Table III. Univariate and multivariate analyses of factors associated with prognosis.

Factor	Hazard ratio	P-value
Univariate analysis		
NOS (Yes vs. no)	1.47 (1.07-1.96)	0.016
Age, years (≥65 vs. <65)	1.39 (1.16-1.68)	<0.001
Gender (male vs. female)	2.01 (1.64-2.49)	<0.001
BMI (≥22 vs. <22)	0.78 (0.66-0.93)	0.005
P-stage (I vs. II-IV)	3.00 (2.53-3.57)	<0.001
Surgical procedure (non-limited vs. limited)	1.22 (0.97-1.55)	0.080
COPD (FEV1.0% ≤70 vs. >70)	1.40 (1.18-1.66)	<0.001
Smoking status (Yes vs. no)	1.81 (1.49-2.21)	<0.001
Histology (Sq vs. non-Sq)	1.66 (1.39-1.98)	<0.001
Vessel invasion (Yes vs. no)	2.17 (1.83-2.58)	<0.001
Lymphatic invasion (Yes vs. no)	2.36 (1.98-2.79)	<0.001
Pleural invasion (P1-3 vs. P0)	2.25 (1.85-2.73)	<0.001
Adjuvant chemotherapy (Yes vs. no)	0.86 (0.70-1.04)	0.140
Multivariate analysis		
NOS (Yes vs. no)	1.40 (1.02-1.86)	0.041
Age, years (≥65 vs. <65)	1.55 (1.28-1.88)	<0.001
Gender (male vs. female)	1.51 (1.16-1.96)	0.002
BMI (≥22 vs. <22)	0.82 (0.69-0.97)	0.025
P-stage (I vs. II-IV)	2.22 (1.84-2.69)	<0.001
COPD (FEV1.0% ≤70 vs. >70)	1.02 (0.84-1.23)	0.818
Smoking status (Yes vs. no)	1.11 (0.86-1.45)	0.409
Histology (Sq vs. non-Sq)	1.23 (1.02-1.49)	0.028
Vessel invasion (Yes vs. no)	1.27 (1.06-1.56)	0.012
Lymphatic invasion (Yes vs. no)	1.55 (1.28-1.88)	<0.001
Pleural invasion (P1-3 vs. P0)	1.24 (1.02-1.49)	0.041

NOS, not otherwise specified; FEV1.0, forced expiratory volume in 1 sec; BMI, body mass index; P-stage, pathological stage; COPD, chronic obstructive pulmonary disease; Sq, squamous cell carcinoma.

Follow-up and overall survival. Of the 1,370 patients in the study who were not known to have succumbed, 908 (66.2%) were lost to follow-up during the initial five-year post-operative periods, and the remaining 462 (33.8%) were followed up for over five years. In the group of patients that remained (NOS and confirmed groups), the median duration of follow-up was 40.8 months (range, 0.4-145 months). Fig. 3 summarizes the overall survival rates observed in the study. The five-year survival rates were 60.5% in the NOS group and 67.1% in the confirmed group (Fig. 3A). Overall survival was significantly poorer in the NOS group than in the confirmed group (P=0.010). Among the 1,168 patients with stage I disease, the five-year survival rates were 70.8% in the NOS group and 80.7% in the confirmed group (P=0.007) (Fig. 3B).

Disease-free survival. The five-year disease-free survival rates were 52.1% in the NOS group and 60.0% in the confirmed group (P=0.100) (Fig. 4A). The disease-free survival rate did not significantly differ between these two groups, but tended to be worse in the NOS group. Among the patients with stage I disease, the five-year survival rates were 71.3% in the NOS group and 60.2% in the confirmed group (P=0.020) (Fig. 4B).

Subtyping. To assign cases to the NOS subtype, cytological and histological methods were relied upon. The association between the different diagnostic methods and the survival differences were analyzed in order to determine any correlations. Cytologically diagnosed NOS cases (n=88) exhibited a 65% five-year survival rate, whereas histologically diagnosed NOS cases (n=63) exhibited a 50.4% five-year survival rate, but this difference was not significant (P=0.378).

Clinical variables. Additionally investigations were made into the associations between the clinical variables and overall survival in the total population (Table III). According to univariate analyses, NOS, age, gender, BMI, pathological stage, COPD, smoking status, histology, vessel invasion, lymphatic invasion and pleural invasion were each significantly associated with post-operative prognosis. Multivariate Cox regression analysis indicated that NOS, age, gender, BMI, pathological stage, histology, vessel invasion, lymphatic invasion and pleural invasion were independent prognostic factors in all the tested patients.

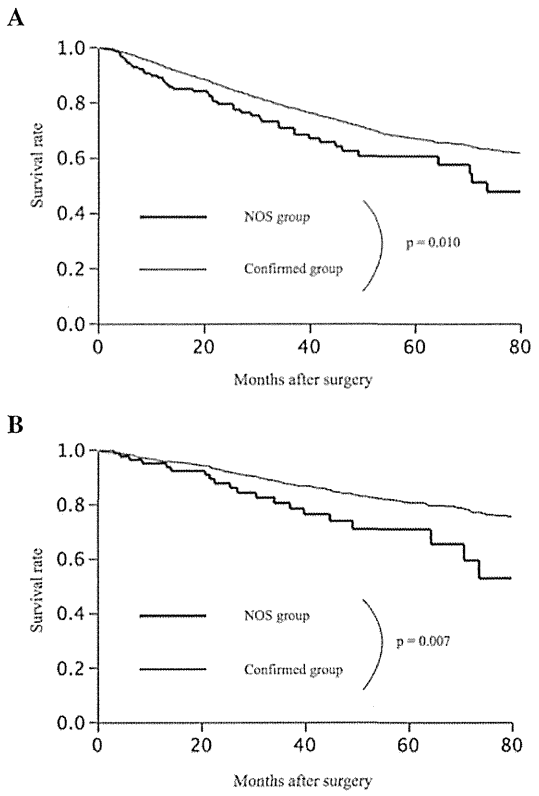

Figure 3. (A) Comparison of overall survival for patients with not otherwise specified (NOS) and confirmed subtype non-small cell lung cancer (NSCLC). (B) Comparison of overall survival for patients with NOS and confirmed subtype NSCLC of pathological stage I.

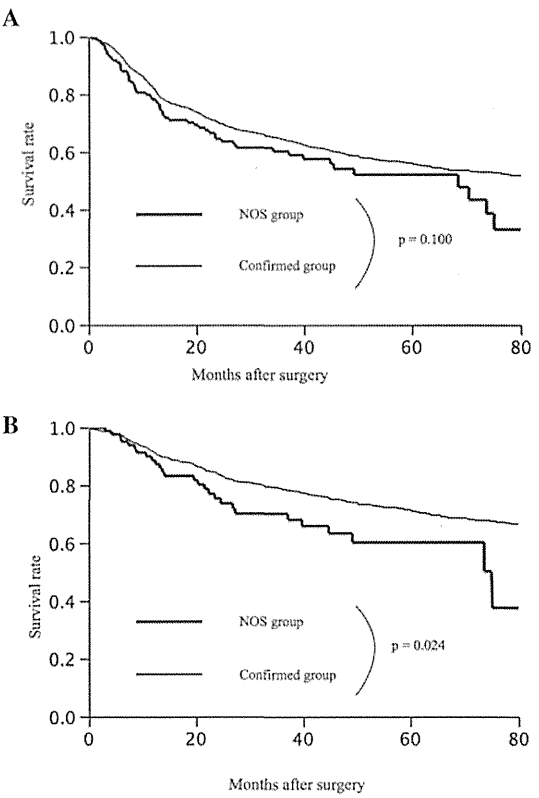

Figure 4. (A) Comparison of disease-free survival for patients with not otherwise specified (NOS) and confirmed subtype non-small cell lung cancer (NSCLC). (B) Comparison of disease-free survival for patients with NOS and confirmed subtype NSCLC of pathological stage I.

Discussion

As novel, molecular targeted agents have type-specific efficacy and adverse effects, accurate identification of the primary lung cancer type is a necessity. For example, among patients with lung cancer who are treated with bevacizumab, those with squamous cell carcinoma are at increased risk from life-threatening hemorrhage (1). A recent study showed that combined cisplatin and pemetrexed treatment resulted in statistically greater survival rates compared with combined cisplatin and gemcitabine, but only for adenocarcinomas and large cell carcinomas (not for squamous cell carcinomas) (2). Moreover, the response to the EGFR-tyrosine kinase inhibitors, gefitinib and erlotinib, is strongly associated with the adenocarcinoma subtype (3). These studies pioneered the use of the histological subtypes as key determinants of treatment strategies for advanced NSCLC. The most current Multidisciplinary Classification of Lung Adenocarcinoma, jointly issued by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society, recommends that NOS be assigned as infrequently as possible (10,11). However, a NOS classification is unavoidable in specific cases, as routine morphology and immunohistochemistry cannot differentiate certain tumor cells. Sigel *et al* (12) found that NOS was diagnosed in 12% of cytology and 6% of biopsy specimens. Where paired specimens were available (representing the two methods), the prevalence of NOS decreased to 4%. In the present study, it was found that 7.9% of cases were classified as NOS, a rate comparable to that previously reported (4,12,13).

NOS is generally diagnosed using cytology or biopsy specimens, and not by surgically resected specimens. For the cases of advanced-stage NSCLC, resected specimens were unavailable in the present study. Consequently, the true histology or correlation between the histological subtypes and the prognosis of the NOS patients could not be determined. Therefore, the study was limited to the resected cases. To the best of our knowledge, the present study is the first to examine whether pre-operative NOS can provide prognostic information for patients who undergo surgical resection for NSCLC.

We hypothesize that there are two principal causes of a NOS diagnosis. First is the nature of the biopsy itself; it can be difficult to obtain more than a scant bronchial specimen, which lacks distinctive features. In the present study, all transbronchial procedures were performed using a conventional bronchoscope under radiographic guidance. However, several recent studies have indicated that endobronchial ultrasound-guided transbronchial biopsy (EBUS-TBNA) is a widely accepted method for diagnosing thoracic tumors (14,15). The EBUS-TBNA scope can be used to assess and diagnose intrapulmonary lesions not visible through a conventional bronchoscope, as long as they are within the reach of the EBUS-TBNA scope. Consequently, EBUS-TBNA provides relatively high yields for diagnosing lung tumors. However, the EBUS-TBNA scope and other novel devices often fail to recover tumoral specimens if the tumor is located in the peripheral lung parenchyma or if the tumor

interior is necrotic. By excluding the 396 (15.7%) cases of suspicious and negative results in the present study, the effect of the variations in transbronchial procedure was minimized.

Second, the NOS subtype may be assigned due to the poor differentiation of certain tumor cells. Pleomorphic cell carcinoma, large cell carcinoma, large cell neuroendocrine carcinoma and adenosquamous carcinoma are classified as poorly-differentiated tumors. In the present study, these tumors were found to be particularly likely to be pre-operatively diagnosed as NOS. Pleomorphic carcinoma accounted for 12.6% of the cases in the NOS group, even though the true prevalence of pleomorphic carcinoma has been reported to be only 1.6% (16). Due to their heterogeneity and poorly-differentiated tumor cells, these tumor types are difficult to diagnose on pre-operative pathological examination. Consequently, resected specimens were necessary to achieve definitive diagnoses. Additionally, these subtypes are associated with a poor prognosis even if the disease is diagnosed at early stages and resected (16,17). The poor prognosis of the NOS group in the present series appears to be affected by the characteristics of these tumor cells.

It has been reported that sublobar resection, including segmentectomy and wedge resection, is not inferior to lobectomy for patients with small-sized NSCLC. Studies by Okada *et al* (18,19) indicated that sublobar resection should be considered as an alternative surgical option for stage IA NSCLC tumors that are ≤2 cm in size, even for low-risk patients. Conversely, in the case of certain aggressive tumors, sublobar resection may be inappropriate for curative surgery. Indeed, Varlotto *et al* (20) showed that, among patients with stage I NSCLC, sublobar resection is associated with a greater risk of local recurrence than lobectomy, particularly for patients with poorly-differentiated tumors or tumors of >2 cm in size. Hattori *et al* (6) showed that sublobar resection is not feasible for purely solid tumors, particularly those with a high maximum standardized uptake value, including small lung cancers. The present results indicate that the NOS classification is associated with poor survival, even for stage I cases. Moreover, the pathological diagnosis of the resected specimens indicated that poorly-differentiated tumors, such as pleomorphic cell carcinoma, are significantly more frequent in NOS patients; a finding that is concordant with the poor prognosis observed for these patients. Therefore, NOS cases may not be good candidates for sublobar resection.

In the present study, 88 cases (58.3%) were diagnosed on the basis of cytomorphology alone and the remaining 63 cases were evaluated histologically. Recent clinical observations of patients with advanced lung cancer have motivated pathologists to exert the additional effort that is necessary to distinguish between the histological subtypes, improving the overall quality of subtyping. In comparison, cytological diagnoses of squamous and non-squamous lung cancer subtypes have only a fair degree of accuracy (21). Moreover, independent pathological review is not available to all oncologists in daily practice, limiting the further subclassification of NSCLC following the initial diagnosis. Several recommendations for the pre-operative evaluation of patients with resectable NSCLC do not indicate definitive pre-operative histological subtyping (22). In the present study, the prognosis did not depend on the mode of NOS diagnosis (cytological or histological), indicating that pre-operative NOS had the role of a prognostic factor regardless of the two differing diagnostic modes.

There are certain limitations to the present study. First, the study data was analyzed retrospectively and without central pathological review, although all diagnoses were reviewed by two expert pathologists. Second, although sublobar resection may be inappropriate for curative surgery in the early stage of NOS cases, the prognoses of the NOS patients undergoing sublobar resection was not evaluated due to the small sample sizes. This matter should be formally investigated and discussed in a larger population in the future.

In conclusion, the present study found that pre-operative NOS diagnosis was associated with significantly poorer survival among patients with NSCLC, even those with stage I disease. In conjunction with other clinicopathological parameters, NOS can be a useful prognostic factor when selecting a treatment strategy for NSCLC.

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References

1. Johnson DH, Fehrenbacher L, Novotny WF, *et al*: Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 22: 2184-2191, 2004.
2. Scagliotti G, Hanna N, Fossella F, *et al*: The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist 14: 253-263, 2009.
3. Mok TS, Wu YL, Thongprasert S, *et al*: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361: 947-957, 2009.
4. Ou SH and Zell JA: Carcinoma NOS is a common histologic diagnosis and is increasing in proportion among non-small cell lung cancer histologies. J Thorac Oncol 4: 1202-1211, 2009.
5. Suzuki K, Asamura H, Kusumoto M, Kondo H and Tsuchiya R: 'Early' peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. Ann Thorac Surg 74: 1635-1639, 2002.
6. Hattori A, Suzuki K, Matsunaga T, *et al*: Is limited resection appropriate for radiologically 'solid' tumors in small lung cancers? Ann Thorac Surg 94: 212-215, 2012.
7. Sobin L and Wittekind CH (eds). TNM Classification of Malignant Tumours. 6th edition. Wiley-Liss, New York, pp99-103, 2002.
8. Travis WD, Brambilla E, Müller-Hermelink HK and Harris CC (eds). World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the Lung, Pleura, Thymus and Heart. IARC Press, Lyon, 2004.
9. Warth A, Muley T, Herpel E, *et al*: Large-scale comparative analyses of immunomarkers for diagnostic subtyping of non-small-cell lung cancer biopsies. Histopathology 61: 1017-1025, 2012.
10. Travis WD, Rekhtman N, Riley GJ, *et al*: Pathologic diagnosis of advanced lung cancer based on small biopsies and cytology: a paradigm shift. J Thorac Oncol 5: 411-414, 2010.
11. Travis WD, Brambilla E, Noguchi M, *et al*: International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6: 244-285, 2011.
12. Sigel CS, Moreira AL, Travis WD, *et al*: Subtyping of non-small cell lung carcinoma: a comparison of small biopsy and cytology specimens. J Thorac Oncol 6: 1849-1856, 2011.
13. da Cunha Santos G, Lai SW, Saieg MA, *et al*: Cyto-histologic agreement in pathologic subtyping of non small cell lung carcinoma: review of 602 fine needle aspirates with follow-up surgical specimens over a nine year period and analysis of factors underlying failure to subtype. Lung Cancer 77: 501-506, 2012.

14. Yasufuku K, Nakajima T, Chiyo M, Sekine Y, Shibuya K and Fujisawa T: Endobronchial ultrasonography: current status and future directions. J Thorac Oncol 2: 970-979, 2007.
15. Nakajima T, Yasufuku K, Fujiwara T, *et al*: Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. J Thorac Oncol 3: 985-988, 2008.
16. Yuki T, Sakuma T, Ohbayashi C, *et al*: Pleomorphic carcinoma of the lung: a surgical outcome. J Thorac Cardiovasc Surg 134: 399-404, 2007.
17. Raveglia F, Mezzetti M, Panigalli T, *et al*: Personal experience in surgical management of pulmonary pleomorphic carcinoma. Ann Thorac Surg 78: 1742-1747, 2004.
18. Okada M, Nishio W, Sakamoto T, *et al*: Effect of tumor size on prognosis in patients with non-small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thorac Cardiovasc Surg 129: 87-93, 2005.
19. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K and Tsubota N: Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. J Thorac Cardiovasc Surg 132: 769-775, 2006.
20. Varlotto JM, Medford-Davis LN, Recht A, *et al*: Identification of stage I non-small cell lung cancer patients at high risk for local recurrence following sublobar resection. Chest 143: 1365-1377, 2013.
21. Sakr L, Roll P, Payan MJ, *et al*: Cytology-based treatment decision in primary lung cancer: is it accurate enough? Lung Cancer 75: 293-299, 2012.
22. Scott WJ, Howington J, Feigenberg S, Movsas B and Pristers K; American College of Chest Physicians: Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidekines (2nd edition). Chest 132 (3 Suppl): 234S-242S, 2007.

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,

GTS

TABLE 1. Patient characteristics

Characteristics	No. of patients (%)	Median (range)
Age, y	1763	71 (36-88)
Sex		
Male/female	1593 (90.4)/170 (9.6)	
BMI, kg/m^2	1746	23.0 (13.7-37.0)
Smoking history		
Never smoker	109 (6.2)	
Ex-smoker	1006 (57.6)	
Current smoker	632 (36.2)	
Brinkman index	1742	1000 (0-5760)
Comorbidity		
Asthma		
−/+	1724 (98.1)/33 (1.9)	
Emphysema		
−/+	1167 (66.5)/589 (33.5)	
Collagen disease		
−/+	1654 (94.2)/102 (5.8)	
History of AE*		
−/+	1741 (98.9)/20 (1.1)	
Preoperative medication for IP		
None/steroids/ others	1638 (93.8)/103 (5.9)/6 (0.3)	
Neoadjuvant chemotherapy		
−/+	1686 (95.8)/73 (4.2)	
Neoadjuvant radiation		
−/+	1728 (98.2)/32 (1.8)	
Radiologic diagnosis		
UIP/non-UIP pattern	1300 (73.7)/463 (26.3)	
Histology		
Squamous cell carcinoma	816 (46.9)	
Adenocarcinoma	721 (41.4)	
Large cell carcinoma	64 (3.7)	
Others	139 (8.0)	
pTNM stage		
1a	547 (31.6)	
1b	481 (27.8)	
2a	70 (4.0)	
2b	241 (13.9)	
3a	244 (14.1)	
3b	114 (6.6)	
4	34 (2.0)	
Surgical procedure		
Wedge resection	275 (15.7)	
Segmentectomy	150 (8.5)	
Lobectomy	1236 (70.4)	
Bilobectomy	61 (3.5)	
Pneumonectomy	33 (1.9)	
Tumor location		
Upper lobe	670 (39.2)	
Middle lobe	77 (4.5)	
Lower lobe	958 (56.0)	
Multiple	5 (0.3)	
VATS		
−/+	964 (54.7)/798 (45.3)	
Node dissection		
0/1/2	331 (17.7)/339 (19.3)/1104 (63.0)	

The pTNM staging was based on the 6th edition of the American Joint Committee on Cancer lung cancer staging. *AE,* Acute exacerbation; *BMI,* body mass index; *IP,* interstitial pneumonia; *UIP,* usual interstitial pneumonia; *VATS,* video-assisted thoracoscopic surgery. *History of treated AE before pulmonary resection.

partial pressure of oxygen, $Paco_2$, VC, %VC, FEV1, FEV1%, %FEV1, DLCO, %DLCO, radiologic findings, pathologic findings, history of AE, preoperative steroid use, pTNM stage, operation time, bleeding amount, transfusion, surgical procedures, tumor location, video-assisted thoracoscopic surgery, and node dissection.

Risk factors for inclusion in the multivariate analysis were selected on the basis of the results of the univariate analyses, statistical independence, and clinical significance for preoperative patient evaluation of AE risk.

Surgical procedures were categorized into 3 groups on the basis of the results of multivariate analyses that adjusted for the other covariates. These groups were wedge resection, lobectomy and segmentectomy, and bilobectomy and pneumonectomy. Multivariate logistic regression analysis using backward elimination was used to identify independent risk factors for AE and to estimate the respective odds ratios (ORs) and their 95% confidence intervals (CIs) of the various risk factors. All reported *P* values were 2-sided. The cutoff value for %VC was set at 80%, which is the widely accepted clinical criteria for restrictive change of pulmonary fibrosis, and is correlated to disease progression and patient survival.[19] For KL-6, 1000 U/mL was determined as the cutoff value on the basis of the results of a preliminary receiver operating characteristic analysis, which showed 1040 U/mL to be the optimal cutoff value with a c-index of 0.583. Data management and statistical analyses were conducted in the Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Incidence of Acute Exacerbation

Postoperative AE developed within 30 days after the operation in approximately 9.3% of patients (95% CI, 8.0-10.8) who had undergone pulmonary resection. AE developed within 10 days after operation in the majority of the patients (64.6%), with postoperative day 4 showing the highest frequency of AE. The mortality rate of each postoperative day varied from 0% to 100%, and showed no particular tendency or trend (Figure 1 and Table 2).

Risk Factor Analysis for Acute Exacerbation

Univariate and multivariate analyses were carried out to identify possible risk factors for AE. The univariate analysis identified sex, KL-6, $Paco_2$, %VC, FEV1.0%, DLCO, radiologic findings, history of AE, preoperative use of steroids,

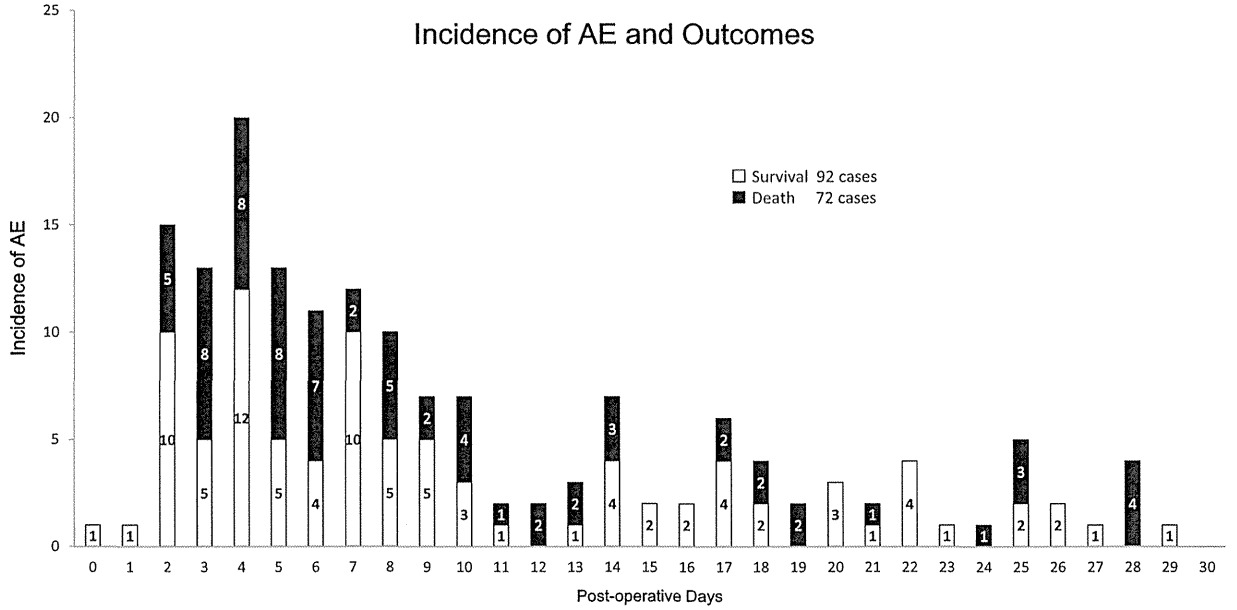

FIGURE 1. Histogram of AE incidence within 30 days after pulmonary resection (n = 164). *Black columns* represent patient death (72 cases, 43.9%), and *white columns* represent patient survival (92 cases, 56.1%). AE developed in the majority of the patients (64.6%) within 10 days after operation, with postoperative day 4 showing the highest frequency of AE. *AE,* Acute exacerbation.

and surgical procedures as candidate risk factors for AE (Table E1). VC and FEV1 were excluded as candidates because these variables were highly correlated with %VC (Spearman's $r = 0.796$ and 0.603, respectively). Multivariate analysis further identified the following risk factors for AE: sex, KL-6, %VC, radiologic findings, history of AE, preoperative steroid use, and surgical procedures (Table 3).

The lobectomy/segmentectomy and the bilobectomy/pneumonectomy groups were both more likely to develop AE than the wedge resection group, with ORs of 3.83 and 5.70, respectively. AE was 3 times more likely to develop in male patients than in female patients. Preoperative steroid use, history of AE, UIP pattern on CT scans, elevated levels of KL-6, and reduced %VC were identified as independent risk factors for AE. Neoadjuvant treatment and video-assisted thoracoscopic surgery showed no association with AE in our study (Table E1).

Surgical Procedures and Acute Exacerbation Risk

Multivariate analysis of surgical procedures adjusting for KL-6, preoperative steroid use, sex, CT findings, %VC, and history of AE was carried out. The associated risk of AE gradually increased according to resected lung volume. By using the wedge resection group as the referent category, the OR for AE in the segmentectomy group was 3.675 (95% CI, 1.586-8.519; $P = .0024$); the OR in the lobectomy group was 3.861 (95% CI, 1.946-7.660; $P < .001$); the OR in the bilobectomy group was 5.055 (95% CI, 1.871-13.660; $P = .001$); and the OR in the pneumonectomy group was 6.953 (95% CI, 2.260-21.390; $P < .001$).

Risk Factor Analysis for Acute Exacerbation in Patients With Usual Interstitial Pneumonia Patterns on Computed Tomography Scan

Subgroup analyses were carried out for the patients with UIP patterns on CT scans. To ensure only patients with UIP/IPF were included in this subgroup analysis, we excluded 65 patients with collagen diseases; a total of 1235 cases were analyzed. Sex, CRP, KL-6, %VC, FEV1, history of

TABLE 2. Incidence of acute exacerbation, its outcomes, and 30-day mortality of patients undergoing pulmonary resection

Categories	No. of patients (%)	Median (range)
30-d mortality	46 (2.6)	
30-d mortality by cause of death		
AE	33 (71.7)	
Infection	3 (6.5)	
Pulmonary embolism	1 (2.1)	
Others	9 (19.5)	
AE		
–	1599 (90.7)	
+	164 (9.3)*	
Days from operation to AE		7 (0-29)
Outcome of AE		
Alive	92 (56.1)	
Death	72 (43.9)	
Days from AE to death		20 (1-82)
Side of AE		
Operation side	22 (14.2)	
Contralateral	39 (25.2)	
Bilateral	94 (60.6)	

AE, Acute exacerbation (occurring within 30 days after pulmonary resection). *9.3%; 95% CI, 8.0-10.8.

TABLE 3. Results of multivariate logistic regression analyses of acute exacerbation in all patients and in the usual interstitial pneumonia subgroup

	All patients (n = 1763)					UIP subgroup (n = 1235)*				
Factors	Patients (n)	AE (%)	OR	95% CI	*P* value	Patients (n)	AE (%)	OR	95% CI	*P* value
Surgical procedures					.0005†					.0005†
Wedge resection	275	10 (3.6)	1.000	—	—	202	10 (5.0)	1.000	—	—
Lobectomy/segmentectomy	1386	138 (10.0)	3.83	1.941-7.567	.0001	955	100 (10.5)	2.91	1.453-5.847	.0026
Bilobectomy/pneumonectomy	94	15 (16.0)	5.7	2.381-13.66	.0001	70	14 (20.0)	5.96	2.413-14.74	.0001
N/A	8	1 (12.5)				8	1 (12.5)			
KL-6 (U/mL)										
<1000‡	834	68 (8.2)	1.000	—	—	571	56 (9.8)	1.000	—	—
≥1000	209	34 (16.3)	2.14	1.344-3.394	.0013	151	27 (17.9)	2.02	1.199-3.408	.0083
N/A	720	62 (8.6)				513	42 (8.2)			
Sex										
Male	1593	158 (9.9)	1.000	—	—	1138	123 (10.8)	1.000	—	—
Female	170	6 (3.5)	0.3	0.126-0.688	.0047	97	2 (2.1)	0.18	0.043-0.737	.0172
%VC										
<80	263	36 (13.7)	1.000	—	—	191	30 (15.7)	1.000	—	—
≥80	1478	126 (8.5)	0.63	0.417-0.959	.0308	1033	94 (9.1)	0.57	0.350-0.884	.0131
N/A	22	2 (9.1)				11	1 (9.1)			
History of AE										
−	1741	158 (9.1)	1.000	—	—	1223	120 (9.8)	1.000	—	—
+	20	6 (30.0)	3.24	1.063-9.897	.0387	10	5 (50.0)	7.67	1.997-29.42	.0030
N/A	2	0 (0.0)				2	0 (0.0)			
Preoperative steroid use										
−	1651	144 (8.7)	1.000	—	—					
+	103	20 (19.4)	2.46	1.356-4.454	.0031					
N/A	9	0 (0.0)								
CT findings										
UIP pattern	1300	134 (10.3)	1.000	—	—					
Non-UIP pattern	463	30 (6.5)	0.59	0.386-0.900	.0143					

AE, Acute exacerbation; *CI,* confidence interval; *CT,* computed tomography; *N/A,* not available; *OR,* odds ratio; *%VC,* percent vital capacity; *UIP,* usual interstitial pneumonia. *Cases with collagen diseases were excluded (n = 65). †*P* value among 3 surgical procedure categories. ‡The cutoff value of 1000 U/mL was determined on the basis of the result of the receiver operating characteristic analysis.

AE, preoperative steroid use, and surgical procedures were identified as possible risk factors of AE in the univariate analyses. Multivariate analysis using these factors identified surgical procedures, history of AE, KL-6, %VC, and male sex as independent risk factors (Table 3).

Prophylactics and Acute Exacerbation

During the perioperative period, 31% of the patients were administered prophylactics. Steroids were the most common drug for this purpose (11.4%), followed by sivelestat (6.7%) and a combination of steroid and sivelestat (5.4%). The results of multivariate analyses adjusted with the aforementioned AE risk factors (surgical procedures, sex, KL-6, preoperative steroid use, %VC, radiologic findings, and history of AE) are shown in Table 4. Drug administration, whether given individually or in combinations, did not show any positive effects in preventing AE.

Morbidity and Mortality of Pulmonary Resection

Outcomes involving the morbidity and mortality of pulmonary resections are summarized in Table 2. The 30-day mortality rate was 2.6%, and the most frequent cause of death was AE. In patients with an AE, the mortality rate was 43.9%. Days from AE to death varied from 1 to 82 days (median, 20 days).

TABLE 4. Use of prophylactics and acute exacerbation

Factors	No. of patients (%)	OR	95% CI	*P* value
Prophylactics				
−	1216 (69)	1.000	—	—
+	544 (31)	1.047	0.724-1.513	.808
Steroid	194 (11.4)	0.862	0.491-1.514	.605
Sivelestat	115 (6.7)	1.397	0.752-2.596	.290
Sivelestat + steroid	92 (5.4)	0.749	0.338-1.661	.477
Ulinastatin	69 (4.0)	2.488	1.266-4.887	.008
Sivelestat + ulinastatin	5 (0.3)	1.302	0.109-15.49	.835
Steroid + ulinastatin	11 (0.6)	0.000	N/A	N/A
Sivelestat + steroid + ulinastatin	4 (0.2)	1.035	0.089-12.03	.978

Adjusted for surgical procedures, KL-6, preoperative steroid use, sex, CT findings, % VC, and history of AE. *CI,* Confidence interval; *OR,* odds ratio.

DISCUSSION

AE of interstitial pneumonia is a rapidly progressive disorder often observed in patients with ILDs. Its clinical course is specific and distinguishable from infectious pneumonia. The criteria for identifying AE of pulmonary fibrosis include an unexplained rapid worsening of dyspnea, severely impaired gas exchange, new radiographic diffuse alveolar infiltrates, and the absence of alternate causes, such as infectious pneumonia, pulmonary embolism, pneumothorax, and heart failure.[20] Thoracic surgery for patients with ILDs, including open lung biopsy and bronchoalveolar lavage, may trigger this decompensating acute respiratory failure.[6,21] The mortality rate of AE is reportedly high[5-8] and has been shown to be the major cause of death for patients with lung cancer after pulmonary resection in a report cumulating more than 10,000 cases from the Japanese Joint Committee for Lung Cancer Registration and in the 2009 annual report of the Japanese Association for Thoracic Surgery.[22,23] In light of these circumstances, identifying the possible risk factors for AE and enabling the stratification of patients according to risk are relevant for chest surgeons to reduce operation-related mortality and improve the outcomes of pulmonary resection in patients with lung cancer. To address these issues, we focused on patients with ILDs with lung cancer and found that the incidence of AE was 0.4% in patients with non–small cell lung cancer and 9.3% in similar patients with ILDs; to the best of our knowledge, these are the first such figures reported with high statistical reliability in a large-scale multi-institutional study. These figures were comparable to the incidences documented in past reports, including those of the aforementioned studies,[21-26] and indicate the difficulties in the treatment of patients with lung cancer with ILDs. The similarities observed in incidences have important implications for further comparisons with other anticancer therapies, such as chemotherapy and radiotherapy, which have been shown to be associated with this fatal complication at the rate of 20% to 42.9%.[3,4]

We identified 7 risk factors for AE: surgical procedures, elevated KL-6, sex, reduced %VC, history of AE, preoperative steroid use, and UIP pattern on CT scan. Surgical procedures showed the strongest association with the incidence of AE. Anatomic resection would result in more serious insult to patients' lungs when compared with wedge resection, because the former requires longer operation time and increased hilar vascular procedures and node dissection, which may hinder the lymphatic flow. In addition to damage caused by perioperative patient management (eg, fluid overload, 1-lung ventilation, positive pressure ventilation, and high concentration oxygen exposure), the resection of larger lung volume likely gives greater stress to the endothelium, which may result in AE. Likewise, the effect of a reduced vascular bed is substantial in patients with lower %VC because their residual lung volume is relatively small, which may result in a higher incidence of AE. These speculations are supported by our findings that the risk of AE gradually increased according to the volume of lung removed (wedge resection < segmentectomy < lobectomy < bilobectomy < pneumonectomy). The less-invasive video-assisted thoracoscopic surgery procedures did not reduce the risk of AE.

The possible effects of blood transfusions on AE also were considered. We conducted a risk-adjusted evaluation using transfusions and the other 7 covariates, which showed a significant association between transfusion and AE (OR, 2.04; 95% CI, 1.22-3.40; $P = .006$). However, transfusion also was observed to be highly correlated to the operative procedures, which may bring about possible effects of multicollinearity if included in the same model. Furthermore, the need for transfusions and operation time are to a large degree unpredictable before surgery, which reduces their potential effectiveness for preoperative identification of patients at high risk of developing AE. However, general operation time and the risk of bleeding can be grouped within the types of surgical procedures. The inclusion of surgical procedures in the regression models may therefore adjust for operation time and transfusions.

There are limited data on the value of serum biomarkers in patients with ILDs. Among the clinical laboratory variables, only KL-6 was identified as an independent risk factor for AE, where patients with KL-6 levels more than 1000 IU had an AE incidence twice that of patients with lower levels. KL-6, a circulating glycoprotein expressed from type 2 alveolar pneumocytes and bronchiolar epithelial cells, has been established as an indicator of damage to alveolar cells.[27,28] Elevated KL-6 levels have been documented in patients who had developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), and this relationship may be used to predict patient outcomes. In interstitial pneumonia, KL-6 is an independent factor reflecting the degree of clinical disease activity, confirmed by Ga-citrate scintigraphy and clinical course.[27] Our observations in which KL-6 was identified as a risk factor have clinical significance because the elevated level of serum KL-6 indicates increased alveolar-capillary permeability, which can lead to diffuse alveolar damage—the initial and essential aspect of AE.

Our results indicated that men had 3 times the risk of developing AE than women. An additional analysis showed that smoking history and the Brinkman index were higher in men than in women; however, the results did not show any significant association between a smoking habit and AE incidence. Ruffini and colleagues documented that ALI/ARDS developed in male patients at approximately 4 times the rate of female patients,[24] so the male lung may be more susceptible to the insult of surgical intervention.

Although %DLCO and %VC have been considered reliable indicators of fibrotic change,[12,13,17] an analysis of lung function (including FEV1, FEV1%, %DLCO, and %VC) showed that only %VC had a significant and independent association with AE incidence, which was congruent with the results reported by Kushibe and colleagues[29] and Shintani and colleagues.[30]

Our analysis showed that preoperative steroid use and history of AE were independent risk factors for AE, which is consistent with clinical expectations. These findings represent the first time that the statistical associations between these factors have been documented.

The findings in which patients with UIP patterns in CT scans had a higher risk of developing AE also are consistent with clinical expectations, because honeycomb lesions have been reported to be associated with IPF and act as a prognostic factor.[31-33] Our own data corroborate this, because patients with distinct honeycomb lesions had a higher risk of developing AE (OR, 1.800; 95% CI, 1.157-2.800; $P = .009$). Further evaluation of the relationship between the extent and the prevalence of honeycomb lesions in CT scans and AE is required, which we were unable to do in our large retrospective cohort study.

There is no current consensus among the numerous studies regarding the relationship between prophylactic use and postoperative AE.[5] Prophylactic steroids are a common agent with an anti-inflammatory and stabilizing effect on alveolar cells. However, previous studies with comparatively large cohorts also have revealed no preventive effects from the perioperative administration of steroids.[16,25] Neutrophil elastase is known to cause endothelial cell injury and increase epithelial permeability, thereby playing an important role in ALI or ARDS. Sivelestat sodium hydrate is a neutrophil elastase inhibitor, and although its clinical efficacy has yet to be clearly demonstrated,[34] it is widely used for the treatment of ALI in Japan. In our cohort, up to 216 patients (12%) had been administered sivelestat in the perioperative period, ostensibly for its prophylactic effects on AE. In our retrospective study, these prophylactics showed no positive effect on AE prevention. A randomized prospective study on the effects of prophylactics, such as macrolides, N-acetylcysteine, and pirfenidone, is required to gain a clearer understanding of this relationship.

Study Limitations

This study has several limitations that should be considered in the interpretation of the results. First, this was a retrospective cohort study, which may not necessarily reflect the characteristics of the entire population with this disease entity. Second, the primary inclusion criterion was CT appearance of ILDs. Although radiologic diagnoses were made by each individual institute following criteria based on widely used guidelines,[12,17] UIP diagnosis may vary among the institutes. We were unable to conduct a centrally controlled review of this aspect of the diagnosis, particularly of the extent and area of honeycomb lesion, which are putative risk factors for the AE.

CONCLUSIONS

In this study, we have clarified the incidence, risk factors, and outcomes of postoperative AE in patients with lung cancer with ILDs who had undergone pulmonary resection. These results provide essential information for comparisons with other anticancer therapies, such as chemotherapy and radiotherapy. We identified 7 risk factors for AE onset. By evaluating the presence and degree of the identified risk factors before surgery, we can stratify patients and identify those at high risk for pulmonary resection. Surgical procedures were found to be the strongest risk factor and may represent a crucial step in reducing the incidence of this potentially fatal complication. The findings in this study provide essential information to support fair and objective decision-making by oncologists in the treatment of this difficult entity.

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References

1. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med*. 2000; 161:5-8.
2. Harris JM, Johnston ID, Rudd R, Taylor AJ, Cullinan P. Cryptogenic fibrosing alveolitis and lung cancer: the BTS study. *Thorax*. 2010;65:70-6.
3. Minegishi Y, Takenaka K, Mizutani H, Sudoh J, Noro R, Okano T, et al. Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. *Intern Med*. 2009;48:665-72.
4. Isobe K, Hata Y, Sakamoto S, Takai Y, Shibuya K, Homma S. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. *Respirology*. 2010;15:88-92.
5. Chiyo M, Sekine Y, Iwata T, Tatsumi K, Yasufuku K, Iyoda A, et al. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outcomes. *J Thorac Cardiovasc Surg*. 2003; 126:1141-6.
6. Kumar P, Goldstraw P, Yamada K, Nicholson AG, Wells AU, Hansell DM, et al. Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. *J Thorac Cardiovasc Surg*. 2003;125:1321-7.
7. Koizumi K, Hirata T, Hirai K, Mikami I, Okada D, Yamagishi S, et al. Surgical treatment of lung cancer combined with interstitial pneumonia: the effect of surgical approach on postoperative acute exacerbation. *Ann Thorac Cardiovasc Surg*. 2004;10:340-6.
8. Watanabe A, Kawaharada N, Higami T. Postoperative acute exacerbation of IPF after lung resection for primary lung cancer. *Pulm Med*. 2011;2011:960316.
9. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1998;157:199-203.
10. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med*. 2000;162:2213-7.
11. Rudd RM, Prescott RJ, Chalmers JC, Johnston ID. British thoracic society study on cryptogenic fibrosing alveolitis: response to treatment and survival. *Thorax*. 2007;62:62-6.
12. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based

guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183: 788-824.
13. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2011;183:431-40.
14. Fujimoto T, Okazaki T, Matsukura T, Hanawa T, Yamashita N, Nishimura K, et al. Operation for lung cancer in patients with idiopathic pulmonary fibrosis: surgical contraindication? *Ann Thorac Surg.* 2003;76:1674-8.
15. Nakajima J, Takamoto S, Murakawa T, Fukami T, Sano A. Is interstitial pneumonia in patients with collagen diseases a contraindication to lung cancer surgery? *Surg Today.* 2007;37:14-8.
16. Watanabe A, Higami T, Ohori S, Koyanagi T, Nakashima S, Mawatari T. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? *J Thorac Cardiovasc Surg.* 2008;136:1357-63, 1363.e1351-2.
17. The Japanese Respiratory Society. *Idiopathic Interstitial Pneumonias: Diagnosis and Treatment.* 2nd ed. Tokyo, Japan: Nankodo; 2011.
18. Yoshimura K, Nakatani T, Nakamori Y, Chonabayashi N, Tachibana A, Nakata K, et al. [Acute exacerbation in idiopathic interstitial pneumonia]. *Nihon Kyobu Shikkan Gakkai Zasshi.* 1984;22:1012-20.
19. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2011;184:459-66.
20. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2007;176:636-43.
21. Utz JP, Ryu JH, Douglas WW, Hartman TE, Tazelaar HD, Myers JL, et al. High short-term mortality following lung biopsy for usual interstitial pneumonia. *Eur Respir J.* 2001;17:175-9.
22. Sawabata N, Fujii Y, Asamura H, Nomori H, Nakanishi Y, Eguchi K, et al. Lung cancer in Japan: analysis of lung cancer registry cases resected in 2004. *Haigan.* 2010;50:875-88.
23. Sakata R, Fujii Y, Kuwano H. Thoracic and cardiovascular surgery in Japan during 2008: annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg.* 2010;58:356-83.
24. Ruffini E, Parola A, Papalia E, Filosso PL, Mancuso M, Oliaro A, et al. Frequency and mortality of acute lung injury and acute respiratory distress syndrome after pulmonary resection for bronchogenic carcinoma. *Eur J Cardiothorac Surg.* 2001;20:30-6.
25. Kutlu CA, Williams EA, Evans TW, Pastorino U, Goldstraw P. Acute lung injury and acute respiratory distress syndrome after pulmonary resection. *Ann Thorac Surg.* 2000;69:376-80.
26. Miyamoto A, Kishi K, Yoshimura K. [A nationwide survey concerning lung surgery for lung cancer associated with idiopathic interstitial pneumonia]. *Nihon Kokyuki Gakkai Zasshi.* 2011;49:148-50.
27. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen ki-6. *Chest.* 1989;96:68-73.
28. Yokoyama A, Kohno N, Hamada H, Sakatani M, Ueda E, Kondo K, et al. Circulating ki-6 predicts the outcome of rapidly progressive idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 1998;158:1680-4.
29. Kushibe K, Kawaguchi T, Takahama M, Kimura M, Tojo T, Taniguchi S. Operative indications for lung cancer with idiopathic pulmonary fibrosis. *J Thorac Cardiovasc Surg.* 2007;55:505-8.
30. Shintani Y, Ohta M, Iwasaki T, Ikeda N, Tomita E, Kawahara K, et al. Predictive factors for postoperative acute exacerbation of interstitial pneumonia combined with lung cancer. *Gen Thorac Cardiovasc Surg.* 2010;58:182-5.
31. Wells AU, Desai SR, Rubens MB, Goh NS, Cramer D, Nicholson AG, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med.* 2003; 167:962-9.
32. Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, et al. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. *Am J Respir Crit Care Med.* 2008;177:433-9.
33. Suzuki H, Sekine Y, Yoshida S, Suzuki M, Shibuya K, Yonemori Y, et al. Risk of acute exacerbation of interstitial pneumonia after pulmonary resection for lung cancer in patients with idiopathic pulmonary fibrosis based on preoperative high-resolution computed tomography. *Surg Today.* 2011;41:914-21.
34. Iwata K, Doi A, Ohji G, Oka H, Oba Y, Takimoto K, et al. Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. *Intern Med.* 2010;49:2423-32.

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APPENDIX E1. PARTICIPATING CENTERS AND INVESTIGATORS

NHO Hokkaido Cancer Center, Hokkaido (H. Adachi); NHO Sendai Medical Center, Miyagi (T. Hasumi); Institute of Development Aging and Cancer Tohoku University, Miyagi (Y. Hoshikawa); Japanese Red Cross Ishinomaki Hospital, Miyagi (S. Suzuki); Ohta Nishinouchi Hospital, Fukushima (Y. Matsumura); Nishi-Niigata Chuo National Hospital, Niigata (T. Watanabe); Niigata University, Niigata (H. Shinohara); Maebashi Red Cross Hospital, Gunma (M. Kamiyoshihara); NHO Nishi-Gunma Hospital, Gunma (O. Kawashima); Dokkyo Medical University, Tochigi (M. Chida); Saitama Cardiovascular and Respiratory Center, Saitama (N. Takahashi); Tokyo Medical University, Tokyo (N. Ikeda); Tokyo Women's Medical University, Tokyo (M. Kanzaki); Tokyo Toranomon Hospital, Tokyo (A. Miyamoto); Juntendo University School of Medicine, Tokyo (T. Matsunaga); Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo (H. Horio); Tokyo Medical and Dental Hospital, Tokyo (K. Okubo); Toho University Omori Medical Center, Tokyo (Y. Hata); The University of Tokyo Graduate School of Medicine, Tokyo (J. Nakajima); Hachioji Medical Center of Tokyo Medical University, Tokyo (H. Miura); Kitasato University School of Medicine, Kanagawa (Y. Satoh); Kimitsu Chuo Hospital, Chiba (T. Iida); Kanagawa Cancer Center, Kanagawa (H. Ito); Fujigaoka Hospital of Showa University, Kanagawa (T. Suzuki); Hamamatsu University School of Medicine, Shizuoka (K. Funai); Seirei Mikatahara General Hospital, Shizuoka (M. Tanahashi); Nagoya University Graduate School of Medicine, Aichi (K. Fukumoto); Aichi Cancer Center Hospital, Aichi (S. Ito); Nagoya Daini Red Cross Hospital, Aichi (H. Yoshioka); Nagoya City University Graduate School of Medical Sciences, Aichi (M. Yano); Aichi Medical University, Aichi (H. Numanami); Kariya Toyota General Hospital, Aichi (T. Yamada); Graduate School of Medicine, Gifu University, Gifu (H. Iwata); National Mie Chuo Hospital, Mie (K. Adachi); Toyama Prefectural Central Hospital, Toyama (H. Miyazawa); Ishikawa Prefectural Central Hospital, Ishikawa (Y. Tsunezuka); NHO Shiga Hospital, Shiga (S. Inoue); Takatsuki Red Cross Hospital, Osaka (M. Suga); Osaka City University Hospital, Osaka (N. Nishiyama); Osaka University Graduate School of Medicine, Osaka (Y. Shintani); Osaka City General Hospital, Osaka (R. Yamamoto); Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka (J. Okami); Kishiwada City Hospital, Osaka (M. Kawashima); Wakayama Medical Center Japanese Red Cross Society, Wakayama (S. Sumitomo); Kobe City Medical Center General Hospital, Hyogo (Y. Takahashi); Hyogo Cancer Center, Hyogo (M. Yoshimura); Nishi-Kobe Medical Center, Hyogo (Y. Otake); Tottori University Hospital, Tottori (H. Nakamura); Okayama University Graduate School of Medicine, Okayama (S. Miyoshi); Kurashiki Central Hospital, Okayama (J. Nakano); Kawasaki Medical School, Okayama (M. Nakata); NHO Yamaguchi Ube Medical Center, Yamaguchi (K. Sugi); Kagawa Prefectural Central Hospital, Kagawa (T. Misao); Kochi Health Sciences Center, Kochi (T. Okamoto); NHO Shikoku Cancer Center, Ehime (S. Sawada); Graduate School of Medical Sciences Kyushu University, Fukuoka (T. Yano); Kyushu Cancer Center, Fukuoka (K. Sugio); Kumamoto Chuo Hospital, Kumamoto (T. Saishoji); Nagasaki University Graduate School of Biomedical Sciences Nagasaki (N. Yamasaki); Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki (I. Sano); Sasebo City General Hospital, Nagasaki (A. Nakamura).

TABLE E1. Univariable analysis for acute exacerbation

Factors	Categories	Numbers	OR	95% CI	*P* value
Age		1763	1.017	0.994-1.041	.141
Sex					
	Male	1593	1.000	—	—
	Female	170	0.332	0.145-0.763	.009
BMI					
		1746	0.980	0.930-1.031	.434
Smoking history					
	Never smoker	109	1.000	—	—
	Ex-smoker	1006	1.336	0.657-2.720	.424
	Current smoker	632	0.893	0.424-1.879	.765
Brinkman index					
		1742	1.000	1.000-1.000	.413
Comorbidities					
Asthma	−	1742	1.000	—	—
	+	33	0.971	0.293-3.217	.962
Emphysema	−	1167	1.000	—	—
	+	589	0.778	0.546-1.109	.165
Collagen disease	−	1654	1.000	—	—
	+	102	0.936	0.463-1.892	.854
Neoadjuvant chemotherapy					
	−	1686	1.000	—	—
	+	73	1.207	0.569-2.562	.624
Neoadjuvant radiation					
	−	1728	1.000	—	—
	+	32	1.401	0.485-4.044	.533
WBC (/μL)					
		1737	1.000	1.000-1.000	.111
CRP (g/dL)					
	<2.0	1462	1.000	—	—
	>2.0	231	1.425	0.923-2.201	.110
LDH (IU/L)					
		1730	1.002	1.000-1.004	.064
KL-6 (U/mL)					
	<1000	834	1.000	—	—
	>1000	209	2.189	1.405-3.409	<.001
CEA (ng/mL)					
		1664	1.000	0.997-1.004	.883
Pao_2 (torr)					
		1552	0.996	0.981-1.011	.609
$Paco_2$ (torr)					
		1547	0.954	0.914-0.995	.030
VC (L)					
		1750	0.566	0.441-0.728	<.001
%VC					
	<80	263	1.000	—	—
	>80	1478	0.588	0.395-0.873	.009
FEV1 (L)					
		1748	0.683	0.496-0.941	.020
FEV1%					
	<70	460	1.000	—	—
	>70	1289	1.500	1.003-2.243	.048
%FEV1					
		1742	0.995	0.987-1.002	.176
DLCO (mL/min/torr)					
		1121	0.957	0.916-0.999	.047

(Continued)

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TABLE E1. Continued

Factors	Categories	Numbers	OR	95% CI	*P* value
%DLCO					
		1128	0.997	0.989-1.006	.532
Radiologic findings					
	UIP pattern	1300	1.000	—	—
	Non-UIP pattern	463	0.603	0.400-0.909	.016
Pathologic findings					
	UIP pattern	709	1.000	—	—
	Non-UIP pattern	418	0.904	0.608-1.343	.616
	No IP diagnosis	426	0.635	0.411-0.981	.041
History of AE					
	−	1741	1.000	—	—
	+	20	4.295	1.628-11.33	.003
Preoperative steroid use					
	−	1651	1.000	—	—
	+	103	2.522	1.504-4.231	<.001
pTNM stage					
	1a	547	1.000	—	—
	1b	481	1.349	0.858-2.120	.195
	2a	70	1.488	0.638-3.474	.358
	2b	241	1.832	1.101-3.049	.020
	3a	244	2.022	1.230-3.323	.006
	3b	114	1.011	0.459-2.229	.979
	4	34	2.309	0.846-6.307	.103
Operation time (min)					
		1753	1.003	1.002-1.005	<.001
Bleeding (mL)					
		1744	1.001	1.000-1.001	<.001
Transfusion					
	−	1629	1.000	—	—
	+	124	2.276	1.392-3.723	.001
Surgical procedures					
	Wedge Resection	275	1.000	—	—
	Segmentectomy/lobectomy	1386	2.930	1.521-5.644	.001
	Bilobectomy/pneumonectomy	94	5.032	2.175-11.64	<.001
Tumor location					
	Upper lobe	670	1.000	—	—
	Middle lobe	77	0.963	0.445-2.083	.924
	Lower lobe	958	0.705	0.502-0.991	.044
	Multiple	5	0.000	N/A	
VATS					
	−	964	1.000	—	—
	+	798	1.199	0.869-1.654	.268
Node dissection					
	0	311	1.000	—	—
	1	339	2.979	1.559-5.694	.001
	2	1104	2.587	1.436-4.661	.002

AE, Acute exacerbation; *BMI,* body mass index; *CEA,* carcinoembryonic antigen; *CI,* confidence interval; *CRP,* C-reactive protein; *DLCO,* diffusing capacity for carbon monoxide; *FEV1,* forced expiratory volume in 1 second; *IP,* interstitial pneumonia; *LDH,* lactate dehydrogenase; *OR,* odds ratio; $Paco_2$, partial pressure of carbon dioxide; Pao_2, partial pressure of oxygen; *UIP,* usual interstitial pneumonia; *VATS,* video-assisted thoracic surgery; *VC,* vital capacity; *WBC,* white blood cell; *%VC,* percent vital capacity; *FEV1%,* percent forced expiratory volume in 1 second; *%DLCO,* percent predicted diffusing capacity for carbon monoxide.

臨床経験

肺非結核性抗酸菌症の治療中に合併した肺癌*

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はじめに

本邦では肺非結核性抗酸菌症（肺NTM）が増加の一途をたどっており，諸外国と比較しても高い罹患率と有病率を示している[1]．それに伴い，肺NTMと肺癌の合併例も散見され，病変が近接した場合には診断が困難であったり，肺癌手術と肺NTMに対する切除術をどのように融合させるかに苦慮することがある．今回，肺NTMの治療中に肺癌を発症し，両疾患に対する切除例を経験したので報告する．

I．症　例

症　例　54歳，男．

主　訴：胸部異常陰影．

既往歴：Crohn病（開腹歴あり，salazosulfapyridine内服中）．

喫煙歴：現喫煙者，40本/日×34年間．

現病歴：2010年1月，肺NTM（*Mycobacterium avium*）の診断で内服加療（rifampicin, ethambutol, clarithromycin）を開始していた．2011年3月，右上葉に結節影が出現し，増大傾向も有するため，肺癌合併の疑いで当院に紹介された．

入院時所見：身長166.3 cm，体重56.3 kg［body mass index（BMI）20］，体温36.6 ℃，performance status（PS）0であった．

血液検査所見：Hb 13.0 g/d*l*で軽度の貧血を認めた．生化学検査ではALP 1,153 IU/*l*で高値を，CRP 1.09 mg/d*l*で軽度高値を示した．腫瘍マーカーはCYFRA 2.2 ng/m*l*で正常値であったが，CEA 9.5 ng/m*l*，pro-GRP 86 pg/m*l*で軽度高値を示した．

呼吸機能検査所見：VC 3.95 *l*，%VC 99.5%，$FEV_{1.0}$ 3.06 *l*，$FEV_{1.0}$% 77.47%と換気機能の障害は認めなかった．

心電図所見：不完全右脚ブロックを認めた．

画像所見：胸部X線像で，右中肺野に3.5 cm大の空洞性病変を認めた（図1）．胸部CTでは，右上葉S^1/S^2縦隔側に1.3 cm大の充実性結節を認め，辺縁は微細鋸歯状で縦隔胸膜に接していた（図2a）．さらに，右下葉S^6に長径3.5 cm大の空洞性病変を認め，その周囲に散布影を伴っていた（図2b）．PET/CTでは，右上葉の結節にFDGの高集積（SUVmax 8.4）を認めたが，有意なリンパ節腫大，胸膜播種や遠隔臓器転移を疑う所見

キーワード：肺非結核性抗酸菌症，肺癌，外科療法

*要旨は第20回日本呼吸器内視鏡学会中国四国支部会において発表した．

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は認めなかった.

気管支鏡検査所見：右下葉S^6の空洞性病変から*Mycobacterium intracellulare*が検出された. 右上葉の結節の診断はできなかった.

以上より，右上葉肺癌（cT1aN0M0，臨床病期IA期）を強く疑い手術の方針とした. 術中に部分切除あるいは針生検で診断し右上葉切除を，肺NTMに関しては右S^6の空洞性病変のみを切除する目的でS^6区域切除を追加予定とすることとした.

手術所見：右上葉の結節は縦隔胸膜に浸潤しており，奇静脈を合併切除した. 針生検を行うも検体採取不十分で診断できなかったが，肺癌を強く疑い右上葉切除を行った. 肺NTMの病変に関しては，予定どおり右S^6区域切除を行った.

術後経過：肺瘻が遷延し癒着療法を要したが，術後10日目に胸腔ドレーンを抜去し，14日目に退院した. 最終病理診断は，腺癌，pT3N0M0PL3（縦隔胸膜）D0E0PM0，病理病期IIB期，洗浄細胞診が陽性であった. S^6の空洞性病変は抗酸菌症の像であった. 術後補助療法は，Crohn病併存や就労も考慮した結果，tegafur・uracil（UFT）内服を選択した. 術後1年9ヵ月の時点では，無再発生存中である. 肺NTMの治療については，2012年4月より内服加療は中止した.

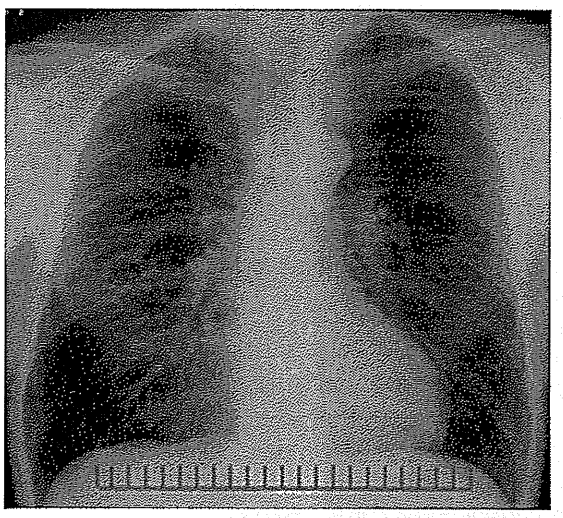
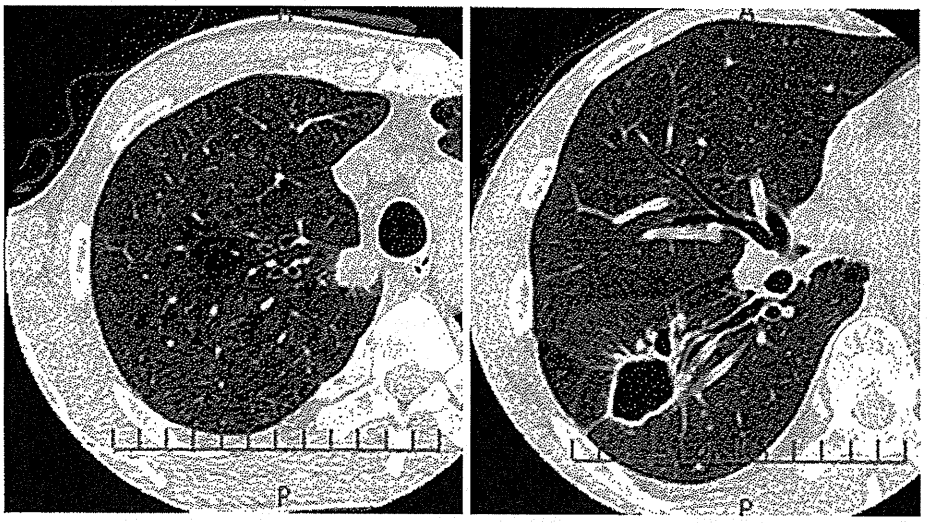


図1. 胸部X線像
右中肺野に空洞性病変を認める.

Ⅱ. 考　　察

肺NTMは，肺結核の罹患率が減少傾向にあるのに対し，増加傾向である. 推定の罹患率は1970年代には人口10万人あたり0.8～1.9，80年代後半には2.1～2.9，2005年には5.7である[2]. この数字は国際的にみてもっとも高いレベルであ



a. 右上葉S^1/S^2. 縦隔側に辺縁不整な充実性結節を認める.　　b. 右下葉S^6. 空洞性病変を認める.

図2. 胸部CT

る[1]．2006年には抗酸菌陽性例の約3割が肺NTMである[2]．

肺結核症は，肺癌発症の危険因子であることが示唆されている一方，肺NTMと肺癌の関連については明確な根拠は存在しないものの，両疾患の合併例の報告が散見される[3,4]．田村らの報告では，肺NTMの肺癌合併頻度は1.8%とされており[4]，肺NTMの増加の状況を合わせて考えると，今後，両疾患の合併例が増加することが予想される．

肺NTMの加療中に肺癌が合併した場合，問題となるのは診断である．肺NTMは，結核類似型，小結節・気管支拡張型，孤立結節型，全身播種型，過敏性肺臓炎型の多彩な画像パターンを呈する[5]ので，肺癌を強く疑う画像所見でなければ，肺NTMの増悪や再燃と判断してしまう場合が多いと考えられる．本例では，新たに出現したのは右上葉の1.3 cm大充実性結節で，辺縁は微細鋸歯状で肺癌を強く疑った．気管支鏡検査では診断にいたらなかったが，診断と治療を兼ねて手術の方針とした．PET/CTが診断に有用であったとの報告もあるが[6]，従来から指摘されているようにPET/CTでは活動性の炎症でも集積が亢進することや，腫瘍径が小さい病変では集積がみられない可能性があること[7]から，最終的には手術で診断にいたる症例が多い[8]．

肺NTM症に対する治療の原則は，rifampicin，ethambutol，clarithromycinの多剤併用療法であるが，時に難治性を示すことがある．2007年の米国胸部疾患学会・感染症学会の公式ガイドラインでは，内科的治療に反応が乏しい，マクロライドに耐性である，喀血などの合併症がある場合に切除の適応があるとしている[9]．これを受けて本邦では，2008年に日本結核病学会から外科治療などに関する指針や見解が示された[10]．外科治療の目的はあくまで病状のコントロールであり，単一大空洞や荒蕪肺，その他の大量排菌源となる粗大病変を摘除することにより，一時的あるいは一過性であっても，病勢の進行抑制や遅延で外科治療が有用な場合が少なからずありえる．

肺NTM症に対する術式に関しては一定の見解はなく，個々の症例で切除範囲に応じて肺葉切除，区域切除，部分切除が選択されているのが現状である[11,12]．本例では，右上葉肺癌に対する治療を優先し，肺NTMに関しては右下葉の空洞性病変を切除することを目的として，右上葉切除術＋右S^6区域切除を施行した．両疾患が同側であったのでS^6区域切除も行ったが，肺NTMの切除対象病変が肺癌と反対側にある場合には，肺NTMに対する外科治療の適応は慎重に考える必要がある．

おわりに

1）肺NTMの治療中に発症した肺癌の1手術例を経験した．

2）化学療法抵抗性の肺NTM＋肺癌に対する手術では，肺NTMに対する治療効果も考慮して術式を検討する必要がある．

文　献

1）倉島篤行：非結核性抗酸菌症の新しい診断と治療．日胸臨 68：999-1012, 2009
2）中山光男：肺非結核性抗酸菌症の治療：外科治療の役割．日外連会誌 34：674-675, 2009
3）玉置伸二，児山紀子，甲斐吉郎ほか：経過中に肺癌を合併した肺非結核性抗酸菌症の2例．気管支学 31：237-243, 2009
4）田村厚久，蛇沢　晶，益田公彦ほか：肺癌と活動性肺抗酸菌症の合併—特徴と推移．日呼吸会誌 45：382-393, 2007
5）中川　拓，小川賢二：肺非結核性抗酸菌症の診断．非結核性抗酸菌症の臨床，佐々木結花，小川賢二（編），新興医学出版社，東京，p16-24, 2010
6）安達勝利，金田正徳，坂井　隆ほか：FDG-PET/CTが診断に有用であった非結核性抗酸菌症治療中に出現した肺腺癌の1例．胸部外科 62：1019-1021, 2009
7）Port JL, Andrade RS, Levin MA et al：Positron emission tomographic scanning in the diagnosis and staging of non-small cell lung cancer 2 cm in size or less. J Thorac Cardiovasc Surg 130：1611-1615, 2005
8）岡田　英，廣野達彦，渡辺健寛：FDG-PETで集積亢進を認め，肺癌を疑われた非結核性抗酸菌症の1例．日呼外会誌 25：144-148, 2011
9）Griffith DE, Aksamit T, Brown-Elliott BA et al：An official ATS/IDSA statement：diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175：367-416, 2007
10）日本結核病学会非結核性抗酸菌症対策委員会：

肺非結核性抗酸菌症に対する外科治療の指針. 結核 83：527-528, 2008
11) 徳島　武, 矢野修一, 池田敏和ほか：肺非結核性抗酸菌症の外科治療の検討. 結核 85：204-206, 2010
12) 水野幸太郎, 立松　勉, 小田梨紗ほか：肺非結核性抗酸菌症に対する肺区域切除術の検討. 日呼外会誌 27：553-557, 2013

SUMMARY

Pulmonary Non-tuberculous Mycobacteriosis Complicated with Lung Cancer

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A 54-year-old man with pulmonary non-tuberculous mycobacteriosis (pulmonary NTM) who had been treated by antituberculous chemotherapy, developed a new nodule of 1.3 cm in size in the segment 1/2 of the right upper lobe. The cavity of 3.5 cm in size in the segment 6 of the right lower lobe from which *Mycobacterium intracellulare* was bronchoscopically detected, was suspected to be pulmonary NTM lesion. Since lung cancer was highly suspected by radiological examinations, right upper lobectomy and S^6 segmentectomy were performed. Pathological diagnosis for the right upper lobe nodule was adenocarcinoma.

KEY WORDS
pulmonary non-tuberculous mycobacteriosis/lung cancer/surgery

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(肺癌. 2014;54:795-799)

CASE REPORT

長期生存中の肺癌肉腫の1切除例

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Resection of Pulmonary Carcinosarcoma with Long-term Survival

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ABSTRACT —— ***Background.*** Pulmonary carcinosarcoma is a rare malignant neoplasm composed of a mixture of carcinoma and sarcoma containing ectopic components, including malignant cartilage, bone and skeletal muscle. ***Case.*** The patient was a 71-year-old man who developed nighttime wheezing. Chest computed tomography (CT) revealed a 5.5-cm tumor shadow in the right lower lobe, although a definitive diagnosis was not reached on bronchoscopy. The patient subsequently underwent resection of the right lower lobe and mediastinal lymph node dissection for suspected lung cancer, and a pathological examination revealed pulmonary carcinosarcoma with mixed components of squamous cell carcinoma and fetal adenocarcinoma as well as sarcoma-like components with cartilage and osteoid. The patient is currently alive without relapse at two years and three months postoperatively. ***Conclusions.*** Carcinosarcoma progresses quickly and has a poor prognosis; however, most patients who undergo complete surgical resection achieve long-term survival. Further research with respect to surgical treatment and chemotherapy for pulmonary carcinosarcoma is thus required.

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KEY WORDS —— Lung cancer, Pulmonary carcinosarcoma

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要旨 —— 背景．肺癌肉腫は，癌腫と悪性の軟骨，骨，骨格筋のような異所性成分を含む肉腫との混在からなる．稀な悪性腫瘍である．症例．71歳，男性．夜間喘鳴で発症した．胸部CTにて右下葉に5.5 cm大の腫瘤影を認めたが，気管支鏡では確定診断に至らなかった．肺癌の疑いで右下葉切除および縦隔リンパ節郭清を行った．病理検査では軟骨，類骨を伴う肉腫様成分と扁平上皮癌，胎児型腺癌様の成分の混在する肺癌肉腫であった．術後は2年3ヵ月無再発生存中である．結論．癌肉腫は進行が早く予後も不良な疾患であるが，外科的完全切除後には長期生存例が少なからず存在する．肺癌肉腫に対する手術適応と化学療法については，さらなる検討が必要である．

索引用語 —— 肺癌，肺癌肉腫

はじめに

肺癌肉腫は，癌腫と悪性の軟骨，骨，骨格筋のような異所性成分を含む肉腫との混在からなる悪性腫瘍である．進行が早く予後も不良な疾患であるが，[1,2] 外科的完全切除後には長期生存例が少なからず存在する．[3]

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