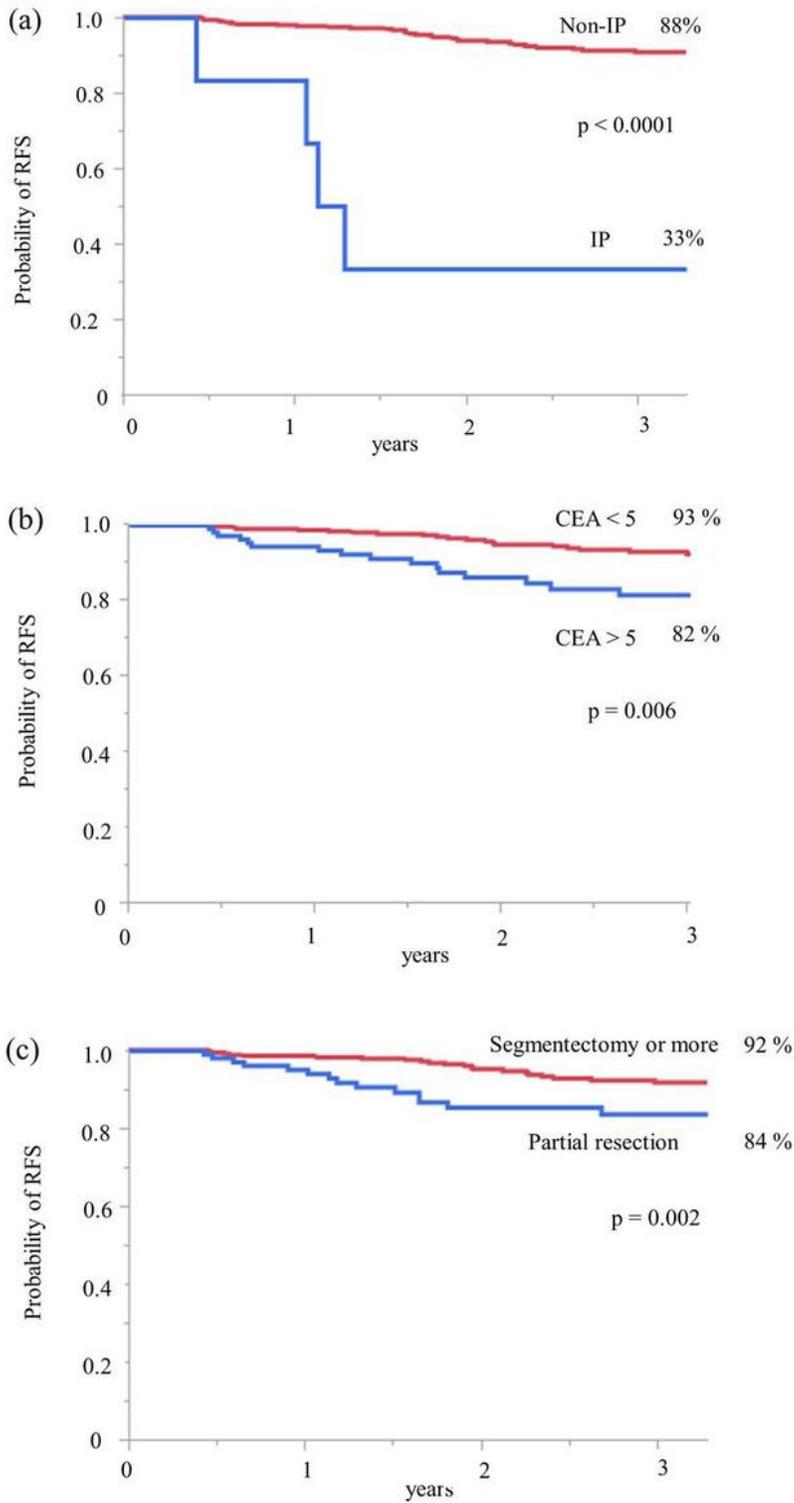
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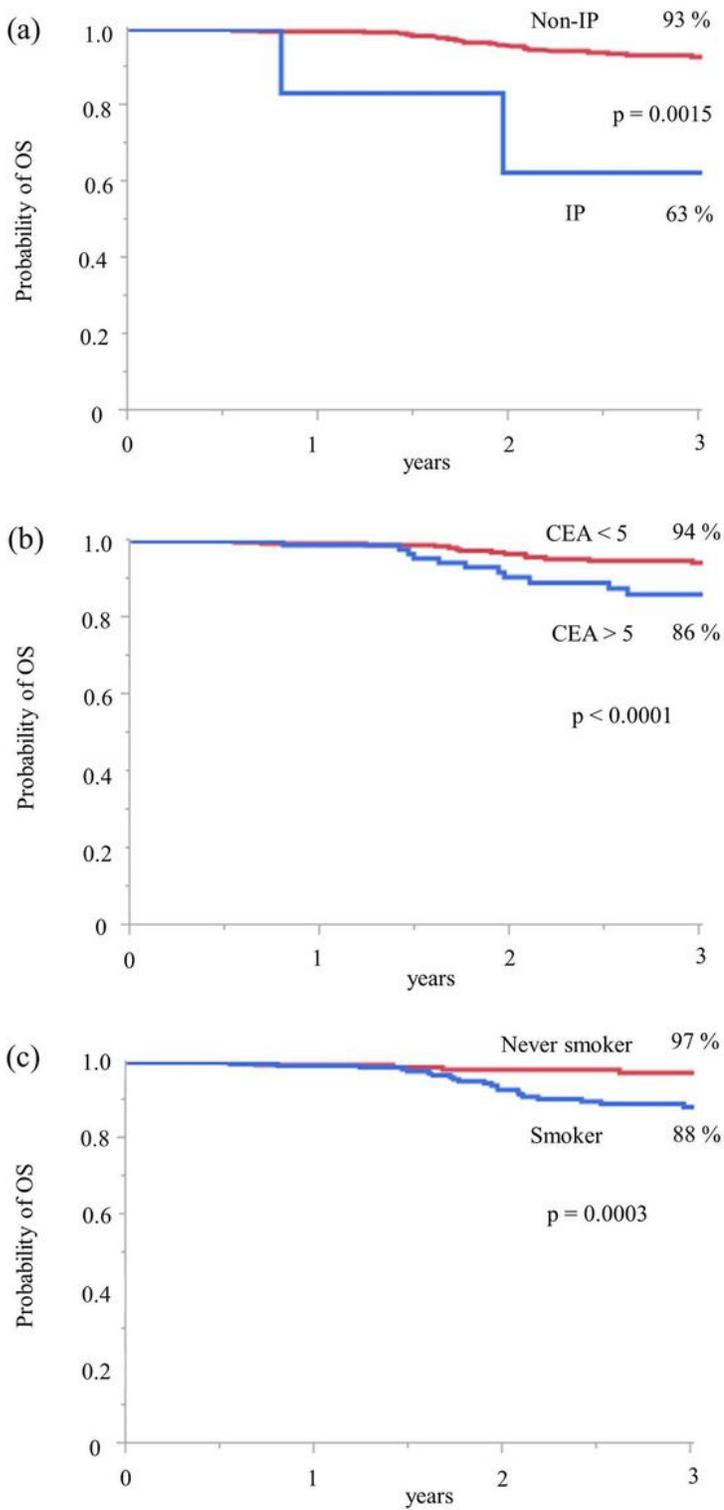
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## Figures



**Figure 1**

Relapse-free survival for non-small cell lung cancer patients with pathological stage IA (a) Coexistence of interstitial lung disease group was significantly worse than the absent of interstitial lung disease group. (b) Positive of carcinoembryonic antigen group was significantly worse than negative of carcinoembryonic antigen group. (c) Partial resection group was significantly worse than segmentectomy or lobectomy group.



**Figure 2**

Overall survival for non-small cell lung cancer patients with pathological stage IA (a) Coexistence of interstitial lung disease group was significantly worse than the absent of interstitial lung disease group. (b) Positive of carcinoembryonic antigen group was significantly worse than negative of carcinoembryonic antigen group. (c) Smoker group was significantly worse than never smoker group.