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Clinical Characteristics and Predictors of Mortality in Patients with Combined Pulmonary Fibrosis and Emphysema Syndrome and Lung Cancer

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Abstract

Rationale: We performed this retrospective study to clarify the clinical characteristics, survival and mortality predictors in patients with combined pulmonary fibrosis and emphysema (CPFE) and lung cancer.

Methods: We retrospectively reviewed the medical records of a total of 123 patients with lung cancer, as confirmed according to histological or cytological examinations. Based on the findings of chest CT, the patients were categorized into four groups: LC+normal (n=70); LC+emphysema (n=26); LC+fibrosis (n=10); LC+CPFE (n=17). The clinical characteristics and survival of the LC+CPFE group were compared with those of the other groups. In addition, mortality predictors were evaluated in the LC+CPFE group.

Results: The proportion of females was significantly higher in the LC+normal group than in the LC+CPFE and LC+emphysema groups. Significantly more patients were diagnosed with squamous cell carcinoma in the LC+CPFE group than in the LC+normal group. The proportion of patients whose primary mass was located in "non-subpleural" areas was significantly higher in patients with CPFE who also had lung cancer in the upper lobe than in those with CPFE who also had lung cancer in the other sites. There were significant differences in survival between the LC+normal group and the other groups, whereas there were no significant differences in survival among the LC+emphysema, LC+fibrosis and LC+CPFE groups. In the LC+CPFE group, the patients with a high level of serum KL-6 at diagnosis and upper lobe lung cancer demonstrated a high risk of death. A high level of serum KL-6 at diagnosis was also independently associated with a high risk of death.

Conclusions: Patients with CPFE and lung cancer may have distinct clinical characteristics. Strict follow-up is required in patients with CPFE and lung cancer whose serum KL-6 level at diagnosis is higher than the normal range and/or the primary mass of lung cancer is located in the upper lobe.

Keywords: CPFE; Emphysema; Pulmonary fibrosis; Lung cancer; KL-6

Introduction

Emphysema and idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis (IPF), are conditions defined by distinct clinical, functional, radiological and pathological characteristics. However, the occurrence of both emphysema and pulmonary fibrosis in the same patient has received increased attention as a syndrome of combined pulmonary fibrosis and emphysema (CPFE) [1-5]. CPFE, which is associated with smoking and has the features of both emphysema and pulmonary fibrosis, may be an independent risk factor for lung cancer. A higher prevalence of lung cancer has been reported in patients with CPFE than in those with emphysema/COPD alone [3,6] or IPF alone [7]. Inversely, the prevalence of CPFE in the lung cancer population has been found to be higher than that of isolated pulmonary fibrosis [8]. Moreover, patients with CPFE and lung cancer have a poorer prognosis than those with emphysema and lung cancer [8]. Nevertheless, it remains unclear whether patients with CPFE and lung cancer have a poorer prognosis than those with IPF and lung cancer, and little is known about mortality predictors in patients with CPFE and lung cancer. A recent matched case-control study revealed that, in addition to lung cancer in IPF patients, lung cancer in CPFE patients occurs more frequently in subpleural areas than does lung cancer in emphysema patients [6]. However, there continues to be a lack of information on the frequency of locations of lung cancer in CPFE patients.

We were interested in the prevalence of CPFE in the lung cancer population, and subsequently performed this retrospective study to clarify the clinical characteristics, survival and mortality predictors in patients with CPFE and lung cancer.

Methods

Subjects

The medical records for a series of all patients with lung cancer, as confirmed according to histological or cytological examinations, who were seen and assessed at Okaya City Hospital between April 2010 and December 2014, were reviewed retrospectively to obtain clinical and demographic data, including age, gender, route of diagnosis, clinical stage of lung cancer, initial treatment for lung cancer and survival. The patients were categorized into four groups: patients with lung cancer who did not have emphysema or fibrosis (LC+normal group); patients with lung cancer who also had emphysema alone (LC+emphysema group); patients with lung cancer who also had fibrosis alone (LC+fibrosis group); patients with lung cancer who also had CPFE (LC+CPFE group). The diagnosis of CPFE, emphysema and fibrosis was made based on imaging criteria as described below. Our institutional review board approved this retrospective study, and provided all necessary ethical permissions.

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Imaging criteria

Emphysema and pulmonary fibrosis were evaluated using chest high resolution computed tomography (HRCT) as previously described [3,9,10]. Briefly, emphysema was scored visually in the bilateral upper, middle and lower lung fields according to the methods of Goddard, et al. [11]. The score for each of the six dimensions was calculated according to the percentage of low attenuation area (%LAA) in each lung field as follows: score 0, %LAA<5%; score 1, 5% ≤ %LAA<25%; score 2, 25% ≤ %LAA<50%; score 3, 50% ≤ %LAA<75%; and score 4, 75% ≤ %LAA. The severity of emphysema was graded in accordance with the sum of the scores of the six dimensions as follows: Grade 0, total score=0; Grade 1, total score=1-6; Grade 2, total score=7-12; Grade 3, total score=13-18; and Grade 4, total score=19-24 [12,13]. The detection of significant pulmonary fibrosis on HRCT, defined as the presence of bulla, honeycombing, reticular opacity, ground-glass opacity, consolidation, traction bronchiectasis, peribronchovascular interstitial thickening and architectural distortion, was performed visually as previously described [1,3,9,10]. The extent of pulmonary fibrosis was scored visually to grade the severity in the LC+CPFE group as previously described [14]. The patients with CPFE were characterized by the coexistence of significant emphysema (Grade 2 or more) and significant pulmonary fibrosis. Meanwhile, the patients with emphysema were characterized by the presence of significant emphysema (Grade 2 or more) without pulmonary fibrosis, and the patients with fibrosis were characterized by the presence of significant pulmonary fibrosis without significant emphysema (none or Grade1).

The locations of the lung cancer were also reviewed on chest HRCT and categorized into three subgroups based on the location of the primary mass as previously described [6]. If the distance between the primary mass and visceral pleura was less than 1 cm, the primary mass was located in "subpleural" areas. If the distance was greater than 1 cm, the primary mass was located in "non-subpleural" areas. If several masses were detected and the distribution was diverse, or the primary mass was too large to determine the area in which it was located, the locations of these masses were considered to be "not differentiated". In order to investigate the predominant location of the primary mass, the patients were also divided into two groups: patients with lung cancer in the upper lobe (Upper lobe lung cancer group); and patients with lung cancer in the other sites (Other sites lung cancer group). In addition, the locations of the lung cancer were categorized into "non-emphysematous area" or "emphysematous area" and into "non-fibrotic area" or "fibrotic area". Moreover, the locations of the lung cancer in "fibrotic area" were also subcategorized into "in-fibrotic area" (in the midst of fibrosis) or "fibrotic junction area" (interface between normal lung and fibrosis).

The CT images were reviewed independently by two pulmonologists (Y.K. and K.F.) with no knowledge of the patients' clinical information. The intra-observer reproducibility of visual scoring was tested by one observer (Y.K.), and the inter-observer reproducibility of visual scoring was determined by two observer (Y.K. and K.F.) in the same way as described in our previous report [13]. The rates of concordance in both intra-observer and inter-observer were more than 90%. In addition, the diagnosis of CPFE, emphysema or fibrosis required a consensus among the reviewers. The other pulmonologists (J.H. and S.H.) selected subjects.

Data analysis

The data are presented as the mean ± standard error or ratios with percentages as appropriate. The Chi-square and Fisher's exact tests were used for comparisons of categorical variables, and an analysis of variance (ANOVA) and Kruskal-Wallis test were used for comparisons of continuous variables among the four groups. The survival was estimated using the Kaplan-Meier method in each group, and differences between the four groups were compared using the log-rank test. In the LC+CPFE group, a univariate Cox proportional hazards regression analysis followed by a multivariate analysis were used to identify risk factors for mortality. Variables with P-value less than 0.15 in the univariate analyses were considered for inclusion in the multivariate model. All statistical analyses were performed using a Windows-compatible software program (StatFlex version 6; Artech Co., Ltd., Osaka, Japan). Variables with P-values less than 0.05 were considered to be significant in all statistical analyses.

Results

Figure 1 shows a flow diagram of subject selection and exclusion. A total of 150 patients were suspected of having lung cancer on chest HRCT. Twenty-seven of these patients were excluded from the study because of insufficient pathologic evidence to support a clinical diagnosis of lung cancer. Data for the remaining 123 patients with lung cancer were reviewed. Seventeen (13.8%) of these 123 patients had CPFE (LC+CPFE group, n=17), 26 patients had emphysema alone (LC+emphysema group, n=26) and 10 patients had fibrosis alone (LC+fibrosis group, n=10). The remainder of the 123 patients did not have either emphysema or fibrosis (LC+normal group, n=70).

Table 1 shows the clinical characteristics of the four groups. The proportion of females was significantly higher in the LC+normal group than in the LC+CPFE and LC+emphysema groups. There were no significant differences in the route of diagnosis among the four groups. Significantly more patients were diagnosed with squamous cell carcinoma and fewer patients were diagnosed with adenocarcinoma in the LC+CPFE group than in the LC+normal group. There were no significant differences in the clinical stage of non-small cell lung cancer (NSCLC), initial treatment for lung cancer or primary site of lung cancer between the four groups. In the LC+CPFE group, the primary mass of lung cancer was located in the upper lobe in seven of 17 patients. The proportion of patients whose primary mass was located in "non-subpleural" areas was significantly higher in patients with CPFE who also had lung cancer in the upper lobe than in those with CPFE who also had lung cancer in the other sites. In the LC+CPFE

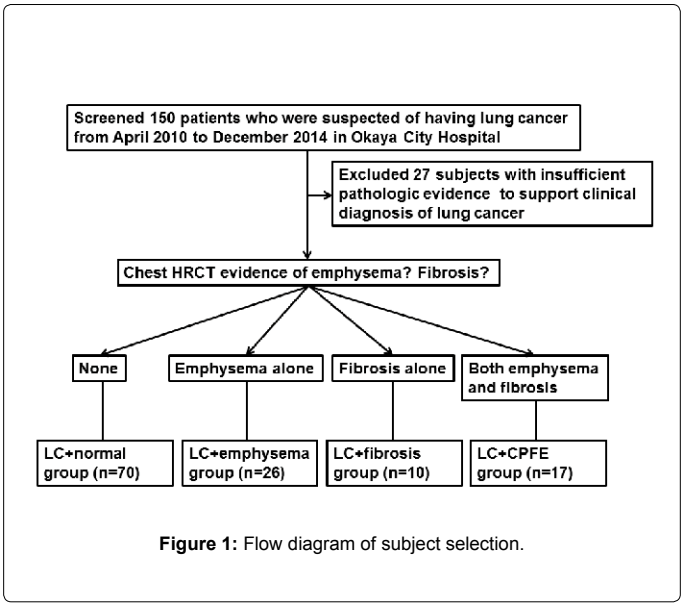

Figure 1: Flow diagram of subject selection.

	LC+normal (n=70)	LC+emphysema (n=26)	LC+fibrosis (n=10)	LC+CPFE (n=17)
Age, years old	72.5 ± 1.5	78.8 ± 2.0	73.8 ± 2.1	73.9 ± 1.9
Gender, female/male	31/39	3/23 *	1/9	1/16 *
Route of diagnosis, n(%)				
Screening, incidental	46 (65.7%)	15 (57.7%)	4 (40.0%)	10 (58.8%)
Symptoms	24 (34.3%)	11 (42.3%)	6 (60.0%)	7 (41.2%)
Histology of lung cancer, n(%)				
Small cell carcinoma	5 (7.1%)	3 (11.5%)	2 (20.0%)	1 (5.9%)
Squamous cell carcinoma	11 (15.7%)	10 (38.5%)	4 (40.0%)	10 (58.8%) **
Adenocarcinoma	50 (71.4%)	11 (42.3%)	4 (40.0%)	5 (29.4%) *
Large cell carcinoma	3 (4.3%)	2 (7.7%)	0 (0.0%)	0 (0.0%)
Other non-small cell carcinoma	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (5.9%)
Clinical stage of non-small cell lung cancer, n(%)				
Stage ⅠA,B	31 (47.7%)	5 (21.7%)	1 (12.5%)	6 (37.5%)
Stage ⅡA,B	5 (7.7%)	5 (21.7%)	1 (12.5%)	5 (31.3%)
Stage ⅢA,B	7 (10.8%)	3 (13.0%)	1 (12.5%)	3 (18.8%)
StageⅣ	22 (33.8%)	10 (43.5%)	5 (62.5%)	2 (12.5%)
Advanced stage(ⅢB, Ⅳ)	27 (41.5%)	11 (47.8%)	5 (62.5%)	5 (31.3%)
Clinical stage of small cell lung cancer, n(%)				
Limited disease	3 (60.0%)	2 (66.7%)	1 (50.0%)	1 (100.0%)
Extended disease	2 (40.0%)	1 (33.3%)	1 (50.0%)	0 (0.0%)
Initial treatment for lung cancer, n(%)				
Surgery	40 (57.1%)	8 (30.8%)	3 (30.0%)	8 (47.1%)
Chemotherapy	15 (21.4%)	7 (26.9%)	2 (20.0%)	7 (41.2%)
Radiation	4 (5.7%)	1 (3.8%)	0 (0.0%)	0 (0.0%)
Best supportive care	14 (20.0%)	10 (38.5%)	5 (50.0%)	2 (11.8%)
Primary site of lung cancer, n(%)				
Right upper lobe	21 (30.0%)	5 (19.2%)	3 (30.0%)	3 (17.6%)
Right middle lobe	3 (4.3%)	1 (3.8%)	2 (20.0%)	0 (0.0%)
Right lower lobe	25 (35.7%)	12 (46.2%)	0 (0.0%)	6 (35.3%)
Right hilum	1 (1.4%)	2 (7.7%)	0 (0.0%)	0 (0.0%)
Left upper lobe	9 (12.9%)	3 (11.5%)	3 (30.0%)	4 (23.5%)
Left lower lobe	10 (14.3%)	3 (11.5%)	2 (20.0%)	4 (23.5%)
Left hilum	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Location of primary mass, n(%)				
Upper lobe	30	8	6	7
Non-subpleural	21 (70.0%)	4 (50.0%)	2 (33.3%)	5 (71.4%)†
Subpleural	9 (30.0%)	3 (37.5%)	3 (50.0%)	2 (28.8%)‡
Not-differentiated	0 (0.0%)	1 (12.5%)	1 (16.7%)	0 (0.0%)
Other sites	40	18	4	10
Non-subpleural	20 (50.0%)	7 (38.9%)	2 (50.0%)	2 (20.0%)
Subpleural	16 (40.0%)	10 (55.6%)	2 (50.0%)	8 (80.0%)
Not-differentiated	4 (10.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)
Non-emphysematous area	N/A	2 (7.7%)	N/A	4 (23.5%)
Emphysematous area	N/A	24 (92.3%)	N/A	13 (76.5%)
Non-fibrotic area	N/A	N/A	3 (30.0%)	4 (23.5%)
Fibrotic area	N/A	N/A	7 (70.0%)	13 (76.5%)
In-fibrotic area	N/A	N/A	0 (0.0%)	4 (30.8%)
Fibrotic junction area	N/A	N/A	7 (100.0%)	9 (69.2%)

*p<0.05 vs. LC+normal; **p<0.01 vs. LC+normal; †p<0.05 vs. Other sites-Non-subpleural; ‡p<0.05 vs. Other sites-Subpleural. N/A: Not Applicable

Table 1: Clinical characteristics of the four groups.

group, the primary mass of lung cancer was located in an area with mixed emphysema and fibrosis on chest HRCT in eleven of 17 patients. The proportion of patients whose primary mass was located in "non-emphysematous area" or "in-fibrotic area" tended to be higher in the LC+CPFE group compared to the other groups, whereas there were no significant differences.

According to the Kaplan-Meier analysis, the log-rank test showed significant differences in the survival between the LC+normal group and the other groups (Figure 2). However, there were no significant differences in survival among the LC+emphysema, LC+fibrosis and LC+CPFE groups (Figure 2). The univariate Cox proportional hazards regression analysis showed that a high level of serum Krebs von den Lungen-6 (KL-6) at diagnosis (HR 11.35, p=0.0233) and upper lobe lung cancer (HR=4.22, p=0.0399) were associated with a high risk of death in the LC+CPFE group (Table 2). Interestingly, a high severity

of fibrosis, emphysema or NSCLC was not associated with a high risk of death (Table 2). The presence of lung cancer in the upper lobe, the presence of lung cancer in the subpleural area, and a high level of serum KL-6 or serum lactate dehydrogenase (LD) at diagnosis were included in the multivariate analysis, which showed that a high level of serum KL-6 at diagnosis (HR=12.47, p=0.0339) was independently associated with a high risk of death (Table 3). There were no significant differences in the clinical stage of NSCLC between the patients with CPFE who also had lung cancer in the upper lobe and the patients with CPFE who also had lung cancer in the other sites, or between the patients with and without a high level of serum KL-6 at diagnosis.

Discussion

We retrospectively investigated the characteristics of patients with CPFE compared to those of patients with emphysema or fibrosis alone in the lung cancer population. Consequently, we found that the primary mass of lung cancer was located in the upper lobe in seven of the 17 patients with CPFE and lung cancer. In five of these seven patients, the lesions were also located in "non-subpleural" areas. Moreover, upper lobe lung cancer was found to be associated with a high risk of death only in the LC+CPFE group. In addition, there were significant differences in survival between the LC+normal group and the other groups, whereas there were no significant differences in survival among the LC+emphysema, LC+fibrosis and LC+CPFE groups. In the LC+CPFE group, the patients with a high level of serum KL-6 at diagnosis and upper lobe lung cancer demonstrated a high risk of death. In contrast, a high severity of fibrosis, emphysema or NSCLC was not associated with a high risk of death. A high level of serum KL-6 at diagnosis was also independently associated with a high risk of death.

Okaya City Hospital is the only public hospital in Okaya. This facility has 300 beds and provides acute care facilities for the residents of Okaya city in Nagano prefecture, population 50,000. Each year, the hospital treats a cumulative total of over 4,000 inpatients and over 150,000 outpatients. The hospital does not have equipment for radiation therapy or lung surgery. As a result, no patients with lung cancer are referred from hospitals in other areas, and almost all patients with lung cancer who live in this area are seen and assessed at this hospital, which results in minimal selection bias at entry. Seventeen of the 123 patients with lung cancer (13.8%) in the present study also had CPFE. On the other hand, a previous study reported that 101 of 1143 patients with lung cancer (8.9%) also had CPFE [8]. The differences in these results may be due to the differences in patient selection and imaging criteria for emphysema as discussed below. In addition, the inclusion of a smaller number of patients in the present study may have affected the results.

A previous study demonstrated that patients with CPFE and lung cancer have a poorer prognosis than those with emphysema and lung cancer [8]. In the present study, there were no significant differences

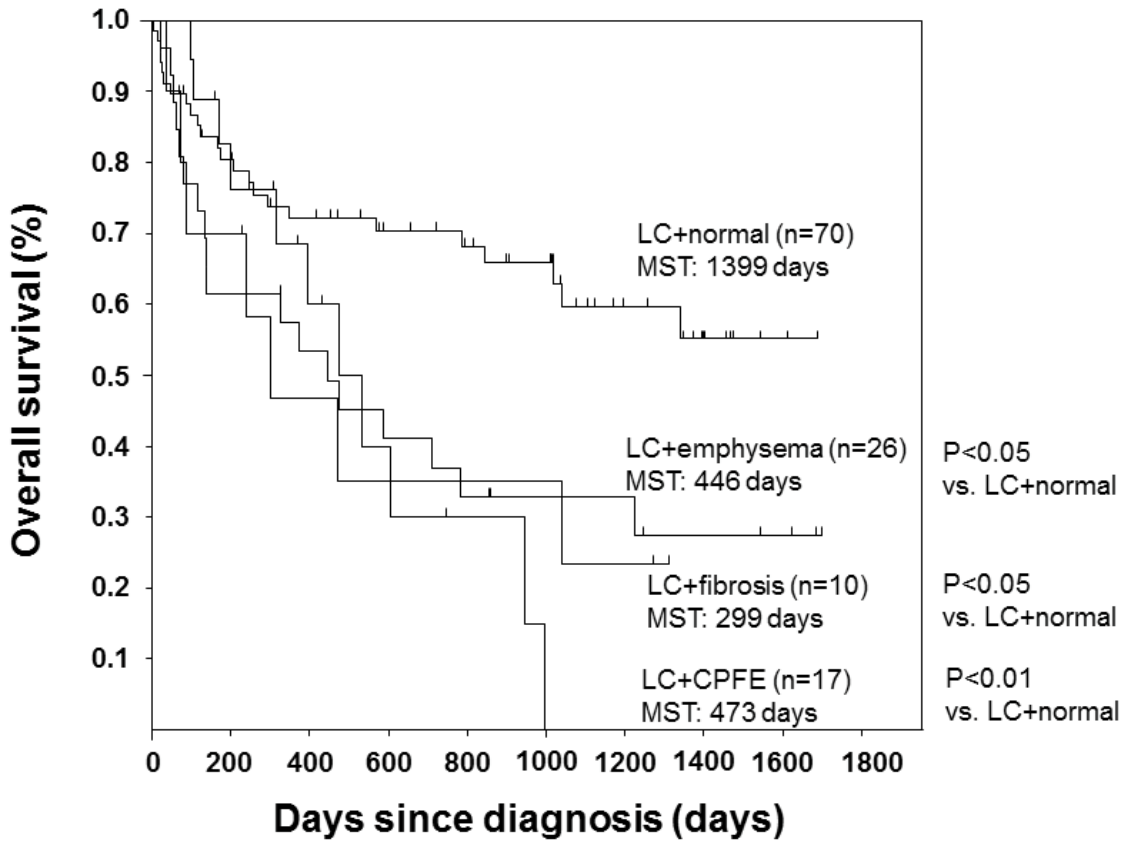

Figure 2: Survival estimated using the Kaplan-Meier method in each group.Differences of the survival were compared using the log-rank test among the four groups. MST, median survival time.

Variable	n	HR	95% CI	p-value
Age years	17	0.95	0.87-1.04	0.2928
Severity of pulmonary fibrosis Minimum, Moderate and Severe	17	0.85	0.40-1.79	0.6681
Severity of emphysema (LAA grade) Grade 1-4	17	0.89	0.50-1.59	0.693
Clinical stage of NSCLC Stage 1-4	16	1.41	0.81-2.45	0.2195
Primary site of lung cancer Upper lobe	17	4.22	1.07-16.66	0.0399
Location of primary mass Subpleural area	17	0.32	0.08-1.26	0.1041
Serum KL-6 at diagnosis higher than the normal range (≥500 U/ml)	17	11.35	1.39-92.56	0.0233
Serum LD at diagnosis higher than the normal range (>230 IU/l)	17	2.72	0.76-9.77	0.1239

LAA: Low Attenuation Areas; NSCLC: Non-Small Cell Lung Cancer; KL-6: Krebs von den Lungen-6; LD: Lactate Dehydrogenase; LD: Lactate Dehydrogenase; HR: Hazard Ratio; CI: Confidence Interval.

Table 2: Univariate Cox proportional hazards regression analysis for the risk of death in the LC+CPFE group.

Variable	n	HR	95% CI	p-value
Primary site of lung cancer Upper lobe	17	3.21	0.23-43.81	0.3827
Location of primary mass Subpleural area	17	4.17	0.30-57.22	0.2847
Serum KL-6 at diagnosis higher than the normal range (≥500 U/ml)	17	12.47	1.21-128.36	0.0339
Serum LD at diagnosis higher than the normal range (>230 IU/l)	17	1.81	0.18-17.97	0.611

KL-6: Krebs von den Lungen-6; LD: Lactate Dehydrogenase; HR: Hazard Ratio; CI: Confidence Interval.

Table 3: Multivariate Cox proportional hazards regression analysis for the risk of death in the LC+CPFE group.

in survival between the LC+CPFE and LC+emphysema groups. The differences in these results may be due to the differences in the imaging criteria for emphysema. In the current study, emphysema in the LC+CPFE and LC+emphysema groups was defined as the presence of significant emphysema of Grade 2 or more as previously described [3,9,10] and patients with little emphysema of Grade 1 were not categorized into these groups. In contrast, the extent of emphysema was not measured in the previous study [8]. Therefore, the proportion of patients with severe emphysema is likely higher in the present study versus the previous study [8]. A specific clinical diagnosis and classified criteria for CPFE must be established. In addition, the shorter duration of follow-up in the present study may have affected the results.

KL-6 is a high-molecular-weight glycoprotein classified as "Cluster 9 (MUC1)" for lung tumors and differentiation antigens according to the findings of immunohistochemical and flow cytometry studies [15,16]. KL-6 has been reported to serve as a sensitive serum marker for interstitial pneumonia [17,18] and is currently clinically used to detect the presence of interstitial pneumonia in Japan. However, previous studies have suggested that this parameter can also be used as a tumor marker, as its origin indicates [19]. Elevated circulating KL-6 levels are frequently observed in patients with NSCLC, pancreatic cancer and breast cancer [19-21]. In the present study, a high severity of fibrosis and NSCLC was not associated with a high risk of death in the LC+CPFE group. These findings suggest that a high level of serum KL-6 at diagnosis may be associated with survival in patients with CPFE and NSCLC regardless of the severity of pulmonary fibrosis and NSCLC. On the other hand, Kishaba et al. reported that the baseline serum KL-6 level is a useful predictor of acute exacerbation (cut-off=1050, receiver operator characteristic curve: 0.7720), which occurs in 24% of the CPFE patients [22]. In the present study, only one of the 17 patients in the LC+CPFE group died of acute exacerbation 105 days after diagnosis and showed a high level of serum KL-6 at diagnosis (1,124 U/ml). There is a possibility that acute exacerbation is associated with a high risk of death in patients with CPFE and lung cancer, although a previous study reported that significantly fewer patients with CPFE died of acute exacerbation than did patients with IPF [14].

Our findings showed that upper lobe lung cancer was predominantly located in "non-subpleural" areas in the LC+CPFE group. In contrast, other sites lung cancer was predominantly located in "subpleural" areas. Previous studies have reported peripheral and lower lobe dominancy in lung cancer development in case of IPF [23,24]. Lung cancer is known to occur frequently in the upper lung in patients with emphysema [25,26]. Kwak et al. reported that lung cancer in CPFE and IPF subjects is predominantly located in "subpleural" areas, and that the similarity of the location of lung cancer in CPFE and IPF patients suggests that emphysema may not have an additive impact on the development of lung cancer in the setting of CPFE [6], although the authors did not categorize the primary site of lung cancer into the upper lobe versus other sites. The exact cause of the difference in the location of the primary mass between their and the current study is not clear. However, we assume that carcinogenesis may occur in the upper lobe in patients with CPFE because of emphysema and that the heterogeneity of CPFE, in which emphysema in the upper lobe coexists with pulmonary fibrosis in the lower lobe, may result in different clinical courses and outcomes between patients with CPFE with upper lobe lung cancer compared to lower lobe lung cancer. In addition, the proportion of patients whose primary mass was located in "non-emphysematous area" or "in-fibrotic area" tended to be higher in the LC+CPFE group compared to the other groups, suggesting that CPFE has different regional susceptibility to lung cancer development.

There are several limitations associated with the present study. First, this was a single-center, uncontrolled design retrospective study with a

lack of statistical power, as the sample size was small in the LC+fibrosis group (n=10). Additional prospective studies with larger sample sizes are required to confirm the present results. Second, the assessment of emphysema on chest HRCT was performed according to a visual scoring method, rather than software-based quantification of the degree of emphysema. However, the reproducibility of visual scoring was demonstrated in our previous report [13]. In addition, we did not measure the exact areas of fibrosis on chest HRCT. Instead, the extent of fibrosis on chest HRCT was assessed semi-quantitatively as previously described [14], because it is difficult to determine the extent of fibrosis in the upper regions of the lungs when mixed emphysema and fibrosis are present.

In conclusion, patients with CPFE and lung cancer may have distinct clinical characteristics. In the current study, there were no significant differences in survival between the patients who also had emphysema, fibrosis and CPFE in the lung cancer population. However, strict follow-up is required in patients with CPFE and lung cancer whose serum KL-6 level at diagnosis is higher than the normal range and/or the primary mass of lung cancer is located in the upper lobe.

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