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Lung cancer risk among patients with combined pulmonary fibrosis and emphysema

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Summary
Although combined pulmonary fibrosis and emphysema (CPFE) might be relevant to lung cancer, no comparison studies have been done. We evaluated the risk of lung cancer among CPFE patients compared to IPF and emphysema patients.

We retrospectively reviewed the medical records of patients who were diagnosed as CPFE, IPF and emphysema using chest CT scans at Seoul National University Hospital from Jan 2000 to Dec 2011. Patients with CPFE were enrolled and matched (1:1:2) with IPF and emphysema patients based on the radiological criteria. The main outcome was time to diagnosis of lung cancer and evaluated with Cox-proportional hazard regression.

Forty-eight CPFE, 48 IPF, and 96 emphysema patients were included in this study. Twenty-five cases of lung cancer occurred. The CPFE group had a higher risk of lung cancer (adjusted HR 4.62, 95% CI 1.58–13.55) than that of the emphysema group. Also, IPF group had a higher risk of lung cancer (adjusted HR 4.15, 95% CI 1.03–16.78) than that of emphysema group. However, there was no statistically significant difference in lung cancer risk between the CPFE and IPF group. Additionally, the CPFE group had a higher risk of lung cancer or death (adjusted HR 4.62, 95% CI 2.25–9.47) than that of the emphysema group.

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In conclusion, patients with CPFE and IPF had a higher risk of lung cancer than those with emphysema, although lung cancer risk was similar between CPFE and IPF.

Introduction

Since the 1990s, the coexistence of pulmonary fibrosis and emphysema in HRCT has been reported [1]. Cottin et al. [2] defined combined pulmonary fibrosis and emphysema (CPFE) as a disease entity characterized by upper lung predominant emphysema and lower lung predominant fibrosis. CPFE is predominant among male smokers and characterized by a relatively preserved lung volume and decreased diffusing capacity [2].

Several studies have evaluated the clinical course and complications of CPFE. Mejia et al. reported the worse survival of CPFE patients compared to those with IPF only, and pulmonary hypertension was an independent predictor of mortality [3]. In our previous study, CPFE patients showed poorer survival than that of the emphysema only group [4]. Also it is reported that CPFE was associated with a slower decline in FVC and DLco over time than that in the IPF only group [5]. However, the association between CPFE and lung cancer has not been fully evaluated, although there have been some descriptive studies. These studies reported a high prevalence of lung cancer in CPFE patients [6], and vice versa, a high prevalence of CPFE compared to IPF in lung cancer patients [7].

Emphysema and IPF have been regarded as independent risk factors for lung cancer development, respectively [8—10]. In addition, smoking, which is more strongly associated with CPFE patients [11], is the most important risk factor for lung cancer [12]. Therefore, we hypothesized that CPFE is a higher risk factor for the development of lung cancer. To test this hypothesis, we attempted to compare the risk for lung cancer development among patients with CPFE, with IPF only, and with emphysema only.

Methods

Patients

All chest CT scans that were performed at Seoul National University Hospital from Jan 2000 to Dec 2011 were evaluated and patients who had the terms 'diffuse, centrilobular emphysema', 'IPF', 'UIP', 'honeycombing' or 'CPFE' in the final CT report were screened. Among the screened patients, firstly we included patients with CPFE (CPFE group) based on the diagnostic criteria described below. Then each CPFE patients was individually matched according to age (±3 years), sex, and initial date (±6 months) of the diagnosis with 1:1:2 ratio (one CPFE patient: one IPF only patient: two emphysema only patients). Patients with IPF only (IPF group) and those with emphysema only (emphysema group) were selected randomly from screened patients and were included if they met the diagnostic criteria described below.

Diagnostic criteria of CPFE, IPF and emphysema was based on radiologic findings on chest CT scans. IPF was diagnosed with the criteria for the UIP pattern as in 'An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management' [13] as follows: subpleural, basal predominant reticular abnormality or honeycombing with or without traction bronchiectasis and the absence of an inconsistent UIP pattern. Emphysema was diagnosed when the extent of low attenuation area with less than −950 Hounsfield unit involved more than 10% of the lung parenchyme at chest CT scans. Patients who met both the criteria for IPF and emphysema were categorized into the CPFE group [14]. Patients who had any malignancy including lung cancer at the time of the initial diagnosis, patients with connective tissue diseases, and patients with other parenchymal lung diseases, such as drug-associated interstitial lung disease, hypersensitivity pneumonitis, sarcoidosis, eosinophilic pneumonia and a lung destroyed by tuberculosis were excluded.

All CT scans of these patients were reviewed by two radiologists and one pulmonologist and a diagnosis of CPFE, IPF or emphysema required a consensus among all the reviewers. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1207-011-415).

Outcome and variables to measure

The main outcome was the time to the diagnosis of lung cancer. The time to diagnosis was obtained using the duration between the entry date and the index date. The entry date was defined as the date when the patients were diagnosed as CPFE, IPF or emphysema using chest CT scans during the study period. The index date was defined as the date of lung cancer diagnosis or the date of the last follow-up during the study period among patients without lung cancer. The time to diagnosis of lung cancer or death was also obtained using the duration between the entry date and the index date. In this case, the index date was defined as the date of lung cancer diagnosis or the date of death during the study period. The index date of survived patients without lung cancer was 31 Aug 2013. Death registration data was provided with the aid of Ministry of Security and Public Administration.

All lung cancer cases were confirmed pathologically. Histological type and clinical staging of lung cancers were reviewed. Clinical staging was measured according to the American Joint Committee on Cancer staging 7th [15]. Locations of the cancer were also reviewed and categorized into three groups by location of the primary mass. When the distance between the primary mass and visceral pleura was less than 1 cm, we determined that these cancers were located at the 'subpleural' area. However, when the