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Impact and prognosis of lung cancer in patients with combined pulmonary fibrosis and emphysema

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Abstract. *Background*: Combined pulmonary fibrosis and emphysema (CPFE) is frequently associated with lung cancer. However, the impact and outcomes of lung cancer in patients with CPFE are unclear. *Objective:* We investigated the impact of lung cancer in patients with CPFE in terms of acute exacerbation (AE) and mortality, and identified the mortality predictors of patients with CPFE and lung cancer. *Methods*: We retrospectively reviewed 12-year medical records of patients at the Korea University Guro Hospital. Based on computed tomography findings, we selected CPFE patients with and without lung cancer, and analyzed age, sex, smoking status and history, body mass index, past medical history, pulmonary function, the gender, age, and physiology (GAP) score, AE, and mortality. *Results*: Of 227 CPFE patients, 61 were diagnosed with lung cancer. While 10 of the 61 patients experienced AE, 41 died during the observation period. Lung cancer was a significant predictor of AE (hazard ratio [HR] 3.27, 95% confidence interval [CI]1.44–7.43, $P<0.01$) and mortality (HR 4.74, 95% CI 2.55–8.81, $P<0.01$) in CPFE patients. AE, rather than age, GAP score, or lung cancer stage, was the most significant factor associated with mortality in patients with CPFE and lung cancer (HR 9.20, 95% CI 1.13–74.70, $P=0.04$). *Conclusions*: Lung cancer has a significant impact on the outcomes of CPFE and is associated with severe complications. AE was the most important mortality predictor in patients with lung cancer combined with CPFE. Therefore, the diagnosis and treatment of lung cancer should be carefully planned in patients with CPFE. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (4): e2020020)*

Key words: combined pulmonary fibrosis and emphysema, exacerbation, lung cancer, mortality, outcome

Introduction

Lung cancer is the most frequently diagnosed cancer with an increasing prevalence and mortality rate (1). Combined pulmonary fibrosis and emphysema (CPFE) has become an individualized distinct disease consisting of upper lobe predominant emphysema and lower lobe predominant fibrosis, and is characterized by a heavy smoking history (2,3,4). Emphysema and idiopathic pulmonary fibrosis (IPF) are risk factors for lung cancer (5). CPFE, which is associated with smoking, has features of both IPF and emphysema, and could, therefore, be an independent risk factor for lung cancer (6,7). Kitaguchi et al. reported a higher risk of developing lung cancer in CPFE than in chronic obstructive pulmonary disease (COPD) (46.8% vs. 7.3%) (8). Moreover, another recent study also reported a higher incidence of lung cancer in patients with CPFE than in those with IPF (50% vs. 14.5%) (9). The development of lung cancer

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in IPF is associated with poor survival and is associated with an increased incidence of severe complications (10).

In patients with lung cancer, concomitant pulmonary fibrosis and emphysema might be related to poorer survival. It has recently been reported that acute exacerbation (AE) risk is higher in patients with CPFE and lung cancer than in those with IPF and lung cancer(11). Despite the higher incidence of lung cancer and AE risk in CPFE patients, its clinical features, outcomes, and prognosis in these patients remain unclear.

It is important to understand the impact and outcomes of lung cancer in CPFE patients to establish a diagnostic and treatment plan. Therefore, we investigated the outcomes and prognosis of lung cancer in CPFE patients regarding AE and mortality. Furthermore, we aimed to identify mortality predictors in patients with both CPFE and lung cancer.

Materials and methods

Study population and assessment

We retrospectively reviewed the medical records and computed tomography (CT) scans of patients admitted to the Korea University Guro Hospital, Seoul, Korea, from January 1, 2004 to December 30, 2016. Patients were diagnosed with CPFE when criteria for both emphysema and pulmonary fibrosis were met. Emphysema was defined as the presence of well-demarcated areas of decreased attenuation marginated by a very thin (< 1 mm) or no wall, and/or multiple bullae (> 1 cm) with upper zone predominance. Pulmonary fibrosis included reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion, and/or traction bronchiectasis. Diagnosis was confirmed by multidisciplinary discussion of specialists in pulmonology, radiology, and pathology. We excluded patients who (i) did not have CT images and pulmonary function testing and (ii) had occupational interstitial lung disease.

Outcomes and variables measured

AE was defined as a sudden aggravation of dyspnea within 30 days of presentation with new bilateral lung infiltration with no evidence of pulmonary infection or other known causes of worsening respiratory function (12). Baseline clinical parameters were obtained within one month of the initial diagnosis of CPFE. Demographic and clinical data including age, gender, smoking history, body mass index (BMI), comorbidities, and pulmonary function test results, were obtained. For the pulmonary function test, we checked physiological data including the forced vital capacity volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, total lung capacity (TLC), and diffusing capacity of carbon monoxide (DL_{CO}) at baseline and at one year according to the American Thoracic Society/European Respiratory Society recommendations. The results were expressed as percentages of the normal predicted values. The gender, age, and physiology (GAP) score was calculated using the method described by Ley et al.(13) Data on the histopathological type, stage of disease, treatment regimen, and outcomes were collected for patients with lung cancer. Survival time was defined as the time interval between the date of first diagnosis to death or the last follow-up. AE-free time was defined as the time interval between the date of first diagnosis to AE or the last follow-up.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables or as percentages for categorical variables. The chi-square and Fisher's exact tests were used for categorical data, and the unpaired t-test and Mann-Whitney U-test were used for continuous data. Univariate Cox proportional hazards models were used to examine the association of selected variables with AE and survival. The multivariate Cox proportional hazards model using the backward elimination method was used for variables found to be significant ($P < 0.1$) in the univariate model. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS v. 20.0 software (IBM, Chicago, Illinois, USA).

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of the Korea University Guro Hospital (2015GR0150).

Results

Patient baseline characteristics

During the screening period, we identified 5118 patients with emphysema and 1134 patients with pulmonary fibrosis. Of these, 458 patients had both emphysema and pulmonary fibrosis. After a final review based on chest CT findings, 227 CPFE patients were analyzed. The mean age of patients with CPFE was 69.4 years, with a mean BMI of 23.1; 96% of them were men. All patients had a history of smoking (mean: 43.2 pack-years). The mean baseline FEV_1 was 83.0%, mean FVC was 85.2%, and mean FEV_1/FVC was 69.0%. The mean DL_{CO} was 59.3% and the mean GAP score was 3.4. During the observation period, 31 (13.7%) patients experienced AE, 61 (26.9%) were diagnosed with lung cancer, and 60 (26.4%) patients died. Patients with lung cancer were significantly older than those without lung cancer. The baseline characteristics of the patients with and without lung cancer are summarized in Table 1.

Incidence of lung cancer

Lung cancer was identified in 61 patients. Figure 1 shows the cumulative incidence curve of lung cancer in patients with CPFE.

Type, staging, and treatment of lung cancer

The most common histological type of lung cancer was squamous cell carcinoma (n = 32, 52.5%). Fourteen patients had adenocarcinoma, and 12 had small cell carcinoma. Three patients had poorly differentiated carcinoma that could not be classified elsewhere. Table 2 summarizes the staging of cancer and the treatment modalities offered for the study patients.

Table 1. Demographic and clinical characteristics of patients with CPFE, with and without lung cancer

	CPFE with Lung Cancer (n = 61)	CPFE alone (n = 166)	*P*-value
Age, years	71.5±6.7	68.6±9.0	0.02
Male sex	60 (98.4)	158 (95.2)	0.28
Smoking			0.46
Ex-smoker	0 (0)	4 (2.4)	
Current smoker	32 (52.5)	82 (49.4)	
Pack-years of smoking	46.5±19.4	42.0±21.0	0.15
BMI, kg/m^2	23.3±3.3	23.1±3.1	0.70
Paraseptal emphysema	9 (14.8)	38 (22.9)	0.18
Pulmonary function test, % predicted			
FVC	84.8±15.9	84.3±18.4	0.84
FEV_1	83.7±18.1	82.8±19.0	0.74
FEV_1/FVC	68.6±12.6	69.2±13.1	0.79
TLC	95.3±16.6	99.0±17.7	0.19
DL_{CO}	60.0±18.7	59.0±18.8	0.74
GAP score	3.6±1.1	3.3±1.3	0.11
AE	10 (16.4)	21 (12.7)	< 0.01

Data are presented as mean ± standard deviation or number (percentage).
CPFE, combined pulmonary fibrosis and emphysema; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced vital capacity volume in one second; TLC, total lung capacity; DL_{CO}, diffusing capacity of carbon monoxide; GAP, gender, age, and physiology; AE, acute exacerbation.

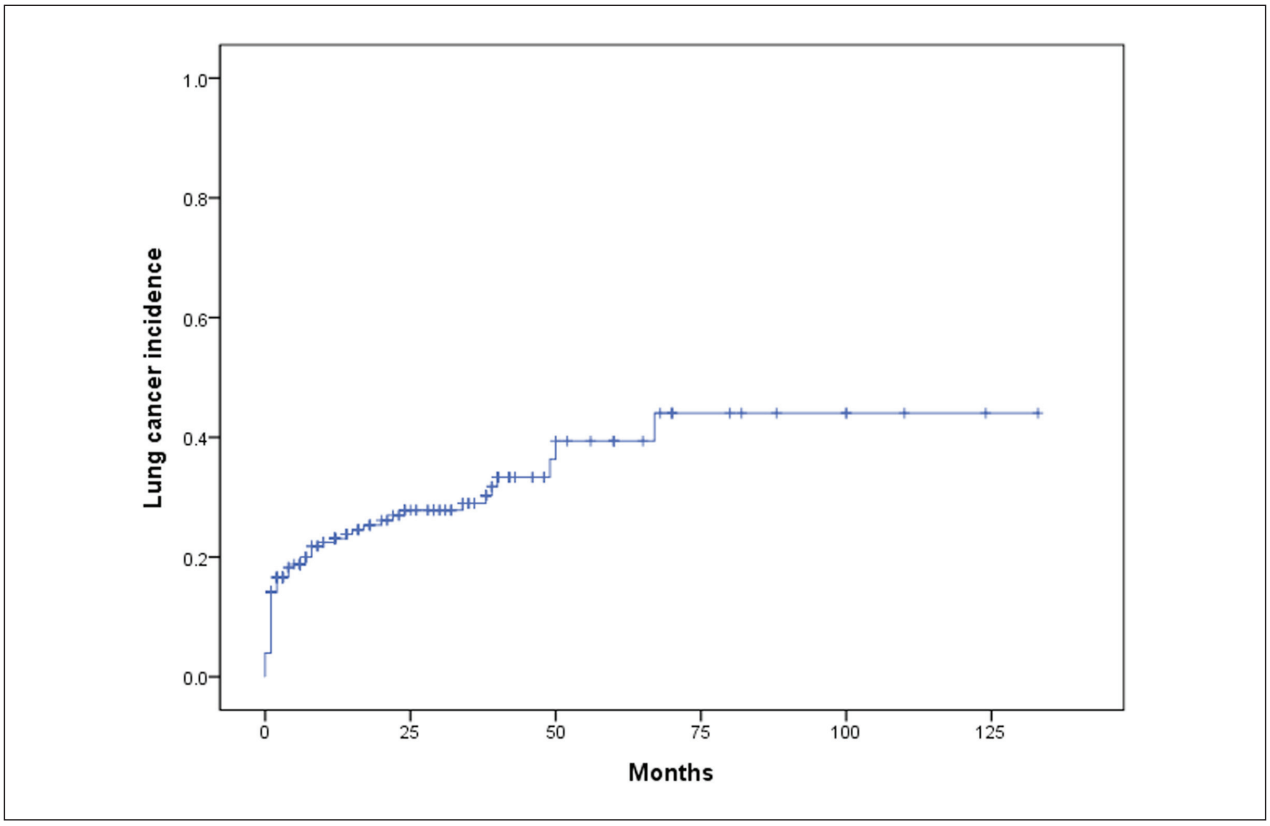

Fig. 1. Cumulative incidence curve of lung cancer in patients with combined pulmonary fibrosis and emphysema Kaplan-Meier analysis revealed that the cumulative incidence of lung cancer at 1 year and 5 years was 21.1% and 26.4%, respectively.

Incidence of AE and impact of lung cancer on AE

Of the 61 lung cancer patients, 10 experienced AE. The estimated median AE-free interval was 96.0 months [95% confidence interval (CI) 55.1–136.9] in patients without lung cancer and 26.0 months (95% CI 2.2–49.9) in patients with lung cancer.

Among the 10 patients who experienced AE, it occurred at 10 days, 4 months and 5 months after lobectomy in three patients. Another patient who underwent lobectomy had a recurrence 8 months later and experienced AE. AE occurred in a patient one month after receiving docetaxel chemotherapy, while it developed in another patient 6 weeks after chemotherapy with erlotinib. Two other patients had AE while receiving supportive care after chemotherapy. AE occurred while being evaluated for recurrence 7 years after lobectomy and adjuvant chemotherapy in one patient and after pericardiocentesis for malignant pericardial effusion in another. On multivariate analysis, lung cancer [hazard ratio (HR) 3.27, 95% CI 1.44–7.43, $P < 0.01$] was found to be a significant predictor of AE after adjusting for significant variables ($P < 0.1$) on univariate analysis (age, presence of lung cancer, FVC, and the GAP score).

Incidence and impact of lung cancer in mortality

Among the 61 patients with lung cancer, 41 died during the study period. The estimated median survival was 96.0 months (95% CI 55.1–136.9) in patients without and 26 months (95% CI 2.2–49.9) in patients with lung cancer.

The causes of death included AE in nine (22.0%) patients, respiratory infections in 20 (48.8%), cancer progression in eight (19.5%), heart failure in one (2.4%), and progression of cancer at a different site in one patient (2.4%). While one (2.4%) patient died on arrival at the hospital, another (2.4%) died after an intracranial surgery for brain metastasis from lung cancer.

Among CPFE patients, lung cancer (HR 4.74, 95% CI 2.55–8.81, $P < 0.01$) was a significant pre-

Table 2. Incidence of AE and mortality in patients with both CPFE and lung cancer according to stage and treatment

	Total (n = 61)	AE (n = 10)	Mortality (n = 41)
Stage			
I	18	3	10
II	6	1	2
III	12	3	9
IV	24	3	20
Unknown	1	0	0
Treatment			
Chemotherapy	23	5	18
Surgery	17	3	10
Radiation	2	0	1
Best supportive care	11	0	8
Surgery + adjuvant chemotherapy	6	2	3
Concurrent chemoradiation	1	0	1
Unknown	1	0	0

AE, acute exacerbation; CPFE, combined pulmonary fibrosis and emphysema.

dictor of mortality after adjusting for factors that were significant ($P < 0.1$) in univariate analysis (presence of lung cancer, FVC, GAP score, and presence of AE).

AE as a mortality predictor in patients with CPFE and lung cancer

Among patients with CPFE and lung cancer, analysis using the multivariate Cox proportional hazards model revealed that AE was a significant predictor of mortality (HR 9.20, 95% CI 1.13–74.70, $P = 0.04$) after adjusting for age, GAP score, and lung cancer stage (Table 3).

Discussion

Our findings indicate that lung cancer is the most significant predictor of poor outcomes, including AE and mortality, in patients with CPFE. AE rather than lung cancer stage was the most significant factor associated with mortality in patients with CPFE and lung cancer.

As a consequence of smoking, lung cancer is common in CPFE, especially among elderly male patients who are heavy smokers. Previous reports have shown that the most common type of lung cancer is squamous cell carcinoma (14-16). Our results are consistent with these reports. The incidence of lung cancer is reported to be 22.4–31.3% in patients with IPF and 6.8–10.8% in patients with COPD (6). Previous studies have shown that CPFE, which has features of both IPF and emphysema, is a more significant risk factor for lung cancer (35.8–46.8%) because of the "triple hit" effect of smoking, emphysema, and pulmonary fibrosis (10). There was a high incidence of lung cancer in patients with CPFE in our study (26.9%), although this is lower than previously reported. The high incidence of lung cancer in CPFE drives the need to evaluate its impact and outcomes in these patients.

Compared to emphysema or fibrosis alone, CPFE has been reported to be a worse prognostic factor for lung cancer (17,18). Usui et al. reported that among patients with lung cancer, those with CPFE had a significantly lower median overall survival and a higher incidence of acute lung injury than

Table 3. Mortality predictors in patients with CPFE and lung cancer

Parameters	HR	95% CI	*P*-value
Multivariate Cox analysis			
Age	0.97	0.73-3.94	0.22
GAP score	1.12	0.79-1.57	0.53
Lung cancer stage			
Stage I–II	ref		
Stage III–IV	1.70	0.73-3.94	0.22
AE	9.20	1.13-74.70	0.04

CPFE, combined pulmonary fibrosis and emphysema; HR, Hazard ratio; CI, confidence interval; GAP, gender, age and physiology; AE, acute exacerbation.

those with emphysema or fibrosis alone (17). CPFE was also a significant, unfavorable prognostic factor in patients with lung cancer after curative resection when compared to patients without CPFE (disease-free survival, HR 2.52; 95% CI 1.24–5.13; $P = 0.01$; overall survival, HR 4.53; 95% CI 1.91–10.70; $P < 0.01$) (18).

Lung cancer is independently associated with a poor prognosis in patients with CPFE. In our study, we found that patients with lung cancer and CPFE have a poor prognosis regarding AE and mortality. These patients had a poor survival comparable to that of lung cancer with IPF (10). Our findings are in line with those of previous studies (11,18-20). In a recent meta-analysis, lung cancer patients with CPFE had a higher 30-day mortality [OR (Odds ratio) 4.72, 95% CI 2.06–10.85, $P < 0.01$], 90-day mortality (OR 5.33; 95% CI 1.39–20.42, $P = 0.01$), and incidence of postoperative complications (OR 5.25, 95% CI 2.38–11.57, $P < 0.01$) (21). Even patients who underwent complete resection at an earlier stage of the disease and had good pulmonary function had a poor postoperative prognosis (18-20). In our study, we confirmed that patients with early stage (I–II) (AE; 16.7%, mortality; 50.0%) and advanced stage (III–IV) lung cancer showed a high incidence of AE (AE; 16.7%, mortality; 80.6%), thereby implying that lung cancer and complications from related procedures have a significant adverse impact on prognosis.

We also found that lung cancer-related mortality was influenced most by AE rather than by cancer stage or lung function. The presence of AE is a well-known risk factor for mortality in both COPD and IPF (22-25). Hata et al. reported that CPFE patients with lung cancer who undergo surgery are at risk of death due to respiratory failure caused by bacterial infection or AE (26). Otsuka et al. reported that among 23 patients with lung cancer and CPFE who underwent surgery, three developed postoperative AEs, which did not affect survival. This could be due to the small sample size of the study (27). However, in our study, we found that survival was significantly affected in patients with lung cancer who underwent procedures or chemotherapy-related AEs. Patients with CPFE often have severe dyspnea and poor cardiopulmonary reserve, and many cannot tolerate invasive procedures (6). Patients with CPFE who are diagnosed with lung cancer often undergo invasive procedures and therapies. These treatment modalities, including surgery, radiation, and chemotherapy, can result in iatrogenic complications and cause mortality. Therefore, procedures and other treatment modalities for CPFE patients with lung cancer should not be as aggressive as for lung cancer patients without CPFE.

Our study has some limitations. Being a retrospective cohort study from a single center, prospective validation is required. However, we believe this study is meaningful because it emphasizes the importance of lung cancer in CPFE and the impact of AE in lung cancer patients with CPFE.

Conclusions

The results of this study suggest that in patients with CPFE, lung cancer is the most significant predictor of poor outcomes, including AE and mortality. AE rather than lung cancer stage was the most significant factor associated with mortality in patients with CPFE and lung cancer. Therefore, the diagnosis and treatment of these patients should be approached cautiously to avoid AE.

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