Characteristics of Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease: A Comparative Analysis

Sibel Kara¹*, Şule Akçay², Zafer Koç³

¹Department of Chest Diseases, Baskent University Adana Dr. Turgut Noyan Teaching and Medical Research Center, Turkey
²Department of Chest Diseases, Baskent University Faculty of Medicine, Ankara Hospital, Ankara, Turkey
³Department of Radiology, Baskent University Adana Dr. Turgut Noyan Teaching and Medical Research Center, Turkey

*Corresponding author: Sibel Kara, Department of Chest Diseases, Baskent University Adana Dr. Turgut Noyan Teaching and Medical Research Center, Dadaloglu Mah 2591 Sok 4/A, 01250, Yüreğir/Adana, Turkey

Citation: Kara S, Akçay S, Koç Z (2020) Characteristics of Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease: A Comparative Analysis. J Oncol Res Ther 5: 1096. DOI: 10.29011/2574-710X.001096

Received Date: 13 July, 2020; Accepted Date: 31 July, 2020; Published Date: 05 August, 2020

Abstract

Background: The link between IPF (Idiopathic Pulmonary Fibrosis) and Lung Cancer (LC) has been known for years. However, little is known about LC in patients with other Interstitial Lung Diseases (ILD). The aim of this study was to investigate and compare the characteristics and mortality of lung cancer patients with IPF and non-IPF Interstitial Lung Disease (ILD).

Methods: We conducted a retrospective analysis of lung cancer patients with IPF and non-IPF ILD who were managed at our center between 2008 and 2018. Patients with LC diagnosed by a pathology examination were identified. The patient characteristics as well as mortality were recorded.

Results: Twenty-one patients with lung cancer [14 Non-IPF ILD, 7 IPF] were evaluated. Among the patient population, 90.4% were male; the mean age was 67 (range 60-75) years. The most common primary site of lung cancer in both groups was the lower lobe (71.4%, 50% respectively) and the area of fibrosis (85.7%, 78.6%, respectively). The most common histological type was adenocarcinoma (n=10) which was followed by squamous cell carcinoma (n=6). The most common stages were stage III and stage IV (85.7%, 78.6%, respectively) in both groups. During the follow-up period, 8 [2 (28.6%) IPF and 6 (42.9%) non-IPF ILD] patients died in both groups.

Conclusions: The majority of patients was male in both groups. The primary site of cancer was often a fibrotic area and lower lobes of the lungs. The most common histological types were NSCLC including adenocarcinoma and squamous cell carcinoma. The majority of patients had advanced disease at the time of diagnosis. No difference was seen concerning lung cancer characteristics and mortality rate.

Keywords: Idiopathic pulmonary fibrosis; Interstitial lung disease; Lung cancer

Background

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults, is limited to the lungs, and is defined by the histopathological and/or radiological pattern of Usual Interstitial Pneumonia (UIP) [1]. Interstitial Lung Disease (ILD), particularly Idiopathic Pulmonary Fibrosis (IPF), is associated with an increased risk of developing lung cancer (LC). The incidence of LC among patients with IPF is estimated to range from 4.4% to 48% [2-5]. However, little is known about LC in patients with other Interstitial Lung Diseases (ILD). In this context, the purpose of our study was to describe and compare the characteristics of lung cancer patients with IPF and non-IPF ILD using our institutional data registries.

Methods

Patients

We examined the patients diagnosed with interstitial lung disease and lung cancer between January 2008 and December 2018 at our center. All patients underwent High-Resolution CT (HRCT), and 21 patients were also evaluated by thorax CT at...
our hospital. CT examinations were performed using a 16 slice-MDCT scanner (Somatom Emotion, Siemens Medical Solutions, Erlangen, Germany). The HRCT images were obtained using the following parameters: 270 mAs and 120 kVp, slice thickness, 1 mm; contiguous 0.75-mm collimation. High Resolution Computed Tomography (HRCT) and thorax CT images of all ILD patients were evaluated and recorded by an experienced radiologist. At our center the diagnosis of ILD is based on the clinical criteria recommended by the American Thoracic Society and the European Respiratory Society [1,6]. Patients diagnosed with ILD were divided into two groups as IPF and non-IPF ILD. Non-IPF ILD refers to ILD caused by a disease other than IPF. Baseline demographics of all the patients including, age, gender, smoking history, follow-up duration, types of Non-IPF ILD, steroid treatment, and mortality were recorded.

Lung cancer was classified according to the World Health Organization classification [7]; LC staging was based on the 7th edition of the TNM classification of malignant tumors [8]. Histopathological findings, staging, location of primary lesions, and metastasis were recorded for all patients with LC.

Statistical analysis
Statistical analyses of the study data were performed using SPSS 17.0 software package. Categorical variables were reported as number and percentage; continuous measurements were reported as mean ± standard deviation or median (minimum-maximum). Chi-square test or Fisher’s exact test was used to compare categorical variables. Comparison of continuous variables between the study groups was performed by the independent samples t-test for the variables meeting the criteria of parametric distribution, and by Mann Whitney U test for the variables with non-parametric distribution. Statistical significance was set at p <0.05.

Results

Patient characteristics
We identified 21 patients with lung cancer [7 IPF, 14 non-IPF ILD] from the medical records between 2008 and 2018. Three patients were excluded from the study because they had a lung nodule or mass on chest CT scan without a pathological diagnosis. Baseline demographic characteristics of the patients are shown in Table 1. Nineteen (90.4%) patients were male and 2 (9.5%) were female; their mean age was 67 years. Smoking rate was substantially high in both groups (85.7%). The underlying cause in the non-IPF ILD-LC group was determined in 2 patients (rheumatoid arthritis, systemic sclerosis). The majority of patients did not receive steroid treatment. During the follow-up period, 8 [2 (28.6%) IPF and 6 (42.9%) non-IPF ILD] patients died. There was no statistically significant difference between the two groups in terms of demographic characteristics.

The characteristics of lung cancer in patients with IPF and non-IPF ILD are shown in Table 2. In both groups, the location of the lung cancer was predominantly lower lobe (71.4%, 50%, respectively) and a fibrotic area (85.7%, 78.6%, respectively). The most common histological type was adenocarcinoma (n=10) followed by squamous cell carcinoma (n=6) and small cell LC (n=3). Cancer stage distribution was also similar in both groups; the most common stages were stage III and stage IV (85.7%, 78.6%, respectively). The most common organ metastasis was to bone (28.5%) in the non-IPF lung cancer group. There was no statistically significant difference between the two groups in terms of demographic characteristics and mortality.

|                         | IPF with LC | Non-IPF ILD with LC | p-value |
|-------------------------|------------|---------------------|---------|
| Age at diagnosis (years),median | 65 (60-75) | 67 (60.75-71.25)     | 0.824   |
| Gender M/W (male %)      | 70(100)    | 12(85.7)            | 0.293   |
| Observation periods, months | 30(12-48) | 45(38-60)           | 0.109   |
| Smoking                 | 7(14.2%)   | 14(14.2%)           | 0.725   |
| Never                   | 1(14.2%)   | 2(14.2%)            |         |
| Former                  | 4(57.2%)   | 10(71.4%)           |         |
| Current                 | 2(28.6%)   | 2(14.2%)            |         |
| Non IPF ILD type not specified | 0 | 12 (85.7%)          |         |
| Rheumatoid arthritis    | 0          | 1(7.1%)             |         |
| Systemic sclerosis       | 0          | 1(7.1%)             |         |
| Steroids                | 7(14.2%)   | 5(35.7%)            | 0.306   |
| Without steroids         | 6(85.8%)   | 9(64.3%)            | 0.306   |
| Mortality over observation period (%) | 2(28.6%) | 6 (42.9%)          | 0.525   |

N: Patient number; IPF: Idiopathic Pulmonary Fibrosis; ILD: Interstitial Lung Diseases; LC: Lung Cancer

Table 1: Baseline demographics of patients with IPF-LC and Non-IPF ILD –LC.
| Variable                  | IPF with LC | Non-IPF ILD with LC | p-value |
|---------------------------|-------------|---------------------|---------|
|                           | N           | Results             | N       | Results             |         |
| Laterality                |             |                     |         |                     |         |
| Left                      | 7           | 5 (71.4%)           | 14      | 6 (42.9%)           | 0.361   |
| Right                     | 7           | 2 (28.6%)           | 14      | 8 (57.1%)           |         |
| Bilateral                 | 7           | -                   | 14      | -                   |         |
| Fibrotic area             | 7           | 6 (85.7%)           | 14      | 11 (78.6%)          |         |
| Primary site              | 7           | -                   | 14      | -                   |         |
| Upper lobe-peripheral     | 7           | 2 (28.6%)           | 14      | 6 (42.9%)           | 0.540   |
| Lower lobe-peripheral     | 7           | 5 (71.4%)           | 14      | 7 (50%)             |         |
| Others                    | 7           | 1 (14.2%)           | 14      | 1 (7.1%)            |         |
| Histology                 | 7           | 2 (28.6%)           | 14      | 4 (28.6%)           | 0.535   |
| SCC                       | 7           | 4 (57.1%)           | 14      | 6 (42.9%)           |         |
| Adenocarcinoma            | 7           | 3 (21.4%)           | 14      | 5 (35.7%)           |         |
| Small cell ca             | 7           | -                   | 14      | -                   |         |
| Others                    | 7           | 1 (14.2%)           | 14      | 1 (7.1%)            |         |
| Stage                     | 7           | 1 (14.2%)           | 14      | -                   | 0.287   |
| I                         | -           | 3 (21.4%)           | 14      | 6 (42.9%)           |         |
| II                        | -           | -                   | 14      | 5 (35.7%)           |         |
| III                       | -           | 1 (14.2%)           | 14      | 1 (7.1%)            |         |
| IV                        | -           | 2 (28.6%)           | 14      | 5 (35.7%)           | 0.103   |
| Metastasis                |             | -                   | 14      | -                   |         |
| Brain                     | -           | 1 (14.2%)           | 14      | 1 (7.1%)            |         |
| Malignant pleural effusion| -           | 1 (14.2%)           | 14      | 1 (7.1%)            |         |
| Bone                      | -           | -                   | 14      | 4 (28.5%)           |         |

N: Patient number, SCC: Squamous cell

Table 2: Comparison of the characteristics of lung cancer in patients with IPF and non-IPF ILD.

The lung cancer computed tomography findings of the two patients with interstitial pulmonary fibrosis are shown in Figures 1 and 2.

Figure 1: A 64-year-old man with interstitial pulmonary fibrosis and pathologically confirmed diagnosis of lung adeno cancer. A-B: Axial high resolution CT image obtained at the level of the lung base shows ground glass opacity and reticular densities. Axial high resolution CT and mediastinal window image show a mass with soft tissue density at the periphery of the left lower lobe (open arrow).
A 72-year-old man with non-interstitial pulmonary fibrosis interstitial lung disease and pathologically confirmed diagnosis of small cell lung cancer A-B: Axial high resolution CT image obtained at the level of the lung base shows ground glass opacity and reticular densities. Axial high resolution CT and mediastinal window image show a mass with soft tissue density at the periphery of the right lower lobe (open arrow).

Discussion

The aim of this study was to identify and compare the characteristics of lung cancer patients with IPF and non-IPF Interstitial Lung Disease (ILD). Interstitial Lung Disease (ILD), particularly Idiopathic Pulmonary Fibrosis (IPF), is associated with an increased risk of developing lung cancer (LC) [2-4]. On its own, pulmonary fibrosis is a risk factor for lung carcinogenesis [9-11]. Moreover, elder age, male sex, history of smoking, and coexisting emphysema are also strong risk factors that contribute to developing LC in IPF patients [12-14]. In our study, the majority of patients with non-IPF ILD were male. The smoking history was common in both groups and the tumor frequently appeared in the fibrotic area.

In the general population, the predominant type of lung cancer is Non-Small Cell Lung (NSCLC) cancer. It is also the most common type of lung cancer in patients with IPF. In addition, adenocarcinoma is the most common subtype of histological NSCLC in the general population [15,16]. Most of the recent studies have shown that squamous cell carcinoma is the most common type of lung cancer, whereas adenocarcinoma is the second most common type in IPF patients, especially in the peripheral lower lobes [17-19]. In our study, the predominant lung cancer type was NSCLC in patients with IPF. However, adenocarcinoma was the most common type while squamous cell carcinoma was the second most common type. We think that this resulted from a small number of patients.

Cancer risk in the non-IPF ILD population is well known. Some phenotypes of non-IPF ILD including rheumatoid arthritis [20], polymyositis/dermatomyositis [21], and systemic sclerosis [22] are known to be associated with increased risk for lung cancer. Although the pathogenic mechanisms underlying LC development in non-IPF ILD remain unknown, chronic inflammation and a fibrotic environment are thought to contribute to tumorigenesis [23,24]. In addition, several studies have shown that chronic inflammation can initiate tumor development by causing DNA damage or by sensitizing cells to mutations [25]. However, little is known about LC in patients with other Interstitial Lung Disease (ILD). In our study, the majority of patients with non-IPF-ILD had no identified disease subtype and the ICD code of mixed connective tissue disease was recorded for such patients. There are also common areas of bilateral fibrosis in the lungs in this group.

Watanabe, et al. reported that lung cancer occurring in patients with connective tissue disease was more common in peripheral and lower lobes; they also showed that the most common histological type was adenocarcinoma and that the cancer was diagnosed at an advanced stage [26]. Similarly, in our study, lung cancer was frequently located in peripheral fibrotic areas and lower lobes in patients with non-IPF-ILD, with the most common histological type being adenocarcinoma that was diagnosed at an advanced stage.

Recent studies have argued that the mortality of lung cancer in patients with IPF is higher than for lung cancer alone, and that the presence of IPF is associated with a prognosis worse than lung cancer per se [18,27]. Similarly, various studies have shown that lung cancer development reduces survival in patients with connective tissue disease-related interstitial lung disease [22,26]. In our study, the mortality rates in patients with IPF and non-IPF-ILD were 28.6% and 42.9%, respectively. Mortality was associated with cancer in both groups.

In general, our data suggest that lung cancer in IPF and non-IPF ILD is phenotypically distinct from “Sporadic” lung cancer.

This study had some limitations. First, it was a retrospective, single-center study. Secondly, the number of patients was small. Therefore, we believe that future multicenter studies are warranted.

Conclusions

The majority of patients with lung cancer with IPF and non-IPF-ILD were male, older, and smokers. The primary site of cancer was often in the fibrotic area and lower lobes. The most common histological types were NSCLC types including adenocarcinoma and squamous cell carcinoma. The majority of patients had advanced cancer at the time of diagnosis. There was no difference in demographics, lung cancer characteristics, and mortality in both groups.

Author’s contribution: In the article, Professor Şule Akçay has contributed to literature support, findings and structuring of tables and figures, and additional contributions in writing discussion.
Professor Zafer Koç contributed to the formation of figures that evaluated the radiological findings of all cases.

**Conflict of interest:** None to declare.

**References**

1. Raghu G, Remy-Jardin M, Myers JL, et al. (2018) American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 198: e44-e68.

2. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A (1980) Cryptogenic fibrosing alveolitis and lung cancer. Thorax 35: 496-469.

3. Matsushita H, Tanaka S, Saiki Y, Hara M, Nakata K, et al. (1995) Lung cancer associated with usual interstitial pneumonia. Pathol Int 45: 925-932.

4. Wells C, Mannino DM (1996) Pulmonary fibrosis and lung cancer in the United States: analysis of the multiple cause of death mortality data, 1979 through 1991. South Med J 89: 505-510.

5. Ozawa Y, Suda T, Naito T, Enomoto N, Hashimoto D, et al. (2009) Cumulative incidence of and predictive factors for lung cancer in IPF. Respirology 14: 723-728.

6. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000; 161: 646-664.

7. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, et al. (2015) The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 10: 1243-1260.

8. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, et al. (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2: 706-714.

9. Karampitsakos T, Tzilas V, Tringidou R, Steiropoulos P, Aidinis V, et al. (2017) Lung cancer in patients with idiopathic pulmonary fibrosis. Pulm Pharmacol Ther. 1:10.

10. Hubbard R, Venn A, Lewis S, Britton J (2000) Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am. J. Respir. Crit. Care Med.

11. Artinian V, Kvale PA (2004) Cancer and interstitial lung disease. Curr. Opin. Pulm. Med. 425-434.

12. Kato E, Takayanagi N, Takaku Y, Kagiyama N, Kanauchi T, et al. (2018) Incidence and predictive factors of lung cancer in patients with idiopathic pulmonary fibrosis. ERJ Open Res: 4.

13. Usui K, Tanai C, Tanaka Y, Noda H, Ishihara T (2011) The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology 16: 326-331.

14. Jafari Nezhad A, Yekta Kooshali MH (2018) Lung cancer in idiopathic pulmonary fibrosis: A systematic review and meta-analysis. PLoS ONE 13: e0202360.

15. Dela Cruz CS, Tanoue LT, Matthay RA (2011) Lung cancer: Epidemiology, etiology, and prevention. Clin. Chest Med 32: 605-644.

16. Ballester B, Milara J, Cortijo J (2019) Idiopathic Pulmonary Fibrosis and Lung Cancer: Mechanisms and Molecular Targets. Int J Mol Sci 20.

17. Lee T, Park JY, Lee HY, Cho YJ, Yoon HJ, et al. (2014) Lung cancer in patients with idiopathic pulmonary fibrosis: clinical characteristics and impact on survival. Respir Med 108: 1549-1555.

18. Kanaji N, Tadokoro A, Kita N, Murota M, Ishii T, et al. (2016) Impact of idiopathic pulmonary fibrosis on advanced non-small cell lung cancer survival. J Cancer Res Clin Oncol 142: 1855-1865.

19. Khan KA, Kennedy MP, Moore E, Crush L, Prendeville S, et al. (2015) Radiologic characteristics, histological features and clinical outcomes of lung cancer patients with coexistent idiopathic pulmonary fibrosis. Lung 193: 71-77.

20. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S (2015) Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 17: 212.

21. Huang YL, Chen YJ, Lin MW, Wu CY, Liu PC, et al. (2009) Malignancies associated with dermatomyositis and polymyositis in Taiwan: a nationwide population-based study. Br J Dermatol 161: 854-860.

22. Enomoto Y, Inui N, Yoshimura K, Nishimoto K, Mori K, Kono M, et al. (2016) Lung cancer development in patients with connective tissue disease related interstitial lung disease: A retrospective observational study. Medicine (Baltimore) 95: e5716.

23. Hubbard R, Venn A, Lewis S (2000) Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med 161: 5-8.

24. Bouros D, Hatzakis K, Labrakis H, Zeibocoglou K (2002) Association of malignancy with diseases causing interstitial pulmonary changes. Chest 121: 1278-1289.

25. Beyerdt R, Beaugerrie L, Van Asche G, Brochez L, Renaud JC, et al. (2013) Cancer risk in immune-mediated inflammatory diseases (imid). Mol Cancer 12: 98.

26. Watanabe S, Saeki K, Waseda Y, Murata A, Takato H, et al. (2018) Lung cancer in connective tissue disease-associated interstitial lung disease: clinical features and impact on outcomes J Thorac Dis 10: 799-807.

27. Tomassetti S, Gurioli C, Ryu JH, Decker PA, Ravaglia C, et al. (2015) The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest 147: 157-164.