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Severity of lung fibrosis affects early surgical outcomes of lung cancer among patients with combined pulmonary fibrosis and emphysema

Takahiro Mimae, MD, PhD[a], Kenji Suzuki, MD, PhD[b], Masahiro Tsuboi, MD, PhD[c], Norihiko Ikeda, MD, PhD[d], Kazuya Takamochi, MD, PhD[b], Keiju Aokage, MD, PhD[c], Yoshihisa Shimada, MD, PhD[d], Yoshihiro Miyata, MD, PhD[a], Morihito Okada, MD, PhD[a,*]

Abstract

Combined pulmonary fibrosis and emphysema (CPFE) is defined as upper lobe emphysema and lower lobe fibrosis, which are representative lung disorders that increase the prevalence of lung cancer. This unique disorder may affect the morbidity and mortality during the early period after surgery. The present study aimed to identify which clinicopathological features significantly affect early surgical outcomes after lung resection in nonsmall cell lung cancer (NSCLC) patients and in those with CPFE.

We retrospectively assessed 2295 patients with NSCLC and found that 151 (6.6%) had CPFE. All were surgically treated between January 2008 and December 2010 at 4 institutions.

The postoperative complication rates for patients with and without CPFE were 39% and 17%, respectively. The 90-day mortality rates were higher among patients with than without CPFE (7.9% vs 1%). Acute exacerbation of interstitial pneumonia was the main cause of death among 12 patients with CPFE who died within 90 days after surgery. Multivariate logistic regression analysis selected CPFE, gender, age, and clinical stage as independent predictive factors for postoperative complications, and CPFE, clinical stage, and sex for 90-day mortality. The severity of lung fibrosis on preoperative CT images was an independent predictive factor for 90-day mortality among patients with CPFE.

The key predictive factor for postoperative mortality and complications of lung resection for NSCLC was CPFE. The severity of lung fibrosis was the principal predictor of early outcomes after lung surgery among patients with CPFE and NSCLC.

Abbreviations: CPFE = combined pulmonary fibrosis and emphysema, CT = computed tomography, CTCAE = Common Terminology Criteria for Adverse Events, FEV1.0 = forced expiratory volume 1 second, NSCLC = nonsmall cell lung cancer, VC = vital capacity.

Keywords: interstitial pneumonia, lung fibrosis, morbidity, mortality, surgery

1. Introduction

Postoperative complications, mortality, and curability should be considered especially among high-risk patients with lung cancer. Lung status is key among preoperative high-risk conditions for lung resection. Both lung fibrosis and emphysematous transformation are major alterations in lung status. Combined pulmonary fibrosis and emphysema (CPFE) is a unique disorder of the lungs that comprises both upper lobe emphysema and lower lobe fibrosis.[1,2] The incidence of lung cancer has increased in patients with chronic obstructive pulmonary disease[3–5] and it is also high in patients with interstitial pneumonia and fibrotic lungs.[6,7] Patients with CPFE also have a high prevalence of lung cancer.[8] However, little is understood about the surgical outcomes of lung cancer for such patients. Thus, predictors of early surgical outcomes, especially postoperative complications and mortality rates after lung resection to treat nonsmall cell lung cancer (NSCLC) in patients with CPFE remain unclear.

We previously identified predictive factors of overall survival for lung cancer including small cell lung carcinoma in patients with CPFE.[9] The present study firstly assessed the clinical background of patients and found that CPFE obviously affected early surgical outcomes. We then aimed to identify factors affecting postoperative mortality and complications of lung resection for NSCLC in patients with CPFE. The present findings will provide useful information that will help physicians and surgeons to select optimal treatment modalities for patients with lung cancer and CPFE.

2. Methods

2.1. Computed tomography imaging of CPFE, extent of emphysema, and severity of lung fibrosis

CPFE were defined based on chest computed tomography (CT) findings. Emphysema was defined as clearly demarcated areas of

Editor: Jian Liu.

The language in this manuscript has been professionally proof-checked by a native English speaker with over 25 years of experience in editing manuscripts prepared by physicians and researchers whose native language is not English.

The authors have no conflicts of interest to disclose.

This study was supported by a Research Grant from GSK Japan to TM.

[a] Department of Surgical Oncology, Hiroshima University, Hiroshima, [b] Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, [c] Division of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, [d] Department of Surgery, Tokyo Medical University, Tokyo, Japan.

[*] Correspondence: Morihito Okada, Department of Surgical Oncology, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan (e-mail: morihito1217@hiroshima-u.ac.jp).

Medicine (2016) 95:29(e4314)

Received: 4 February 2016 / Received in final form: 7 June 2016 / Accepted: 28 June 2016

http://dx.doi.org/10.1097/MD.0000000000004314

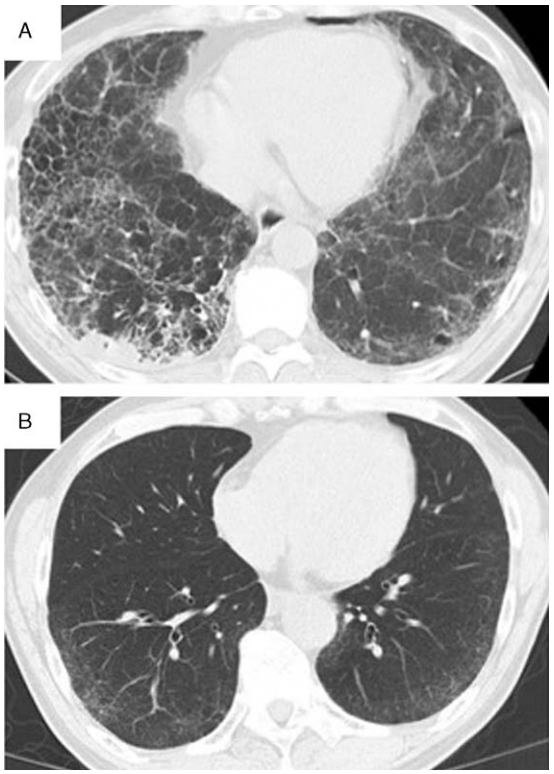

Figure 1. Representative computed tomography findings of lung fibrosis. (A) Distribution throughout entire lung. Fibrosis has extended to inner two-thirds of lung. (B) Peripheral distribution. Fibrosis is localized to only outer third of lung.

decreased attenuation compared with a contiguous normal lung, having an absent or very thin (<1 mm) wall, and/or multiple bullae (>1 cm) with upper zone predominance; diffuse parenchymal lung disease with significant pulmonary fibrosis visualized as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis; focal ground-glass opacities and/or associated areas of alveolar condensation that may be present but not prominent.[2] All CT images of all patients with lung cancer who were treated by surgical resection between 2008 and 2010 at 4 institutions were retrospectively assessed. Pulmonary specialists and experienced radiologists at each institution diagnosed CPFE after reaching consensus at a central conference regarding representative and borderline CT images.

The extent of emphysema was classified as involving 1 or more than 1 lobe according to areas occupied by multiple bullae (>1 cm). The severity of lung fibrosis was defined based on fibrosis that had localized at the lung periphery or had spread throughout the lung to include peripheral and central areas. Central fibrosis was diagnosed when CT findings including infiltration or honeycombing extended to the inner two-thirds of the lung.[10]- Figure 1 shows representative images.

2.2. Patients

The present retrospective study included 2456 consecutive patients with primary lung cancer that had been completely surgically resected at Hiroshima University Hospital (Hiroshima, Japan), Juntendo University School of Medicine (Tokyo, Japan), National Cancer Center Hospital East (Kashiwa, Japan), and Tokyo Medical University (Tokyo, Japan) between January 2008 and December 2010. The Institutional Review Boards at all participating institutions (Hiroshima University, eki-799) approved the study and waived the requirement for informed consent from individual patients, because the study comprised a retrospective review of a prospective database. We compared data from 151 and 2144 patients with NSCLC and with and without CPFE, respectively, or those with complete information about the extent of the surgery and lung function data including % vital capacity (VC) and forced expiratory volume 1 second (FEV1.0) %. All patients who were staged according to the TNM Classification of Malignant Tumors, 7th edition were assessed by high resolution CT and fluorodeoxyglucose-positron emission tomography/CT and then treated by curative R0 resection[11]. Patients who underwent palliative limited resection were also included. Preoperative assessment, the extent of curative lung resection, and postoperative follow-up therapy proceeded as described.[12–14]

2.3. Postoperative complications

Morbidity and mortality data were collected according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0).[15] Three or more grades of morbidity were taken as postoperative complications. Thirty- and 90-day mortality rates after surgical resection were calculated. The most causative complication of postoperative death was defined as grade 5.

2.4. Statistical analysis

Data from patients with primary NSCLC were included in the analysis. Continuous variables were analyzed using the Mann–-Whitney *U* test and categorical variables were assessed using the Chi-squared test or Fisher exact test. *P* values and odds ratios in multivariate analyses were calculated using backward stepwise logistic regression models to identify predictors of postoperative mortality and complication. Variables with $P < 0.1$ in univariate analyses were included in multivariate analyses. All data were statistically analyzed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan),[16] which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6-3), which includes statistical functions that are frequently used in biostatistics. $P \leq 0.05$ was considered to indicate statistical significance. Missing data were excluded from analysis.

3. Results

Table 1 shows the preoperative clinical findings of patients with NSCLC including 151 (7%) with CPFE and Table 2 shows the operative, pathological, and postoperative findings. Adenocarcinoma was the most frequent histological type (70%) followed by squamous cell carcinoma (20%). The main surgical procedure was lobectomy and only 3% of patients underwent pneumonectomy. The postoperative complication rate was 18% (423 of 2295) and the 90-day mortality rates were 1.48% (34 of 2295), respectively. Most patients with CPFE were male (92%) and the rate of smoking ≥40 pack-years was higher (75%) than that among patients without CPFE. Squamous cell carcinoma was the most frequent histological type (50%) followed by adenocarcinoma (38%) among patients with CPFE (Table 2), which differed from those without CPFE. The postoperative morbidity and

Table 1

Preoperative clinicopathological findings of nonsmall cell lung cancer patients with and without combined pulmonary fibrosis and emphysema.

Variables	Without CPFE (n = 2144)	With CPFE (n = 151)	P
Gender			
Female	856 (40)	12 (8)	<0.001
Male	1288 (60)	139 (92)	
Age			
Median (interquartile range)	67 (61–74)	73 (66.5–77)	<0.001
Clinical stage			
I	1642 (77)	110 (73)	0.34
II	305 (14)	25 (17)	
III	171 (8)	16 (11)	
IV	20 (1)	0	
Unknown	6 (0.3)	0	
Performance status			
0	910 (42)	130 (86)	0.020
1	71 (3)	20 (13)	
2	2 (0.1)	1 (1)	
Unknown	1161 (54)	0	
Smoking (pack-year)			
<40	1494 (70)	38 (25)	<0.001
≥40	650 (30)	113 (75)	
%VC (%)			
Median (interquartile range)	100.6 (89.2–112.2)	98.0 (89.5–108.0)	0.32
FEV1.0% (%)			
Median (interquartile range)	75.6 (69.2–80.7)	71.6 (65.12–76.0)	0.19
%DLCO (%)			
Median (interquartile range)	64.5 (52.3–76.9)	43.15 (34.4–51.4)	<0.001

Missing data are excluded from analysis. Data are presented as numbers and ratios (%) or medians and interquartile ranges, as appropriate.

CPFE = combined pulmonary fibrosis and emphysema, DLCO = diffusing capacity for carbon monoxide, FEV1.0% = forced expiratory volume 1 second %, VC = vital capacity.

Table 2

Operative and postoperative findings of nonsmall cell lung cancer patients with and without combined pulmonary fibrosis and emphysema.

Variables	Without CPFE (n = 2144)	With CPFE (n = 151)	P
Pathological stage			
0	3 (0.1)	0 (0)	<0.001
I	1416 (66)	76 (50)	
II	338 (16)	38 (25)	
III	323 (15)	37 (25)	
IV	31 (1)	0 (0)	
Unknown	33 (1)	0 (0)	
Histology			
Adenocarcinoma	1558 (73)	57 (38)	<0.001
Squamous cell carcinoma	385 (18)	75 (50)	
Large cell carcinoma	85 (4)	6 (4)	
Pleomorphic carcinoma	15 (1)	7 (5)	
Others	97 (5)	6 (4)	
Unknown	4 (0.2)	0 (0)	
Procedure			
Pneumonectomy	62 (3)	5 (3)	0.29
Lobectomy	1710 (80)	129 (85)	
Segmentectomy	165 (8)	7 (5)	
Wedge resection	207 (10)	10 (7)	
Postoperative complication			
+	366 (17)	59 (39)	<0.001
−	1778 (83)	92 (61)	
90-day mortality			
+	22 (1)	12 (8)	<0.001
−	2122 (99)	139 (92)	

Missing data are excluded from analysis. Data are presented as numbers and ratios (%) or as medians with interquartile ranges, as appropriate.

CPFE = combined pulmonary fibrosis and emphysema.

90-day mortality rates were high among NSCLC patients with CPFE (39% and 8%, respectively; Table 2).

Table 3 shows the results of a univariate analysis of postoperative complications and 90-day mortality. Subsequent multivariate logistic regression analysis selected CPFE, sex, age, and clinical stage as independent predictive factors for postoperative complications of lung resection for NSCLC. Independent predictive factors for 90-day mortality comprised CPFE, clinical stage, and sex (Table 4). Thus, CPFE was the most significant independent predictive factor for both mortality and postoperative complications. Hence, we further analyzed data from patients with NSCLC and CPFE.

Univariate analysis did not uncover any clinicopathological findings that were related to postoperative complications. In contrast, lung fibrotic severity and clinical stage were significantly and marginally associated with 90-day mortality (Table 5). Multivariate logistic regression analysis selected severity of fibrosis (whole vs periphery) on preoperative CT as an independent predictive factor for 90-day mortality but not for postoperative complications among NSCLC patients with CPFE (Table 6). In support of the above findings, acute exacerbation of interstitial pneumonia was the main cause of 90-day mortality in 4 (33%) of 12 patients followed by acute respiratory distress syndrome and bronchopleural fistula in 2 (17%) of 12 patients each. Two patients each died of pneumonia and empyema. One patient died of recurrent lung cancer and only 1 died of a complication that was not respiratory-related, namely strangulation ileus.

Table 3

Univariate analysis of postoperative complications and 90-day mortality of patients with nonsmall cell lung cancer after lung resection.

	Postoperative complication			90-day mortality		
Variables	Positive (n = 425)	Negative (n = 1870)	P	Positive (n = 34)	Negative (n = 2261)	P
Age						
<70	196	1107	<0.001	15	1288	0.16
≥70	229	763		19	973	
Gender						
Female	96	772	<0.001	1	867	<0.001
Male	329	1098		33	1394	
Pack-year						
<40	237	1295	<0.001	22	1510	0.86
≥40	188	575		12	751	
CPFE						
Absent	366	1778	<0.001	22	2122	<0.001
Present	59	92		12	139	
Clinical stage						
I	282	1470	<0.001	15	1737	<0.001
II + III + IV	143	400		19	524	
Procedure						
Limited	55	334	0.18	3	386	0.25
Standard	370	1536		31	1875	

CPFE = combined pulmonary fibrosis and emphysema.

Table 4

Multivariate analysis of postoperative complications and 90-day mortality of patients with nonsmall cell lung cancer after lung resection.

	Postoperative complication		90-day mortality	
Variables	Odd ratio (95% CI)	P	Odd ratio (95% CI)	P
Age (≥70 y vs <70 y)	1.7 (1.4–2.1)	<0.0001	—	—
Sex (male vs female)	2.0 (1.5–2.6)	<0.0001	1.2 (1.5–85.9)	0.018
CPFE (present vs absent)	2.2 (1.5–3.2)	<0.0001	5.9 (2.8–12.4)	<0.0001
Clinical stage (II + III + IV vs I)	1.6 (1.2–2.0)	0.00032	3.2 (1.6–6.4)	0.0013

CI = confidence interval, CPFE = combined pulmonary fibrosis and emphysema.

4. Discussion

The present study assessed postoperative mortality and complications of lung resection for NSCLC in patients with CPFE defined by Cottin[2,17] in 2005 as lung fibrosis and emphysema that both destroy lung structures and lead to a loss of lung function. Interstitial pneumonia and emphysema provoke more risks for postoperative complications and mortality.[10,18–22]

Table 5

Univariate analysis of postoperative complications and 90-day mortality after lung resection for nonsmall cell lung cancer among patients with combined pulmonary fibrosis and emphysema.

	Postoperative complications			90-day mortality		
	Positive (n = 59)	Negative (n = 92)	P	Positive (n = 12)	Negative (n = 139)	P
Age, y						
<70	20	37	0.49	4	53	1
≥70	39	55		8	86	
Sex						
Female	2	10	0.13	0	12	0.60
Male	57	82		12	127	
PS						
0	51	79	1	10	120	0.67
≥1	8	13		2	19	
Pack-year						
<40	14	24	0.85	4	34	0.50
≥40	45	68		8	105	
Clinical stage						
I	38	72	0.091	6	104	0.089
II + III	21	20		6	35	
%VC						
<100	36	48	0.32	9	75	0.23
≥100	23	44		3	64	
FEV1.0%						
<70	30	38	0.32	5	63	1.00
≥70	29	54		7	76	
Extension of emphysema						
One lobe	32	55	0.51	4	83	0.13
>One lobe	27	37		8	56	
Severity of fibrosis						
Peripheral	46	73	0.84	6	113	0.021
Whole	13	19		6	26	
Procedure						
Limited	4	13	0.20	10	124	0.63
Standard	55	79		2	15	

FEV1.0% = forced expiratory volume in 1 second %, PS = performance status, VC = vital capacity.

Table 6

Multivariate analysis of 90-day mortality after lung resection for nonsmall cell lung cancer in patients with combined pulmonary fibrosis and emphysema.

	90-day mortality	
Variables	Odd ratio (95% CI)	P
Severity of fibrosis (whole vs periphery)	4.4 (1.3–14.6)	0.017

CI = confidence interval.

Here, we identified a predictive factor for postoperative mortality in patients with NSCLC and CPFE in a multiinstitutional setting.

The most powerful independent predictive factor for both early postoperative mortality and complications among all patients with NSCLC was CPFE. The rates of postoperative 90-day mortality and complications were 8% and 39% in patients with NSCLC and CPFE, which were notably higher than in all patients with NSCLC but without CPFE. These rates were also higher than previous postoperative 30-day mortality and complication rates for NSCLC in Japan (0%–0.9% and about 20%, respectively).[18,20,22–25]. Hence, modalities for treating NSCLC in patients with CPFE should be carefully determined. On the other hand, age and clinical stage were also predictive factors for postoperative complications. More advanced clinical stage includes the likelihood of more invasive and complex surgery.

The severity of lung fibrosis on the preoperative CT predicted postoperative mortality after lung resection for NSCLC in patients with CPFE, whereas the extent of emphysematous lesions on CT did not. This is supported by the finding that the main cause of 90-day mortality was acute exacerbation of interstitial pneumonia. This concurred with the fact that exacerbation of interstitial pneumonia is also the main cause of postoperative mortality in Japan,[23–25] and it is apparently associated with the extent of lung fibrosis. Emphysema characterized as the destruction of alveolar walls due to increased cell death in the walls via processes such as apoptosis[26] is the main predictor of perioperative mortality and respiratory morbidity after routine surgery or general lung resection.[19,21] However, the potential to reflect the severity of postoperative lung status was lower for emphysema than for interstitial pneumonia among patients with CPFE. A surgical indication for patients with fibrosis occupying the entire lung from the periphery to the center should be cautiously determined. The present study examined %DLCO in only about 30% of patients with NSCLC and CPFE and thus it was excluded from analysis. However, since %DLCO represents the extent of lung fibrosis,[27,28] it might be a potential predictor of prognosis or of postoperative mortality and morbidity. Further analysis is necessary to resolve this matter.

Smoking adversely affects not only lung function but also the cardiovascular system.[29–31] However, smoking status was not a predictive factor of postoperative mortality in patients with CPFE. This might be because almost all patients with CPFE were previous or current smokers and a main cause of CPFE is smoking. The effect of smoking is difficult to evaluate in patients with CPFE because an objective comparison of status between smokers and nonsmokers is impossible. Even though smoking status was not a predictive factor in the present multivariate analysis, it does not mean that the patients were permitted to smoke. Thus, the present findings of all patients with NSCLC indicated that smoking might exert a more adverse influence on lung disorders such as CPFE.

We found that %VC and FEV1.0% that are representative spirometric parameters of lung function were not predictive factors of postoperative mortality and complications in the present study although %VC can predict the prognosis of patients with lung cancer and CPFE.[9] Spirometric lung function parameters are unquestionably important for assessing the ability to tolerate surgery including lung resection for NSCLC. However, the lung function of patients with CPFE is apparently normal,[1,32] rendering a surgical indication difficult to determine based on lung function determined by spirometry. Therefore, a surgical indication should be selected based on the preoperative degree of lung fibrosis on CT, smoking status, and preoperative lung function.

One limitation of the present study is the retrospective design. In addition, 12 mortality events in patients with CPFE may not be sufficient to determine predictive factors. However, 12 events were not so insignificant because the 90-day mortality rate after lung resection was <10% in patients with CPFE and 5% to 10% of patients with operable NSCLC also have CPFE. Thus, the results should help surgeons to determine indications for the surgical resection of NSCLC in patients with CPFE. Incomplete %DLCO and KL-6 data that could indicate the severity of lung fibrosis comprise another limitation. Furthermore, other comorbidities were not analyzed due to the absence of such information in the database. Nonetheless, the present study found that CPFE is a very useful predictor of postoperative mortality and complications after lung resection among patients with NSCLC.

In summary, CPFE appears to be a highly significant predictor of mortality and morbidity after lung resection for NSCLC. The severity of lung fibrosis appears to be the principal factor affecting early surgical outcomes, namely 90-day mortality, after lung surgery for NSCLC among patients with CPFE and should therefore be carefully evaluated using preoperative CT. Further analysis is needed to validate the present results.

Acknowledgment

We are grateful to Aritoshi Hattori, MD, Tomoharu Yoshiya, MD, Shinsuke Sasada, MD, and Norifumi Tsubokawa, MD for collecting data about the patients at the participating institutions.

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