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The Impact of Lung Cancer on Survival of Idiopathic Pulmonary Fibrosis

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BACKGROUND: Lung cancer (LC) is frequently associated with idiopathic pulmonary fibrosis (IPF). Despite this well-known association, the outcome of LC in patients with IPF is unclear. The objective of this study was to evaluate the impact of LC on survival of patients with associated IPF.

METHODS: A total of 260 patients with IPF were reviewed, and 186 IPF cases had complete clinical and follow-up data. Among these, five cases were excluded because LC was radiologically suspected but not histologically proven. The remaining 181 cases were categorized in two groups: 23 patients with biopsy-proven LC and IPF (LC-IPF) and 158 patients with IPF only (IPF). Survival and clinical characteristics of the two groups were compared.

RESULTS: Prevalence of histologically proven LC was 13%, and among those with LC-IPF cumulative incidence at 1 and 3 years was 41% and 82%. Patients with LC were more frequently smokers (91.3% vs 71.6%, $P = .001$), with combined pulmonary fibrosis and emphysema (52% vs 32%, $P = .052$). Survival in patients with LC-IPF was significantly worse than in patients with IPF without LC (median survival, 38.7 months vs 63.9 months; hazard ratio = 5.0; 95% CI, 2.91-8.57; $P < .001$). Causes of death in the study group were respiratory failure in 43% of patients, LC progression in 13%, and LC treatment-related complications in 17%.

CONCLUSIONS: In patients with IPF, LC has a significant adverse impact on survival. Diagnosis and treatment of LC in IPF are burdened by an increased incidence of severe complicating events, apparently as lethal as the cancer itself. CHEST 2015; 147(1):157-164

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ABBREVIATIONS: AE = acute exacerbation; CPFE = combined pulmonary fibrosis and emphysema; CPI = composite physiologic index; DLCO = diffusing capacity of the lung for carbon monoxide; HR = hazard ratio; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; LC = lung cancer; UIP = usual interstitial pneumonia

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Idiopathic pulmonary fibrosis (IPF) is a form of chronic progressive interstitial pneumonia with a median survival of 3 to 5 years. The incidence of lung cancer (LC) is markedly increased among patients with IPF ranging from 4.4% to 48%.[1-3] The only retrospective study estimating the cumulative incidence of LC in IPF shows 3.3%, 15.4%, and 54.7% incidences of LC, respectively, after 1, 5, and 10 years of follow-up for IPF.[4] A higher incidence of LC has been described in older male smokers and in patients with combined pulmonary fibrosis and emphysema (CPFE),[5] in which emphysema shares with IPF and cancer possible pathogenetic links.[6-9] High-resolution CT (HRCT) scan studies have clearly shown that LC arises in the peripheral area of fibrotic lesions and that LC pathology in IPF is peculiar, showing a prevalence of peripheral squamous cell carcinomas or "enteric" adenocarcinoma.[10-14] Despite large retrospective studies that have compared LC profiles in patients with and without IPF,[15,16] the impact of LC on prognosis of patients with IPF is currently unclear; current guidelines discourage LC surveillance in these patients.[17] However, there is growing evidence that treating LC in patients with IPF might be indicated, especially at an early stage of LC and in selected patients with an appropriate level of functional impairment.[18-22] It is still debated whether patients at inoperable stages of LC or postoperative recurrence of cancer could be potential candidates for radiation therapy or chemotherapy. At present, there is neither evidence nor consensus with regard to whether aggressive approaches are appropriate for a noncurative treatment strategy of LC in patients with IPF.[23-29] It was within this context that we sought to define the outcome for patients with primary pulmonary carcinoma and IPF, and to address whether LC therapy as used in our current clinical practice is associated with any benefit.

Materials and Methods

This study was approved by the Area Vasta Romagna Review Board, Italy (#2614/2010). Systematic search of the patient database revealed 260 patients who satisfied the current diagnostic criteria for IPF[17] seen at Pulmonary Unit, G. B. Morgagni Hospital, Forlì, Italy, during the period of January 1, 2000 to March 31, 2012. We selected 186 patients diagnosed with IPF and then followed at our institution according to a prospective protocol of clinical management that include one annual HRCT scan and pulmonary function tests every 4 months. Among them, five cases were excluded because they were not histologically proven (invasive procedures were not performed due to advanced age and poor general conditions). The remaining 181 cases were categorized in two groups: 23 patients with biopsy-proven LC and IPF (LC-IPF group) and 158 patients with IPF only (IPF group). Sporadic and familial forms of IPF were defined by criteria outlined in current guidelines.[17] Acute exacerbation (AE) was defined as acute respiratory worsening for which a cause could not be identified and meeting all criteria for as proposed by Collard et al.[30] Survival analyses were performed in all cases from the time of IPF presentation.

LCs were classified according to the World Health Organization classification. Staging of LC has been established by the TNM system current at the time of diagnosis. Side effects of treatments were assessed using the National Cancer Institute Common Toxicities Criteria (NCI-CTC version 3.0). Evaluation of tumor response to chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).[31] Operative mortality and mortality related to oncologic treatment were defined as death occurring within 30 days of treatment. Vital status and date of death were verified using phone calls, public records review, Italian death registry review, and review of subsequent patient visits.

Statistical Methods

Patient demographics and characteristics were compared using the two-sample rank-sum test for continuous variables and the χ^2 (exact) test for categorical variables. Cumulative time-to-event distributions (survival, progression, AE) were estimated using the Kaplan-Meier method. Time-to-event outcomes were compared between the LC and non-LC groups using time-dependent proportional hazards regression models. In all cases, P values $< .05$ were considered statistically significant.

Results

Patient Characteristics

Among 181 patients with IPF followed at our institution, we found 23 patients with LC-IPF (13%). Among the 23 patients with LC-IPF, seven (30%) were diagnosed as having primary pulmonary LC at the same time of IPF diagnosis. The other 16 patients (70%) developed LC 18.5 $\pm$ 23.8 months (median, 30 months; range, $-$27.5-84.1 months) after diagnosis of IPF during the observational period. All cases of LC were incidental findings, except for one symptomatic patient with back pain due to a vertebral metastasis of primary lung adenocarcinoma. Cumulative incidence is shown in Figure 1. Clinical and BAL findings in the 181 patients with IPF grouped according to the presence or absence of LC are detailed in Table 1.

HRCT Scan Findings

Among the entire cohort of 181 patients with IPF, 94 (52%) showed a "definite UIP" pattern on HRCT scan, with an equal distribution between LC cases and control subjects. The median extent of fibrosis seen on the HRCT scan performed at the time of diagnosis of IPF was 50% (20%-80%) of the total lung parenchyma, with no difference between those with and without LC. CPFE was identified in 12 patients (52%) with primary LC and in 50 patients without LC (32%; $P = .052$).