# Pulmonary Resection for Lung Cancer in Patients With Idiopathic Interstitial Pneumonia

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*Background.* **After pulmonary resection, patients with lung cancer who have idiopathic pulmonary fibrosis (IPF) have been reported to have higher pulmonary morbidity and mortality and poorer outcomes than patients without IPF. However, whether morbidity, mortality, and outcomes differ according to the subtype of idiopathic interstitial pneumonia (IIP) remains unclear.**

*Methods.* **The clinical records of 678 patients with non-small cell lung cancer who underwent pulmonary resection were reviewed retrospectively. A total of 103 patients had IIP and were classified into an IPF group and a non-IPF group in accordance with the 2011 statement.**

*Results.* **The IPF group comprised 46 patients, and the non-IPF group comprised 57. The 5-year survival rate was significantly higher in the non-IPF group (53.2%) than in the IPF group (22.1%; $p = 0.0093$). Cause of death was IIP-related respiratory failure in 26.1% (12 of 46) of the patients in the IPF group as compared with 7.0% (4 of 57) of patients in the non-IPF group ($p = 0.008$). Multivariate Cox analysis indicated that IPF was a significant predictor of long-term survival (hazard ratio 1.910, 95% confidence interval: 1.102 to 3.313; $p = 0.021$).**

*Conclusions.* **Idiopathic pulmonary fibrosis is independently associated with poorer overall survival in patients with lung cancer who undergo pulmonary resection. The decision whether to perform surgery in patients who have lung cancer with IIP should therefore take into account the subtype of IIP and the poorer outcomes associated with IPF.**

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Idiopathic pulmonary fibrosis (IPF) is chronic, diffuse progressive interstitial lung disease of unknown etiology that occurs primarily in older adults and is limited to the lung. Several studies have demonstrated that the median survival time of patients with IPF ranges from 2 to 3.5 years from the time of diagnosis [1–8]. The outcomes of IPF are worse than those of other types of idiopathic interstitial pneumonia (IIP) [2–4, 9]. Therefore, an accurate diagnosis of IPF is essential when making treatment-related decisions and advising on prognosis. Idiopathic pulmonary fibrosis is associated with an increased risk of lung cancer [10, 11]. However, treating patients with both lung cancer and IPF is complicated not only by the poor prognosis of IPF itself but also by the high morbidity and acute exacerbation (AE) rates and the high mortality rate after pulmonary resection.

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Several studies have reported that pulmonary morbidity and mortality are substantially higher and outcomes are much poorer after pulmonary resection for lung cancer among patients with IPF than among patients without IPF [12–15]. However, whether morbidity, mortality, and outcomes differ according to the subtype of IIP remains unclear. In particular, no previous study has evaluated the effects of the subtype of IIP as defined by the official classification of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association (ATS/ERS/JRS/ALAT), based on the 2011 statement [8], on morbidity, mortality, and long-term survival after pulmonary resection for lung cancer.

In the present study, we compared background characteristics and postoperative pulmonary morbidity, mortality, and long-term survival according to the subtype of IIP (IPF versus non-IPF) among patients with IIP who underwent pulmonary resection for lung cancer.

## Material and Methods

We retrospectively reviewed the medical records of 678 consecutive patients with non-small cell lung cancer who



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**Abbreviations and Acronyms**

| | | |
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| AE | = | acute exacerbation |
| ATS/ERS/JRS/ALAT | = | American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association |
| FVC | = | forced vital capacity |
| HRCT | = | high-resolution computed tomography |
| IIP | = | idiopathic interstitial pneumonia |
| IPF | = | idiopathic pulmonary fibrosis |
| KL-6 | = | Krebs von den Lungen-6 |
| $PaO_2$ | = | partial pressure of oxygen |
| SP-D | = | surfactant protein-D |
| UIP | = | usual interstitial pneumonia |

underwent pulmonary resection in the department of thoracic surgery, Kanagawa Cardiovascular and Respiratory Center, between January 2004 and December 2011. A total of 114 patients (16.8%) concurrently had interstitial lung disease. Eleven patients were excluded because they had a history of environmental exposure or collagen-related interstitial lung disease. The remaining 103 patients (15.2%) with IIP were studied. The study protocol was approved by the Institutional Review Board of Kanagawa Cardiovascular and Respiratory Center. Informed consent was waived because this was a retrospective study. The IIP was diagnosed and categorized by a pulmonologist and a radiologist, each of whom specialized in the diagnosis of pulmonary lesions. High-resolution computed tomography (HRCT) images were used in the preoperative evaluation at our hospital. Patients with IIP were categorized into three patterns based on the 2011 ATS/ERS/JRS/ALAT statement [8]: usual interstitial pneumonia (UIP) pattern, possible UIP pattern, or inconsistent with UIP pattern. Two pulmonary pathologists histopathologically reviewed all resected lung specimens and classified the patterns of interstitial pneumonia. The IPF group comprised patients who were given a diagnosis of IPF, probable IPF, or possible IPF in according with the 2011 ATS/ERS/JRS/ALAT statement (Fig 1). All other patients were allocated to the non-IPF group (Fig 1).

We considered the respiratory function and chance of cure when determining the extent of lung resection. Since 2007, we have switched the procedure for resection of lung cancer from thoracotomy to using video-assisted thoracic surgery at our hospital. We administered no prophylactic drugs perioperatively, although intraoperative high oxygen concentrations and high airway pressures were avoided if IIP had been diagnosed preoperatively. Minimal oxygen was provided to maintain postoperative oxygen saturation of 93% or greater. Acute exacerbations were diagnosed if the following criteria were fulfilled within 1 month: (1) increased dyspnea; (2) new ground-glass opacities appeared on chest HRCT in addition to previous honeycomb lesions; (3) the resting partial pressure of oxygen ($PaO_2$) was more than 10 mm Hg lower than the previous measurement; and (4) obvious causes, such as infection, pneumothorax, cancer, pulmonary embolism, and congestive heart failure, were excluded [16]. Air leakage was considered prolonged if it lasted for more than 7 days or required operation or pleurodesis for repair. Home oxygen therapy was permitted if the $PaO_2$ remained low and was at a level that required oxygen inhalation at the time of hospital discharge.

Patients with IIP in whom respiratory failure was caused by AE or by spontaneous deterioration were given steroid pulse therapy, immunosuppressant therapy, or both, by pulmonologists. We also used pirfenidone, an oral antifibrotic agent approved in Japan since 2008.

Medical records were reviewed to obtain clinical and demographic data, including age, sex, smoking history, respiratory function, blood gas analysis, and serum level of Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D). In addition, we collected data on histologic characteristics, pathologic stage of lung cancer, and surgical procedures, as well as data on postoperative pulmonary morbidity, mortality, causes of death, and survival.

### *Statistical Analyses*

Data were analyzed using SPSS 11.0.1 software (SPSS, Chicago, IL). To compare differences between the IPF group and the non-IPF group, Student's $t$ test was used to analyze continuous variables, and the $\chi^2$ test or Fisher's exact test was used to analyze categoric variables. Survival rate was estimated by the Kaplan-Meier method and was compared between the two groups by the log rank test. A multivariate analysis was performed using a Cox proportional hazards model to identify prognostic factors. All $p$ values of less than 0.05 were considered to indicate statistical significance.

## Results

### *Classification of IIP Into IPF and Non-IPF*

The details of the IPF and non-IPF groups are summarized in the flow chart in Figure 1. The IPF group comprised 46 patients; IPF was diagnosed on HRCT analysis in 39 patients and on histopathology examination in 7. The remaining 57 patients were classified into the non-IPF group.

### *Patient Characteristics*

The clinical characteristics of the patients in the IPF group and the non-IPF group are summarized in Table 1. The two groups were similar with respect to age (older), sex (male predominance), smoking index, and smoking status (high). On pulmonary function testing, percent forced vital capacity (%FVC) was significantly lower in the IPF group than in the non-IPF group, and percent forced expiratory volume in 1 second was significantly lower in the non-IPF group than in the IPF group. However,