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Original Article

Surgical Outcomes of Lung Cancer Patients with Combined Pulmonary Fibrosis and Emphysema and Those with Idiopathic Pulmonary Fibrosis without Emphysema

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Objectives: Combined pulmonary fibrosis and emphysema (CPFE) is a unique disorder. The aim of this study was to compare the surgical outcomes of lung cancer patients with CPFE and those with idiopathic pulmonary fibrosis (IPF) without emphysema.
Methods: A total of 1548 patients who underwent surgery for primary lung cancer between January 2001 and December 2012 were retrospectively reviewed.
Results: Of the 1548 patients, 55 (3.6%) had CPFE on computed tomography (CT), and 45 (2.9%) had IPF without emphysema. The overall and disease-free 5-year survival rates for patients with CPFE were not significantly worse than those for patients with IPF without emphysema (24.9% vs. 36.8%, p = 0.814; 39.8% vs. 39.3%, p = 0.653, respectively). Overall, 21 (38.1%) patients with CPFE and nine patients (20.0%) with IPF without emphysema developed postoperative cardiopulmonary complications. Patients with CPFE had significantly more postoperative cardiopulmonary complications involving pulmonary air leakage for >6 days, hypoxemia, and arrhythmia than patients with IPF without emphysema (p = 0.048).
Conclusions: There was no significant difference in survival after surgical treatment between CPFE patients and IPF patients without emphysema, but CPFE patients had significantly higher morbidity than IPF patients without emphysema.

Keywords: cardiopulmonary complication, combined pulmonary fibrosis and emphysema, home oxygen therapy, idiopathic pulmonary fibrosis, lung cancer

Introduction

Combined pulmonary fibrosis and emphysema (CPFE) was described by Cottin et al.[1)] Pulmonary emphysema and fibrosis are dissimilar physiologic entities. Emphysema causes increased pulmonary compliance and lung volumes with reduced maximal expiratory flow rates and reduced lung elastic recoil. On the other hand, pulmonary fibrosis results in decreased pulmonary compliance, reduced lung volumes with preserved or even increased maximal expiratory flow rates at a given lung volume, and increased lung elastic recoil.

CPFE is characterized by dyspnea, unexpected subnormal spirometry findings, upper lobe emphysema, and lower lobe interstitial fibrotic changes. The pathogenesis

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of CPFE is probably related to tobacco smoking, a common risk factor for both emphysema and fibrosis.[2,3] Thus, CPFE is predicted to be a common disease in patients with lung cancer. However, the clinical characteristics of CPFE in patients with lung cancer have not been well studied, especially after surgical resection. We hypothesized that lung cancer patients with CPFE had some different clinical characteristics and surgical outcomes than those with idiopathic pulmonary fibrosis (IPF) without emphysema.

In this study, the clinical characteristics and surgical outcomes of lung cancer patients with CPFE and those with IPF without emphysema were compared.

Methods

Patients

The medical records of all patients with non-small cell lung cancer (NSCLC) admitted to the Division of Thoracic and Cardiovascular Surgery at Niigata University Hospital and the Department of Thoracic Surgery at Nishi-Niigata Chuo National Hospital from 2001 to 2012 were retrospectively reviewed, and those diagnosed with IPF before surgical treatment for lung cancer were identified. A total of 1548 patients were enrolled into this study. Of these, 55 patients (3.6%) had CPFE, and 45 (2.9%) patients had IPF without emphysema. The Institutional Review Boards approved this study (Niigata University, 135) and waived the requirement for informed consent from individual patients because the study was a retrospective review.

Radiologic assessment

IPF patients were identified based on the following criteria: (1) computed tomography (CT) showing patterns compatible with IPF proposed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS),[4] with bilateral reticular opacities and/or honeycombing of a predominantly peripheral, subpleural, and basal location; and (2) absence of known causes of pulmonary fibrosis, such as hypersensitivity pneumonitis, pneumoconiosis, sarcoidosis, eosinophilic pneumonia, lymphangioleiomyomatosis, drug-induced lung disease, and collagen vascular disease. On the other hand, CPFE patients were identified based on the following criteria, as described by Cottin et al.:[1] (1) the presence of obvious emphysema on CT, defined as well-demarcated areas of low attenuation delimitated by a very thin (<1 mm) wall or no wall with upper zone predominance; and (2) the presence of diffuse parenchymal lung disease with significant pulmonary fibrosis defined as reticular abnormalities with basal and subpleural predominance, traction bronchiectasis and/or honeycombing, and with minimal ground-glass opacities on CT, with >10% of the lung affected with emphysematous changes. To evaluate emphysema, high-resolution CT (HRCT) images were taken with a window setting appropriate for the lungs (window level from –900 to –970 Hounsfield units [HU]; width from 800 to 1000 HU). The percentage of emphysema on HRCT in each patient was assessed visually by one thoracic radiologist (HI) and one thoracic surgeon (SS) who were blinded to clinical data.

Clinical assessment

The medical records were reviewed to obtain patient demographic and clinical characteristics, chest CT, pulmonary function test (PFT) results, including percent vital capacity (%VC), percent forced expiratory volume in one second (FEV1%), and percent diffusing capacity for carbon monoxide (%DLCO), surgical procedure, histological findings, postoperative morbidity occurring within 30 days of surgery, including pulmonary air leakage, hypoxia, arrhythmia, pneumonia, cardiac failure, and pyothorax, postoperative acute exacerbation (AE) of interstitial pneumonia, start of postoperative home oxygen therapy (HOT), and survival. Pulmonary air leakage was defined as prolonged if it lasted for more than 7 days. Hypoxia was defined as oxygen saturation ≤91% on room air. Pneumonia was diagnosed by the presence of new or progressive pulmonary infiltration, or both, on chest X-ray associated with a fever exceeding 38.0°C. Cardiac failure was defined as that requiring dopamine or a cardiotonic drug. There were few differences in the indications for HOT between the two institutions. Briefly, postoperative HOT was indicated for patients with PaO_2 less than 55 mmHg at rest or less than 60 mmHg on exercise at the time of hospital discharge. AE was defined as: (1) increased respiratory distress; (2) fibrosis, newly developed ground glass opacity, and infiltrative shadow on chest X-ray; (3) decline in resting partial pressure of arterial oxygen of more than 10 mm Hg; and (4) absence of heart failure or infectious lung disease.[5]

Pathological cancer stage was determined using the International Union Against Cancer tumor node metastasis staging system 7th edition.[6] Survival information was obtained for all survivors, either during office visits or by telephone interviews with the patient or a relative.

Statistical analyses

Characteristics were compared between IPF without emphysema and CPFE using the chi-square test or Fisher's

Table 1 Comparison of the clinicopathological features of CPFE patients and IPF without emphysema patients

Variable	CPFE N = 55	IPF without emphysema N = 45	p value
Sex			0.042*
Male	53	38	
Female	2	7	
Age (y)	71.8 ± 7.3	69.9 ± 7.1	0.197
BMI (kg/m^2)	23 ± 3.4	23.7 ± 2.8	0.257
SI	1236 ± 596	1014 ± 699	0.090
CEA (ng/ml)	8.8 ± 7.6	7.4 ± 6.0	0.320
CRP (mg/dl)	0.85 ± 1.96	0.28 ± 0.36	0.055
KL-6 (U/ml)	833 ± 552	737 ± 446	0.407
%FVC	96.4 ± 20.2	91.0 ± 19.5	0.176
FEV1%	78.5 ± 8.5	82.2 ± 6.2	0.016
pO_2 (mmHg)	83.4 ± 8.6	85.6 ± 10.5	0.266
pCO_2 (mmHg)	40.0 ± 3.8	41.0 ± 3.8	0.202
%DLCO(%)†	54.8 ± 10.4	55.2 ± 8.3	0.930
Preoperative comorbid cardio-pulmonary disease	18/55 (32.7%)	15‡/45 (33.3%)	0.949
Hypertension	11	13	
Atrial fibrillation	2	2	
Coronary artery disease	3	1	
Others	2	1	
Size (mm)	29.8 ± 16.4	27.8 ± 12.7	0.510
Operation procedure			0.584
Wedge	18	11	
Segmentectomy	4	5	
Lobectomy	33	29	
Node dissection			0.506
ND0	20	12	
ND1	2	1	
ND2	33	32	
Histology			0.081
Adenocarcinoma	14	21	
Squamous cell carcinoma	34	19	
Others	7	5	
Histological grade			0.341
Well or moderate	34	32	
Poor	18	11	
Pathological stage			0.781
I	34	25	
II	8	8	
III	11	9	
IV	2	3	

*Fisher's exact test. †%DLCO values were obtained from 7 CPFE and 9 IPF without emphysema cases. ‡Two patients had two comorbidities each. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; BMI: body-mass index; SI: smoking index; CEA: carcinoembryonic antigen; CRP: C-reactive protein; KL-6: sialylated carbohydrate antigen; FVC: forced vital capacity; FEV: forced expiratory volume; %DLCO: percent diffusing capacity for carbon monoxide; ND: node dissection

exact test for categorical variables. Fisher's exact test was used if there were five or fewer observations in a cohort. Student's *t*-test was used to compare quantitative parameters. Prognosis was analyzed using the Kaplan-Meier method with the log-rank test. Differences were considered significant if the *P*-value was less than 0.05. All statistical analysis was performed using SPSS for Windows Version 19.0 (SPSS, Inc., Chicago, IL, USA).

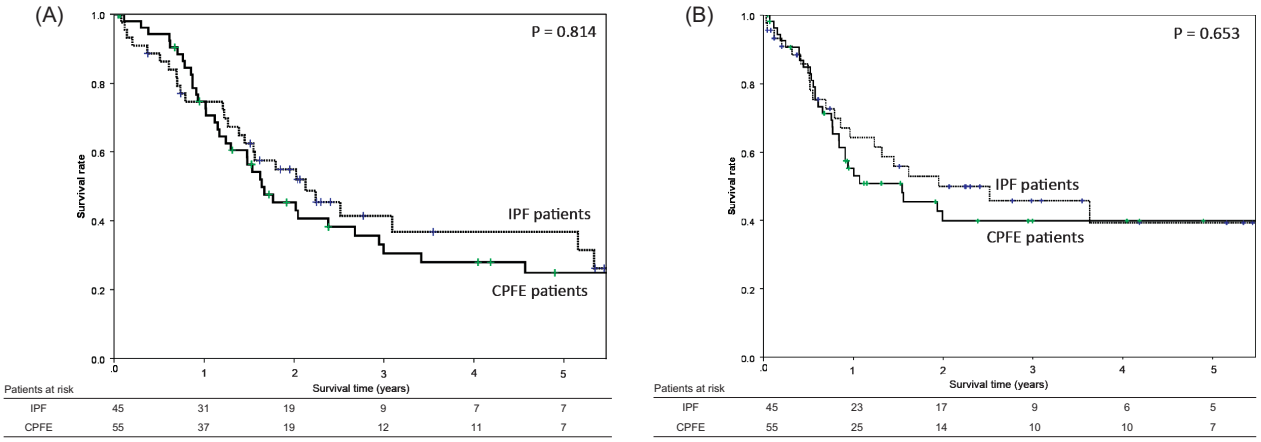

Fig. 1 Comparisons of overall survival curves (**A**) and relapse-free survival curves (**B**) between CPFE patients and IPF patients without emphysema. There are no significant differences in the 5-year survival rates between the two groups. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis

Results

Patients' characteristics

A total of 100 patients were diagnosed as having IPF based on HRCT findings. The median follow-up period after the surgical procedure was 27.7 (range, 0.5–129.3) months. The demographic data for the 100 patients are shown in **Table 1**. Forty-five patients had IPF without emphysema, and 55 patients had CPFE. There were more males than females with CPFE than with IPF without emphysema, and there were significantly more smokers with CPFE than with IPF without emphysema.

On PFT, %VC did not differ significantly between CPFE and IPF without emphysema (96.4% vs. 91.0%, respectively). However, FEV1% was less with CPFE than with IPF without emphysema (78.5% vs. 82.2%, respectively, p = 0.013). Of the 100 patients, %DLCO data were obtained from seven CPFE patients and nine patients with IPF without emphysema, and there was no significant difference between them.

With respect to the surgical procedure and lymph node dissection, in the case of poor pulmonary function and a preoperative comorbid cardiac disorder, partial resection without lymph node dissection was performed. In CPFE patients 18 patients (32.7%) underwent partial resection, and 33 patients (60.0%) underwent lobectomy. In IPF patients without emphysema, 11 patients (24.4%) underwent partial resection, and 29 patients (64.4%) underwent lobectomy. Mediastinal lymph node dissection was performed in 33 CPFE patients (60.0%) and 32 IPF patients without emphysema (71.1%). There was no significant difference between the cohorts in the surgical procedure. After lung resection, there was a confirmed pathological diagnosis in 23 (41.8%) CPFE patients and 19 (42.2%) patients with IPF without emphysema.

Survival

When the prognoses were compared between CPFE and IPF without emphysema, the 5-year overall survival (OS) rates were 24.9% and 36.8%, respectively (p = 0.814) (**Fig. 1A**); there was no significant difference between the two cohorts. In terms of relapse-free survival (RFS), the 5-year rates were 39.8% with CPFE and 39.3% with IPF without emphysema, with no significant difference between them (p = 0.653) (**Fig. 1B**). For pathological stage I, OS rates were 32.3% and 50.5%, respectively (p = 0.896) (**Fig. 2A**), and RFS rates were 48.6% and 52.4%, respectively (p = 0.546) (**Fig. 2B**), for CPFE and IPF without emphysema.

Morbidity and mortality of pulmonary resection

Postoperative cardiopulmonary complications within 30 days of surgery occurred in 21 CPFE patients (38.1%) and nine patients (20.0%) with IPF without emphysema, and the difference was significant (p = 0.048). The breakdown of postoperative cardiopulmonary complications is shown in **Table 2**. There were more cases of pulmonary air leakage for >6 days, hypoxemia, and arrhythmia in CPFE patients than in IPF patients without emphysema.

AE developed in three patients (5.5%) with CPFE and three patients (6.7%) with IPF without emphysema; the difference was not significant (p = 0.56).

Postoperative HOT was begun in eight CPFE patients but in only two patients with IPF without emphysema; more

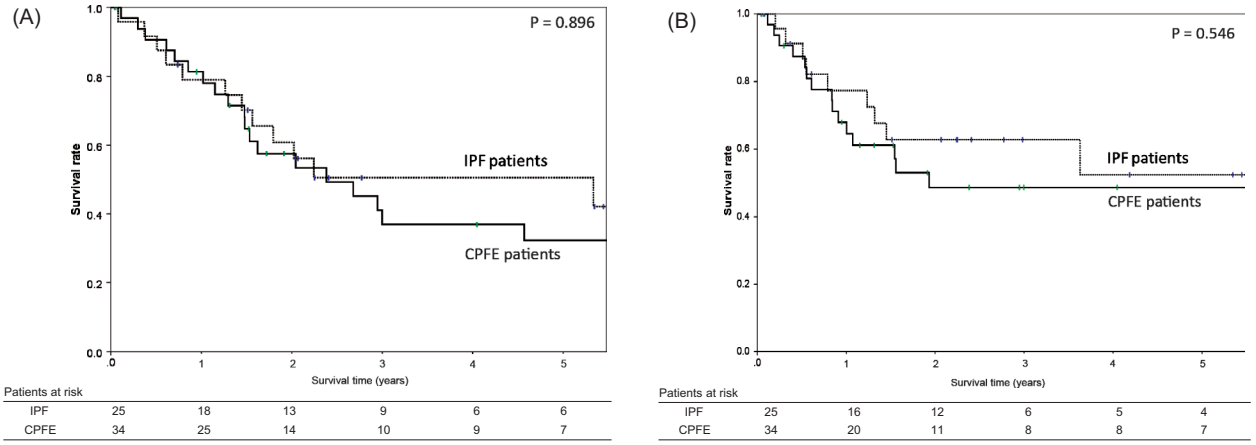

Fig. 2 Comparisons of overall survival curves (**A**) and relapse-free survival curves (**B**) for pathological stage I between CPFE patients and IPF patients without emphysema. There are no significant differences in the 5-year survival rates between the two groups. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis

Table 2 Postoperative cardio-pulmonary complications, and 30-day, and 90-day mortality

Complication	No. of patients*	
	CPFE (N = 55)	IPF without emphysema (N = 45)
Pulmonary air leakage	6 (10.9%)	2 (4.4%)
Hypoxia	5 (9.1%)	2 (4.4%)
Arrhythmia	4 (7.3%)	1 (2.2%)
Pneumonia	3 (5.5%)	2 (4.4%)
Cardiac failure	1 (1.8%)	1 (2.2%)
Pyothorax	1 (1.8%)	0
AE	3 (5.5%)	3 (6.7%)
30-day mortality	0	1 (2.2%)
90-day mortality	1 (1.8%)	3 (6.7%)

*Some patients had more than one complication. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; AE: acute exacerbation

patients had a tendency to require HOT in the CPFE group than in the IPF without emphysema group (p = 0.088).

In the CPFE and IPF without emphysema groups, the 30- and 90-day mortality rates were 0% and 1.8%, and 2.2% and 6.7%, respectively.

Cause of death

Table 3 shows the causes of death and details of respiratory failure deaths. In the CPFE and IPF without emphysema groups, death due to cancer was the main cause of mortality (27/37, 73.0% and 18/27, 66.7%, respectively), and death due to respiratory failure (8/37, 21.6% and 8/27, 29.6%, respectively) was the second most common cause of death. Details of the respiratory failure deaths were as follows: three CPFE patients (37.5%) and seven IPF patients without emphysema (87.5%) died of exacerbation of interstitial pneumonia.

Discussion

This study examined the clinical characteristics and surgical outcomes of lung cancer patients with CPFE and those with IPF without emphysema. The diagnosis of CPFE was established after HRCT imaging, but a consensus definition of CPFE does not currently exist. Thus, as with the previous report by Mejia et al.,[7] CPFE was defined in the present study as the presence of IPF with emphysema, with >10% of the lung affected by emphysematous changes.

In terms of patients' clinical characteristics, there were more males and more heavy smokers in the CPFE group

Table 3 Cause of death and details of respiratory failure deaths

Categories	Cases (%)	
	CPFE	IPF without emphysema
Cause of death		
Lung cancer	27 (73.0%)	18 (66.7%)
Respiratory failure	8 (21.6%)	8 (29.6%)
Others	2 (5.4%)	1 (3.7%)
Death due to respiratory failure		
Postoperative AE*	2 (25.0%)	3 (37.5%)
Chronic exacerbation†	1 (12.5%)	4 (50.0%)
Others	5 (67.5%)	1 (12.5%)

*Exacerbation of interstitial pneumonia within 30 days after surgery.
†Exacerbation of interstitial pneumonia occuring ≥31 days after the operation. CPFE: combined pulmonary fibrosis and emphysema; IPF: idiopathic pulmonary fibrosis; AE: Acute exacerbation

than in the IPF without emphysema group. The patients' clinical characteristics were consistent with those previously reported.[1,7–13)]

A PFT analysis was also performed. In this study, the baseline ventilatory capacity characteristics of the CPFE group were similar to those described by others,[7,8,10,14)] in that lung volumes were well preserved, and FEV1% appeared normal. The relatively normal lung volumes in CPFE are usually the result of the counterbalancing effects of the restrictive defect of pulmonary fibrosis and the propensity to hyperinflation seen in emphysema. Furthermore, patients with severely symptomatic IPF were usually considered inoperable, and almost all patients were asymptomatic (subclinical IPF) in this surgical study. Jankowick et al.[15)] assumed that the preservation of FEV1 may be attributed to the increase in traction caused by fibrosis, preventing the expiratory airway collapse seen in emphysema,[16)] and a stiffening of the small airways by peribronchial fibrosis.[17)] However, the previous studies[8,10–12)] reported that, in CPFE, the decrease in diffusing capacity (DLco) was substantial because of the additive effect of emphysema and fibrosis. In the present study, there were few cases with data available on DLco, but it would be important to compare the rate of decrease of postoperative DLco in CPFE patients and IPF patients without emphysema.

In patients with CPFE, the median survival in reported cases[1,7,8,10,12,14)] has ranged from 2.1 to 8.5 years after diagnosis of IPF. However, whether patients with CPFE have worse survival than patients with isolated pulmonary fibrosis is unknown. A study by Mejia et al.[7)] reported worse survival in a group with CPFE compared with a group with IPF without emphysema, but other studies[8,10,12,14,18)] have reported comparable or better survival in CPFE than in IPF without emphysema. There was only one study[19)] of the surgical outcomes of lung cancer patients with CPFE. Mimae et al. reported that the five-year OS rate for all patients with CPFE was about 30%, which was similar to the present outcome. With regard to clinical stage I, they reported that the five-year OS rate was about 40%. Although they were pathological stage I, the present results might be worse than theirs. This may be part of the reason that 20 (36.4%) of 55 cases were ND0, so it was possible that there were some cases of inaccurate staging.

As above, the survival rates of CPFE and IPF without emphysema have varied among the studies. In the present study, there was no significant difference in the survival rate between the two groups. Jankowich et al.[15)] noted that the basis for these conflicting results is unclear and may include the relative proportion of non-IPF pathology in patients with CPFE in individual studies and the effects of emphysema subtypes.

So far, there have been no reports that compared morbidity between CPFE and IPF without emphysema. Previous studies[20–25)] reported that postoperative respiratory complications were found in 26%–54.0% of patients with IPF, moderately higher than in the present study, in which the CPFE group had a significantly higher rate of cardiopulmonary morbidity than the IPF alone group; this was assumed to be due to the fact that postoperative PFT decreased unexpectedly in CPFE, involving both %VC and FEV1%, because the CPFE patients experienced AE at almost the same rate as IPF patients without emphysema and required more HOT than IPF patients without emphysema. Moreover, previous studies[7,9,10,14)] noted that CPFE was highly associated with pulmonary hypertension, which might be regarded as a cause of more

arrhythmias. Mimae et al.[19] reported that postoperative pulmonary complications occurred in 20% of CPFE patients. Similarly, in the present study, pulmonary complications developed in 16 CPFE cases (29.1%), and CPFE patients had more postoperative pulmonary complications than those with IPF without emphysema.

The present study has some limitations. First, a vague definition of CPFE was used, in that the percentage of emphysematous lesions on HRCT was not considered. There have been few reports that dealt with the percentage of emphysematous change. Because target cases were different among the studies, it is difficult to compare them directly. Second, the percentage of emphysema on HRCT was evaluated in a visual manner by two thoracic specialists, but objective quantitation, such as "density mask" analysis, was not performed.[26] Therefore, it was possible that there were a few false-positives cases in the CPFE group. Third, in the present study, patients were selected based on criteria, and pathological examinations of idiopathic pulmonary fibrosis were not obtained in all cases. There are many cases of IPF alone diagnosed on CT, and the diagnosis may not be accurate in some cases. Fourth, this was a retrospective, two-institution study, and the sample size was limited. To confirm these observations, prospective studies that include a large number of patients are needed.

In conclusion, surgical outcomes of lung cancer patients with CPFE and those with IPF without emphysema were compared. Survival in patients with CPFE was not significantly worse than in those with IPF without emphysema, but in terms of morbidity, patients with CPFE had more postoperative cardiopulmonary complications than those with IPF without emphysema. Thus, careful postoperative management is needed for both patients with IPF without emphysema and those with CPFE.

Disclosure Statement

The authors have no conflict of interest to declare.

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