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ORIGINAL ARTICLE

Prevalence, risk factors and survival of lung cancer in the idiopathic pulmonary fibrosis

Kyung Jong Lee[1], Man Pyo Chung[1], Young Whan Kim[2], Jae Ho Lee[2], Kyu-Sik Kim[3], Jeong Seon Ryu[4], Hong Lyeol Lee[4], Sung Woo Park[5], Choon Sik Park[5], Soo-Tak Uh[5], Yong Chul Lee[6], Seoung Ju Park[6], Kwan Hyoung Kim[7], Young June Jeon[8], Won Il Choi[8], Yong Bum Park[9], Dong Soon Kim[10], Sung Hwan Jeong[11], Jin Hwa Lee[12] & Moo Suk Park[13]

1 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
2 Department of Internal Medicine, Seoul National University College of Medicine, South Korea
3 Department of Internal Medicine, Chonnam National University College of Medicine, South Korea
4 Department of Internal Medicine, Inha University College of Medicine, South Korea
5 Department of Internal Medicine, Soon Chun Hyang University College of Medicine, South Korea
6 Department of Internal Medicine, Chonbuk National University College of Medicine, South Korea
7 Department of Internal Medicine, Catholic University College of Medicine, South Korea
8 Department of Internal Medicine, Keimyung University School of Medicine, South Korea
9 Department of Internal Medicine, Hallym University College of Medicine, South Korea
10 Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan, South Korea
11 Department of Internal Medicine, Gachon University College of Medicine, South Korea
12 Department of Internal Medicine, Ewha Womans University College of Medicine, South Korea
13 Department of Internal Medicine, Yonsei University College of Medicine, South Korea

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Correspondence
Moo Suk Park, Department of Internal Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, South Korea.
Tel: +82 2 2228 1981
Fax: +82 2 393 6884
Email: pms70@yuhs.ac

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Abstract

Background: The aim of this study was to evaluate the prevalence, risk factors, and survival of lung cancer in patients with idiopathic pulmonary fibrosis (IPF).
Methods: IPF with lung cancer from tertiary hospitals consisted of 1685 patients who had been diagnosed between 2003 and 2007. We reviewed their medical records retrospectively to evaluate the prevalence, risk factors and prognosis of lung cancer in IPF patients.
Results: Among all patients with IPF, 114 cases (6.8%) had lung cancer with IPF. The incidence of lung cancer in patients with IPF was 1.03 persons per 100 person-year (25 patients/2408 years). Most cases of lung cancer (73/114, 68.9%) were located in IPF-associated areas; the lung cancer typically developed in peripheral and lower lobe areas. The study revealed that forced vital capacity (% predicted) at the initial diagnosis and development of lung cancer were independent prognostic factors in patients with IPF.
Conclusions: Lung cancer in patients with IPF was significantly related with the IPF prognosis. An active evaluation should be performed in patients with IPF to detect lung cancer early.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common interstitial lung disease of unknown etiology.[1] Since the first description of lung cancer associated with IPF,[2] the combination of lung cancer and IPF has been found to be especially common in males and in current smokers.[3–5] Several studies have demonstrated associations between lung cancer and IPF, with the prevalence of lung cancer in IPF patients ranging from 4.8% to 48%.[3,5,6]

However, limitations are found in most of the studies regarding the association of IPF with lung cancer as they do

not confirm the histology of usual interstitial pneumonia (UIP) or include connective tissue disease or other such interstitial diseases. In addition, small numbers of cases indicates limited power of statistical differences for comparison of clinical characteristics.[7]

The Korean Interstitial Lung Disease Research Group retrospectively examined the multicenter database from 2003 to 2007 to show the prevalence of IPF with lung cancer and to determine the risk factors, survival and prognosis in IPF patients with lung cancer. We reviewed clinical data and corresponding radiologic and pathologic findings simultaneously to identify the different findings of IPF with lung cancer compared with IPF without lung cancer, and independent variables affecting the survival of patients who had been histologically and clinically diagnosed with IPF according to American Thoracic Society/European Respiratory Society (ATS/ERS) classification.

Methods

Patient selection

The Scientific Committee at the Korean Academy of Tuberculosis and Respiratory Diseases contacted all tertiary and teaching university hospitals of more than 500 beds that employ pulmonary specialists in South Korea to identify the total sample of Korean IPF patients. Newly diagnosed adult (≥20 years) IPF patients were enrolled in the present study between 2003 and 2007. All hospital databases were screened to find patients with diagnoses of IPF according to ATS/ERS criteria.[8]Specialists at each hospital, in pulmonary medicine, radiology, and pathology, confirmed the diagnoses. The Scientific Committee atthe Korean Academy of Tuberculosis and Respiratory Diseases reviewed all the data by criteria. Ethical committees of the university hospitals approved the study.

Diagnostic criteria

IPF was defined as interstitial pneumonia with fibrosis limited to the lung that showed a histological pattern of UIP and diagnosed according to the ATS/ERS consensus classification. Patients with defined connective tissue diseases, left ventricular failures, occupational and/or environmental exposures that may induce pulmonary fibrosis, or histories of exposure to drugs or agents known to cause pulmonary fibrosis were excluded from the study.Smoking history was not considered exclusion criteria since it was difficult to show the close relationship to interstitial pneumonia as a risk factor of lung fibrosis. IPF was also considered likely in the absence of a surgical lung biopsy when patients met the clinical criteria that are suggested in the ATS/ERS guidelines.[8]

Data collection

The medical records of all IPF patients were reviewed to obtain data regarding age, smoking history, method used to diagnose IPF, time of IPF diagnosis, pulmonary function tests, high-resolution computerized tomography (HRCT) findings, comorbidities including malignancy, follow-up duration, and outcome. In order to determine the clinical characteristics of lung cancer in IPF patients, the time of diagnosis of lung cancer, location of lung cancer including the IPF-associated area, histology of lung cancer, and the stage of lung cancer were analyzed. All cases of lung cancer were confirmed by pathologic biopsies, and the time of lung cancer was defined as the date that the diagnosis was confirmed by biopsy. "Smoking" was categorized as never smoking, or smoking less than 100 cigarettes over one's lifetime, while "smokers" included current and past smokers of more than 100 cigarettes over one's lifetime. Pack years were calculated for smokers. The findings of HRCT scans were classified as reticular, honeycomb, ground-glass opacities, and nodular patterns. The location of lung cancer in HRCT was classified as either peripheral or central and evaluated to detect any associations between locations of lung cancer and locations of IPF-related lesions in the same patient. Histologic classification and stages of lung cancer were evaluated in each lung cancer patient. IPF patients who were diagnosed with lung cancer were classified according to the time of diagnosis of lung cancer, which was either diagnosed simultaneously as IPF, or during follow-up of IPF.

Statistical analysis

Data is expressed as numbers or means, because the majority of the data was normally distributed, except for the follow-up duration of IPF. IPF patients were grouped according to the presence or absence of lung cancer. Continuous variables were analyzed using an unpaired *t*-test; categorical variables were analyzed using a Pearson's χ^2 test in each group. Logistic regression analysis was performed to assess the risk of lung cancer in IPF patients. Survival was estimated using Kaplan-Meier curves. The survivals of patients in the IPF only group and the IPF with lung cancer group were compared using a log rank test. Cox's proportional hazards regression analysis was used to identify significant variables that affect the survival of IPF patients, and to estimate hazard ratios and 95% confidence intervals (CI) for predictors of survival. In patients with lung cancer and IPF, we conducted comparisons according to the IPF-associated area (i.e., the area in the lung where lesions were found) and diagnosis time. All tests were two-tailed, and P-values <0.05 were considered statistically significant. SPSS software Version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Clinical characteristics

The study sample consisted of 1685 patients who were diagnosed with IPF either surgically (39.1%) or clinically (60.9%) at tertiary hospitals in South Korea between 2003 and 2007. The clinical characteristics of these IPF patients are summarized in Table 1. The mean age at diagnosis of IPF was 67.9 ± 9.6 years, and 72.4% of IPF patients were male. The prevalence of lung cancer in IPF patients was 6.8%. Other malignancies aside from lung cancer were observed in 4.5% of patients, including stomach cancer (34%), bladder cancer (9.2%), and colorectal cancer (5.2%). A history of smoking was recorded for 57.3% of IPF patients, with a mean of 36.6 pack-years. The average duration of follow-up was 13.4 months, with a total follow-up of 2408 person-year.

In this sample, 89 patients (78.1%) with lung cancer were simultaneously diagnosed with IPF, and 25 patients (21.9%) were diagnosed with lung cancer after the diagnosis of IPF. The incidence density of lung cancer in IPF patients was 1.03 persons per 100 person-year. The median follow-up duration between the diagnosis of IPF and lung cancer was 17.2 months, ranging from 0.8 months to 48.3 months. When comparing IPF patients with lung cancer to those without, there were significant differences in gender, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio, total lung capacity (TLC), smoking status, pack-year, and other malignancies accompanying IPF.

Table 1 Demographics of patients with idiopathic pulmonary fibrosis

Variables	All IPF	IPF with LC	IPF only	P-value
Subject, n	1685	114 (6.8)	1571 (93.2)	
Age, year	67.9 ± 9.6	68.5 ± 8.4	67.8 ± 9.7	0.421
Gender; male	1220 (72.4)	108 (94.7)	1112 (70.8)	0.000
Diagnostic method				
Surgical	658 (39.1)	54 (47.4)	604 (38.4)	0.059
Clinical	1027 (60.9)	60 (52.6)	967 (61.6)	
FVC (% pred)	75.0 ± 18.6	81.8 ± 17.5	74.6 ± 18.6	0.001
FEV_1 (% pred)	85.6 ± 20.3	90.0 ± 20.7	85.4 ± 20.3	0.022
TLC (% pred)	83.3 ± 19.7	89.0 ± 15.4	83.0 ± 20.0	0.035
DLCO (% pred)	62.2 ± 21.6	63.9 ± 20.6	62.0 ± 21.6	0.464
Smoking, n	1518	106	1412	0.000
Non-smoker	553 (36.4)	15 (14.2)	538 (38.1)	
Smoker	965 (63.6)	91 (85.8)	874 (61.9)	
Smoking history, pack-years	36.6 ± 21.2	44.3 ± 23.8	35.9 ± 20.8	0.000
Follow-up, n	1685	114	1571	
Median (range)	13.5 (0–72)	7.1 (0–61)	13.9 (0–72)	0.003

Data are presented as mean ± SD, percentage or median (min-max), unless otherwise indicated. % pred, percentage of the predicted value; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GGO, ground glass opacity; n, number; TLC, total lung capacity.

Table 2 Multivariate analysis of risk factors for predicting the development of lung cancer in idiopathic pulmonary fibrosis

Variables	OR	95% CI	P-value
Gender; male	0.411	0.096–1.760	0.231
Smoker	1.525	0.193–12.03	0.689
Pack-year	1.014	1.005–1.023	0.003
Other malignancy†	2.299	1.084–4.877	0.030

†Include stomach c. (*n* = 26), bladder c. (*n* = 7),colorectal c. (n = 4), hematologic malignancy (*n* = 4), esophageal c. (*n* = 3), gallbladder c. (*n* = 3), larynx c. (*n* = 2), cervix c. (*n* = 3), endometrial c. (*n* = 2), etc. CI, confidence interval; OR, odds ratio.

Risk factor analysis of lung cancer and IPF survival

We analyzedvariables including gender, smoking, pack-year, and other malignancies except for lung cancer, to assess possible risk factors for the development of lung cancer in IPF patients. Multivariate regression after adjustment for significant factors indicates that pack-year and other malignancies were significant independent predictors of lung cancer in IPF patients (Table 2). Cox regression hazard ratio (HR) analysis was performed to identify variables that affect survival in IPF patients. Lung cancer accompanying IPF was one of the most significant independent predictors of survival in IPF patients (HR 2.441, CI 1.373–4.339). Table 3 summarizes the HR of each variable in the total sample of patients with IPF. The Kaplan-Meier curve of survival in IPF is shown in Figure 1. The median survival time was 26.9 months in patients who had both IPF and lung cancer group (95% CI 14.67–39.05).

Table 3 Predictors for survival in patients with idiopathic pulmonary fibrosis

Variables	Hazard Ratio	95 % CI	P-value
Age, year	1.008	0.988–1.029	0.431
Gender; male	0.486	0.187–1.266	0.140
Smoker	0.582	0.255–1.331	0.200
Pack-year	0.995	0.985–1.006	0.377
FVC (% pred)	0.964	0.942–0.988	0.003
FEV_1 (% pred)	1.021	1.000–1.043	0.055
TLC (% pred)	0.995	0.983–1.008	0.462
DLCO (% pred)	0.990	0.980–1.001	0.063
Lung cancer	2.441	1.373–4.339	0.002
Other malignancy†	1.448	0.617–3.396	0.395

†Include stomach c. (n = 26), bladder c. (n = 7), colorectal c. (n = 4), hematologic malignancy (n = 4), esophageal c. (n = 3), gallbladder c. (n = 3), larynx c. (n = 2), cervix c. (n = 3), endometrial c. (n = 2), etc.% pred, percentage of the predicted value; CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity.

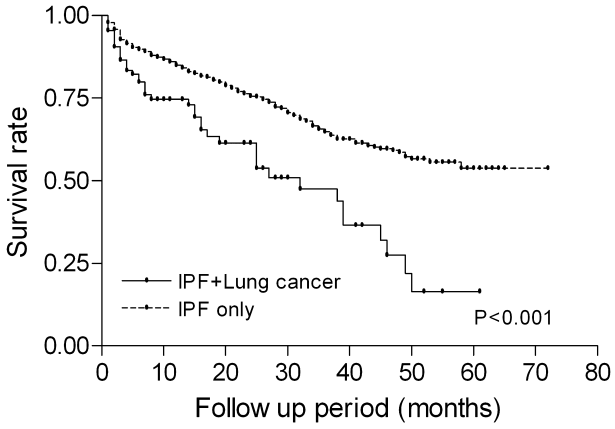

Figure 1 Comparison of survival between idiopathic pulmonary fibrosis with lung cancer patients and idiopathic pulmonary fibrosis (IPF) only patients; Kaplan-Meier survival curve.

This survival time was significantly different between patients with IPF only and patients with IPF and lung cancer (P = 0.000 by log-rank test).

Comparisons according to the location of lung cancer

The frequency of lung cancer in IPF patients was 6.8%, 114 out of 1685 patients. Most of the cancerous lesions were located in peripheral areas of the lung (77.1%). Adenocarcinoma (36%) and squamous cell carcinoma (33%) were the most common histological findings among patients with lung cancer and IPF. We also evaluated HRCT findings of IPF and lung cancer location in IPF patients: 68.9% of lung cancers were located in IPF-associated lesions in the same patients. Comparisons between patient groups according to the location of lung cancer revealed a significant difference between the two lesions (Table 4). There were no significant differences in gender, pack-year, histology, or stage of lung cancer, according to the location of lung cancer in IPF patients.

Discussion

Our data reveals that the prevalence of IPF patients with lung cancer is 6.8% in South Korea, and that the person-year incidence density of lung cancer in the IPF group is 1.03 persons per 100 person-year. To our knowledge, this is the first report to investigate the incidence density of lung cancer in IPF patients who were diagnosed according to ATS/ERS criteria in tertiary hospitals. Our data suggests a lower prevalence of lung cancer in IPF patients than the 9.8% prevalence reported by Turner*et al.* between 1955 and 1973.[6] However, they used different criteria for the diagnosis of IPF, as their studies were conducted before the adoption of ATS/ERS guidelines, and their lung cancer data was obtained from death certificates. We believe that our estimates of the prevalence of lung cancer in IPF is distinguished from estimates presented by previous studies, because IPF was diagnosed either pathologically or clinically using ATS/ERS guidelines in all patients, and suspicions of lung cancer during IPF follow-up were confirmed by histology at tertiary hospitals in South Korea.

Recent autopsy data (1999) from Japan reported a high prevalence rate of 45.7% for lung cancer in UIP,[9] but the conclusions that can be drawn are limited because the data regarding rates of lung cancer were obtained from autopsy data, a process that may be affected by selection bias and may not reflect actual clinical status. A population-based cohort study in the UK suggested that the incidence of lung cancer in IPF increased markedly to a 7.31 rate ratio among patients with IPF when compared to patients without IPF. However, a proportion of this sample was probably limited, because the base data was retrieved from a general practice research database and was not histologically confirmed.[3]

The results of the two studies appear to contradict any relationship between IPF and lung cancer.[10,11] Wells*et al.* analyzed data reflecting multiple causes of mortality from 1979–1991 to evaluate the relationship between lung cancer and IPF using death certificates in the United States. Lung cancer prevalence in IPF, based on the American death certificate data, was only 4.8%, which is lower than the prevalences reported in other studies.[11] This low sensitivity, resulting from negative bias inherent to using death certificate data, may influence the prevalence of lung cancer associated with IPF,

Table 4 Comparison according to location of lung cancer in idiopathic pulmonary fibrosis patients

	All LC in IPF	LC in IPF–associated area	LC in IPF-not associated area	P-value
Subject, n	106	73 (68.9)	33 (31.1)	
Age, year	68.5 ± 8.4	67.8 ± 8.2	69.0 ± 9.3	0.507
Gender, male	108 (94.7)	68 (93.2)	32 (97.0)	0.663
Pack-years	44.3 ± 23.7	42.6 ± 25.2	48.5 ± 23.0	0.317
Centrality, n	105	73	32	0.000
Central	24 (22.9)	9 (12.3)	15 (46.9)	
Peripheral	81 (77.1)	64 (87.7)	17 (53.1)	
Tumor site, n	104	73	31	0.000
Upper lobe	36 (34.6)	13 (17.8)	23 (74.2)	
Middle lobe	4 (3.8)	4 (5.5)	0 (0.0)	
Lower lobe	61 (58.7)	55 (75.3)	6 (19.4)	
Stage, n	96	68	28	0.300
I	23 (24.0)	19 (27.9)	4 (14.3)	
II	10 (10.4)	8 (11.8)	2 (7.1)	
IIIA	18 (18.8)	11 (16.2)	7 (25.0)	
IIIB	24 (25.0)	18 (26.5)	6 (21.4)	
IV	21 (21.9)	12 (17.6)	9 (32.1)	

Data are presented as mean ± SD or number (percentage), unless otherwise indicated. IPF, idiopathic pulmonary fibrosis; LC, lung cancer.

and in turn result in an underestimation of the rate of lung cancer. A recent report suggested that the cumulative incidence of lung cancer in IPF increases over time after the initial diagnosis of IPF.[12] A study in the UK suggested that the incidence of lung cancer is significantly increased in IPF patients compared to the general population, and that smoking is an independent predictor of lung cancer development.[4]

Cigarette smoking was identified as a risk factor for lung cancer in IPF patients in our study (odds ratio [OR] 1.014, CI 1.005-1.023). Nagai*et al.* previously suggested that the risk of lung cancer is higher in smokers, and that the risk increases with the duration of a smoking habit.[13] A study that compared characteristics between IPF patients with lung cancer and patients with IPF only, reported that patients with simultaneous IPF and lung cancer were predominantly male and were more likely to be smokers, which is in agreement with our data.[7] Cigarette smoking is thought to be a major cause of lung cancer that may confound studies of lung cancer in patients with IPF.

In this study, a high proportion (64 out of 73 patients; 87.7%) of lung cancer lesions in IPF patients were located in the most peripheral areas associated with IPF. In contrast, cases of lung cancer that were not concurrent with cases of IPF developed more often in the central areas of the lungs (46.9%) and less often in areas that were already associated with IPF (12.3%). We hypothesize that an additional mechanism, other than smoking, may affect the development of lung cancer in IPF patients, and that this may support the interpretation of cigarette smoking as a disease modifier that affects fibrosis and epithelial changes that in turn play a role in tumorigenesis of IPF.[14]

In the cases of lung cancer associated with IPF included in our data, most of the tumors (68.9%) were located in the associated area of IPF lesions. Lung cancer were located in peripheral areas of the lung that were associated with IPF significantly more often than in unassociated areas. The concordant locations of lung cancer and IPF were predominantly in the lower lobe. In a previous Japanese study that analyzed clinical features of IPF in lung cancer patients, the frequency of lung cancers in the lower lobes overall was about 60%, and in particular located in peripheral areas was above 90%.[14] The locations of lung cancer in peripheral areas and lower lobe predominance, especially in the fibrosis area, support the theory that the inflammatory process is associated with bronchiolar metaplasia in the pathogenesis of lung cancer.[9] A previous study by Vassilakis*et al.* investigated microsatellite variation in 26 patients with IPF, and detected frequent genetic alterations, primarily microsatellite instability and loss of heterogeneity in IPF patients.[15] We believe that genetic alterations in IPF patients and inflammation that is typically associated with fibrosis of the peripheral lung may explain the high rates of lung cancer in peripheral and lower lobes that we observed in our sample.

In multivariate Cox regression models, we observed decreased risks of mortality associated with increases in FVC (% predicted) at baseline (HR 0.964, CI 0.942–0.988). In turn, increased mortality was associated with lung cancer (HR 2.441, CI 1.373–4.339). Serial changes in FVC (% predicted) are considered to the best predictors of subsequent mortality in IPF patients, according to the results of other studies.[16] In addition to serial changes in FVC (% predicted), FVC (% predicted) at baseline is also considered a predictor of mortality. It should also be noted that baseline FEV_1 (% predicted) and diffusing capacity of the lung for carbon monoxide (DLCO) (% predicted) were lower in patients diagnosed simultaneously with lung cancer and IPF, compared to IPF patients who were diagnosed with lung cancer during IPF follow-up.

Even though this survey was conducted using a large sample of IPF patients, and 39.1% IPF cases that we included were confirmed surgically, there are several limitations to be considered when interpreting our results. Our data was obtained from multiple tertiary care centers by reviews of medical records. Therefore, the incidence and prevalence of IPF that we observed cannot be extended to the general population. The prevalence of lung cancer in the general South Korean population was estimated at 28.8 persons per 100 000 persons in 2005.[17] Although it is not possible to directly compare our sample of IPF patients with the general population, we did observe that the prevalence of lung cancer in our sample was high compared to that in the general population. Many of our patients were lost to follow-up, which affects the results of survival and Cox regression model analyses. Compared to other studies, a large proportion of the IPF patients in our sample were diagnosed via surgical biopsy (39.1%). However, many patients (60.9%) were diagnosed with IPF based on clinical criteria drawn from the ATS/ERS guidelines. Despite these limitations, this study represents the first report of incidence density for lung cancer development after IPF; we present evidence that lung cancer is associated with IPF in South Korea, and we identify clinical characteristics of lung cancer in IPF. We observed that the risk of mortality increased with the development of lung cancer in IPF patients.

Conclusion

The person-year incidence density of lung cancer in the IPF group was 1.03 persons per 100 person-year in this study. Prevalence of lung cancer in IPF patients was high in males and in smokers; also lung cancer was most likely developed in peripheral and lower lobes. Because the presence of lung cancer in IPF patients is an independent predictor of mortality in IPF, thorough evaluations and regular follow up in IPF patients should be performed for early detection of lung cancer.

Disclosure

No authors report any conflict of interest.

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