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

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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 transfor-

mation 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...
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. 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. 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. 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.

2.3. Postoperative complications

Morbidity and mortality data were collected according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0). 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), 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 < 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
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 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 (3)                   | 0                   |     |
| Performance status |                     |                     |     |
| 0               | 910 (42)                | 130 (66)            | 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)            |     |
| %DLCO (%)       |                         |                     |     |
| 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 |
| %VC (%)         |                         |                     |     |
| 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.

### 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 | 365 (18) | 75 (50) |     |
| Large cell carcinoma | 85 (4)  | 6 (4)  |     |
| Pleomorphic carcinoma | 15 (1)  | 7 (5)  |     |
| Others          | 97 (6)                  | 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 medians with interquartile ranges, as appropriate.

CPFE = combined pulmonary fibrosis and emphysema.

### Table 3
Univariate analysis of postoperative complications and 90-day mortality of patients with nonsmall cell lung cancer after lung resection.

| Variables       | Positive (n = 429) | Negative (n = 1870) | P    |
|-----------------|------------------|---------------------|------|
| Age             |                   |                     |      |
| <70             | 196               | 1107                | <0.001 |
| ≥70             | 229               | 763                 |      |
| Gender          |                   |                     |      |
| Female          | 96                | 772                 | <0.001 |
| Male            | 329               | 1098                |      |
| Smoking (pack-year) |               |                     |      |
| <40             | 237               | 1295                | <0.001 |
| ≥40             | 188               | 575                 |      |
| CPFE            |                   |                     |      |
| Absent          | 366               | 1778                | <0.001 |
| Present         | 59                | 92                  |      |
| Clinical stage  |                   |                     |      |
| I               | 282               | 1470                | <0.001 |
| II              | 143               | 400                 |      |
| III + IV        |                   |                     |      |
| Procedure       |                   |                     |      |
| Limited         | 55                | 334                 | 0.18  |
| Standard        | 370               | 1536                | 0.25  |

CPFE = combined pulmonary fibrosis and emphysema.
The present study assessed postoperative mortality and complications of lung resection for NSCLC in patients with CPFE defined by Cotrin et al. 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.\[10,18\]

4. Discussion

The present study assessed postoperative mortality and complications of lung resection for NSCLC in patients with CPFE defined by Cotrin et al.\[10,18\] 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 4
Multivariate analysis of postoperative complications and 90-day mortality of patients with nonsmall cell lung cancer after lung resection.

| Variables                      | Postoperative complication | 90-day mortality |
|-------------------------------|-----------------------------|------------------|
|                               | Odd ratio (95% CI)         | P                | Odd ratio (95% CI) | P |
| Age (≥70 y vs <70 y)          | 1.7 (1.4–2.1)              | <0.0001          | 1.3 (1.2–1.5)       | 0.989 |
| Sex (male vs female)          | 2.0 (1.5–2.6)              | <0.0001          | 1.2 (1.5–8.5)       | 0.018 |
| CPFE (present vs absent)      | 2.2 (1.5–3.2)              | <0.0001          | 5.9 (2.8–12.4)      | 0.0001 |
| Clinical stage <I vs ≥I       | 1.6 (1.2–2.0)              | 0.00032          | 3.2 (1.6–6.4)       | 0.0013 |

### 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.

| Variables                      | 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              | 0.13                         | 0     | 12   | 0.60 |      |
| Sex                           |                            |                |                              |      |
| Female                        | 2                          | 10              | 0.13                         | 0     | 12   | 0.60 |      |
| Male                          | 57                         | 82              | 0.12                         | 12    | 127  |     |      |
| PS                            |                            |                |                              |      |
| 0                             | 51                         | 79              | 0.10                         | 1     | 120  | 0.67 |      |
| ≥1                            | 8                          | 13              | 0.85                         | 4     | 34   | 0.50 |      |
| Pack-year                     |                            |                |                              |      |
| <40                           | 14                         | 24              | 0.65                         | 4     | 34   | 0.50 |      |
| ≥40                           | 45                         | 68              | 0.8                          | 8     | 105  |     |      |
| Clinical stage                |                            |                |                              |      |
| ≤I                            | 38                         | 72              | 0.091                        | 6     | 104  | 0.089 |      |
| II + III vs IV                | 21                         | 20              | 0.6                          | 6     | 35   |     |      |
| %VC                           |                            |                |                              |      |
| <100                          | 36                         | 48              | 0.32                         | 9     | 75   | 0.23 |      |
| ≥100                          | 23                         | 44              | 0.3                          | 6     | 34   | 0.64 |      |
| FEV1.0%                        |                            |                |                              |      |
| <70                           | 30                         | 38              | 0.32                         | 5     | 63   | 1.00 |      |
| ≥70                           | 29                         | 54              | 0.7                          | 7     | 76   |     |      |
| Extension of emphysema        |                            |                |                              |      |
| One lobe                      | 32                         | 55              | 0.51                         | 4     | 83   | 0.13 |      |
| ≥One lobe                     | 27                         | 37              | 0.8                          | 6     | 56   |     |      |
| Severity of fibrosis          |                            |                |                              |      |
| Peripheral                    | 46                         | 73              | 0.84                         | 6     | 113  | 0.021 |      |
| Whole                         | 13                         | 19              | 0.6                          | 6     | 26   |     |      |
| Procedure                     |                            |                |                              |      |
| Limited                        | 4                          | 13              | 0.2                          | 10    | 124  | 0.63 |      |
| Standard                      | 55                         | 79              | 0.5                          | 2     | 15   |     |      |

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

Smoking adversely affects not only lung function but also the cardiovascular system.\[25–31\] 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 current 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.11 Spriometric 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,11,12 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.

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