Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer

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Objective: The study objective was to examine the incidence, risk factors, and mortality rate of acute exacerbation of interstitial lung diseases in patients with lung cancer undergoing pulmonary resection in a large-scale multi-institutional cohort.

Methods: We retrospectively analyzed 1763 patients with non–small cell lung cancer who had undergone pulmonary resection and presented with a clinical diagnosis of interstitial lung diseases between January 2000 and December 2009 at 61 hospitals in Japan. The incidence and outcomes of acute exacerbation within 30 days from the operation were investigated. Univariate and multivariate logistic regression analyses were used to identify independent risk factors of acute exacerbation.

Results: Acute exacerbation occurred in 164 patients (9.3%; 95% confidence interval, 8.0-10.8), with a mortality rate of 43.9%, and was the top cause of 30-day mortality (71.7%). The following 7 independent risk factors of acute exacerbation were identified: surgical procedures, male sex, history of exacerbation, preoperative steroid use, serum sialylated carbohydrate antigen KL-6 levels, usual interstitial pneumonia appearance on computed tomography scan, and reduced percent predicted vital capacity. Surgical procedures showed the strongest association with acute exacerbation (using wedge resection as the reference, lobectomy or segmentectomy: odds ratio, 3.83; 95% confidence interval, 1.94-7.57; bi-lobectomy or pneumonectomy: odds ratio, 5.70; 95% confidence interval, 2.38-13.7; $P < .001$). The effect of perioperative prophylactics, such as steroids and sivelestat, was not confirmed in this study.

Conclusions: Pulmonary resection for patients with lung cancer with interstitial lung diseases may provoke acute exacerbation at a substantially high rate and has high associated mortality. Surgical procedures that proved to be a risk factor for acute exacerbation should be chosen cautiously for these high-risk patients. (J Thorac Cardiovasc Surg 2014;147:1604-11)

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The investigators and institutions participating in this study are listed in Appendix E1.

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Interstitial lung diseases (ILDs) are associated with an increased risk of lung cancer.[1,2] Therapeutic modalities for patients with lung cancer with ILDs should be selected carefully because interventions may provoke exacerbation of ILDs.[3,4] Pulmonary resection has been shown to be associated with high postoperative morbidity and mortality in these patients. Postoperative acute exacerbation (AE) of interstitial pneumonia is one such possible comorbidity and is associated with mortality rates between 33.3% and 100%.[5-8] In addition to treatment-related morbidity and mortality, the prognosis of ILDs itself—particularly in patients with idiopathic pulmonary fibrosis (IPF)—can be a life-limiting factor. Several retrospective studies suggest a median survival time of patients with IPF from 2 to 3 years after diagnosis.[9-13] Whether

Abbreviations and Acronyms

AE = acute exacerbation
ALI = acute lung injury
ARDS = acute respiratory distress syndrome
CI = confidence interval
CRP = C-reactive protein
CT = computed tomography
DLCO = diffusing capacity for carbon monoxide
FEV1 = forced expiratory volume in 1 second
FEV1% = percent forced expiratory volume in 1 second
ILD = interstitial lung disease
IPF = idiopathic pulmonary fibrosis
OR = odds ratio
$Paco_2$ = partial pressure of carbon dioxide
%DLCO = percent predicted diffusing capacity for carbon monoxide
%VC = percent vital capacity
UIP = usual interstitial pneumonia
VC = vital capacity

pulmonary resections are indicated for patients with lung cancer with fibrosis remains a matter of debate.[8,14-16]

To determine the most appropriate treatment strategy, a reliable assessment of the risks and benefits of the various interventions is required. However, no cohort study of a sufficiently large scale for this purpose has been conducted. The purpose of this study was therefore to clarify the incidence, risk factors, and outcomes of postoperative AE in patients with lung cancer with ILDs who had undergone pulmonary resection. At the initiative of the Japanese Association for Chest Surgery, we have conducted a large-scale multi-institutional retrospective cohort study to inform the decision-making process for these patients.

MATERIALS AND METHODS

Study Design and Patients

The design of the study was planned by Drs Sato, Teramukai, and Date with assistance from the advisory board of the Japanese Association for Chest Surgery and the Project Team for Diffuse Lung Diseases, organized by the Japanese Ministry of Health, Labour and Welfare. The study protocol was approved by the institutional review boards of all participating hospitals, including that of the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine (Approval Number: E-982).

The original data for analysis were obtained from patients with non–small cell lung cancer who had undergone pulmonary resection and presented with a clinical diagnosis of ILD between January 2000 and December 2009 at 64 institutions throughout Japan.

The primary end point for outcomes analysis was postoperative AE of interstitial pneumonitis within 30 days after pulmonary resection. Medical records of the patients were reviewed for age; sex; comorbidities, including collagen and respiratory diseases; smoking history; blood work and physiologic data, including white blood cells, C-reactive protein (CRP), lactate dehydrogenase, KL-6 (sialylated carbohydrate antigen KL-6), carcinoembryonic antigen, partial pressure of oxygen, partial pressure of carbon dioxide ($Paco_2$), vital capacity (VC), percent vital capacity (%VC), forced expiratory volume in 1 second (FEV1), percent FEV1 (FEV1%), percent predicted FEV1, diffusing capacity for carbon monoxide (DLCO), and percent predicted DLCO (%DLCO); operation time; bleeding amount; perioperative prophylactics, including steroids, sivelestat sodium hydrate, ulinastatin, and combinations thereof; surgical procedures; tumor location; pathologic diagnosis; and cancer pTNM stages based on the 6th edition of the American Joint Committee on Cancer lung cancer staging.

Inclusion Criteria for Patients With Interstitial Lung Diseases

Diagnoses of ILDs were confirmed on the basis of a combination of clinical and radiologic findings according to the clinical criteria proposed by the Japanese Respiratory Society,[17] which are consistent with the guidelines of the American Thoracic Society in 2011.[12] The cases were categorized into 2 groups according to their radiologic appearance on computed tomography (CT) scan: (1) usual interstitial pneumonia (UIP) pattern: characterized by the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions, with multiple equal-sized cystic lesions of 2 to 10 mm diameter with a thick wall; and (2) non-UIP pattern: characterized by the presence of basal-predominant ground glass opacities and infiltrative shadows inconsistent with UIP patterns.

Definition of Postoperative Acute Exacerbation

AE caused by pulmonary resection was defined on the basis of criteria proposed by the American Thoracic Society Guidelines[12] and Yoshimura and colleagues.[18] These criteria were (1) onset within 30 days after pulmonary resection, (2) intensified dyspnea, (3) increase in the interstitial shadow on chest radiograph and chest CT scan, (4) decrease in arterial oxygen tension of more than 10 mm Hg under similar conditions, (5) no evidence of pulmonary infection, and (6) exclusion of alternative causes, such as cardiac failure, pulmonary embolism, or other identifiable causes of lung injury. Exacerbations occurring from 31 days onward were defined as chronic exacerbations.

Patient Characteristics

Data were initially obtained from 41,742 consecutive patients with lung cancer who had undergone pulmonary resections in 64 institutions; 2418 of these patients presented with ILDs. Because of poor quality of data, 404 cases from 3 institutions were excluded from the study. In addition, 135 cases were excluded because their fibrotic changes were pathologically confirmed, but there were no apparent fibrotic changes detected on CT scans. After reviewing all data for eligibility, completeness, and consistency, 116 more cases were excluded, leaving 1763 cases with ILDs deemed eligible for final analysis in this study.

The demographics of the cohort used in this study are shown in Table 1. The majority of patients were men (90.4%) and ex- or current smokers (93.8%). History of AE of interstitial pneumonia treated before the index pulmonary resection was observed in 1.1% of patients. Approximately 6.2% of patients had been treated preoperatively with steroids and other immunosuppressant drugs, 4.2% of patients had induction chemotherapy, and 1.8% of patients had radiation therapy. UIP diagnoses were made in 73.7% of patients by CT scan, and 45.7% of patients were confirmed pathologically with resected specimens as having UIP. Squamous cell carcinoma was the most common type of lung cancer.

Statistical Analyses

Univariate logistic regression analysis was performed to preliminarily evaluate the associations between the incidence of AE and the following candidate patient characteristics: age, sex, body mass index, smoking history, Brinkman index, comorbidities (asthma, emphysema, and collagen disease), neoadjuvant chemotherapy, neoadjuvant radiation therapy, white blood cells, CRP, lactate dehydrogenase, KL-6, carcinoembryonic antigen,

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