# Impact of antifibrotic therapy on lung cancer development in idiopathic pulmonary fibrosis

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**ABSTRACT**

Patients with idiopathic pulmonary fibrosis (IPF) are at a high risk for lung cancer (LC). Antifibrotic therapy slows disease progression and possibly prolongs survival. However, whether antifibrotic therapy affects LC-development in IPF patients remains unknown. This multi-centre retrospective study evaluated 345 IPF patients. The incidence and prevalence of LC were significantly lower in IPF patients receiving antifibrotic therapy than those not. Subsequently, LC-related mortality was significantly lower in IPF patients receiving antifibrotic therapy. These results suggest that antifibrotic therapy was possibly associated with a reduced risk of LC-development in IPF patients, which may be partly associated with its survival benefit. (100 words)

**Keywords:** Idiopathic pulmonary fibrosis, lung cancer, antifibrotic therapy, incidence, prevalence

## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease with an unknown aetiology and a poor prognosis[1 2]. To date, epidemiologic studies have shown that patients with IPF have a significantly higher risk for developing lung cancer (LC). Further, LC is a major cause of mortality in patients with IPF [3-5].

Antifibrotic therapy using pirfenidone and nintedanib reportedly slows disease progression[2] and possibly improves survival [6 7]. However, whether these drugs can affect the development of LC and LC-related mortality in patients with IPF is not fully elucidated [8]. Thus, the current study assessed the impact of antifibrotic therapy on the incidence and prevalence of LC and the rate of LC-related mortality in patients with IPF.

## METHODS

This retrospective study reviewed 378 consecutive patients with IPF. Thirty-three patients who were concomitantly diagnosed with LC and IPF or had a previous history of LC before IPF diagnosis were excluded. The remaining 345 patients with IPF were classified according to antifibrotic therapy initiation; 189 patients who received antifibrotics were classified as the IPF-antifibrotic therapy (+) group and 156 patients who did not receive antifibrotics as the IPF-antifibrotic therapy (-) group. The incidence, prevalence and cumulative incidence of LC development were assessed. The details of the study design and statistical analyses are provided as **Supplementary data**.

## RESULTS

### Impact of antifibrotic therapy on the incidence, prevalence and LC-related mortality

The characteristics of IPF-antifibrotic therapy (+) and IPF-antifibrotic therapy (-) patients are shown in **Table 1**. There were no significant differences between them except for BMI and smoking status at IPF diagnosis. IPF-antifibrotic therapy (+) patients included fewer current smokers and more never smokers than IPF-antifibrotic therapy (-) patients at the diagnosis.

During the observation period, 35 patients developed LC. The incidence and prevalence of LC development were significantly lower in IPF-antifibrotic therapy (+) patients than those in IPF-antifibrotic therapy (-) patients (incidence: 1.07 vs. 4.53 per 100 person–year, prevalence: 2.65 vs. 19.2%, respectively) (**Table 2 and Supplementary Table S1**). The characteristics of developing LCs are depicted in **Supplementary Table S2**.

Consequently, the proportion of LC-related mortality was significantly lower in IPF-antifibrotic therapy (+) patients compared with that in IPF-antifibrotic therapy (-) patients (1.6% vs 15.2%, respectively, p = 0.0001) (**Table 2**).

### Cumulative incidence and risk factors for LC development

The cumulative incidence of LC in patients with IPF managed with antifibrotic therapy was lower than that in those who were not (2.2% vs. 4.4% at 1 year, 2.2% vs. 6.7% at 3 years and 3.3% vs. 9.7% at 5 years, respectively, p = 0.004) (**Figure 1A**). Regardless of antifibrotics, the cumulative incidence of LC development was significantly lower in patients with IPF receiving antifibrotics than that in those who did not (**Figures 1B and 1C**). A significantly lower fitted probability for the development of LC in IPF-antifibrotic therapy (+) patients than IPF-antifibrotic therapy (-) patients was also noted in the Markov multistate model (**Supplementary Figure S2)**. The subgroup analyses are also provided as **Supplementary data**.

Both the univariate and multivariate Fine–Gray proportional hazard analysis identified that antifibrotic therapy was a significant low-risk factor for LC development (**Supplementary Table S3**).

## DISCUSSION

The current study investigated the impact of antifibrotic therapy on LC development in patients with IPF. Results showed that antifibrotic therapy reduced the incidence and prevalence of LC by 76% and 86%, respectively. Moreover, antifibrotic therapy was a significantly independent low-risk factor for LC development. Subsequently, the LC-related mortality rate was found to be lower in patients who received antifibrotic therapy. Taken together, these data indicated that antifibrotic therapy was associated with reduced LC development in IPF, which may be partly responsible for its possible survival benefit.

The overall incidence and prevalence of LC in our cohort were 2.14 per 100 person–year and 10.1%, respectively. These findings were consistent with those of previous studies in which the incidence and prevalence of LC ranged from 0.88 to 4.71 (overall: 2.07) per 100 person–year and from 3.71% to 31.31% (overall: 13.4%), respectively [4 5 9 10]. Importantly, the current study revealed that the incidence and prevalence of LC were significantly lower in IPF-antifibrotic therapy (+) patients than in IPF-antifibrotic therapy (-) patients (incidence: 1.07 vs. 4.53 per 100 person–year, prevalence: 2.65 vs. 19.2%, respectively). In addition, the cumulative incidence of LC development was lower in patients with IPF treated with antifibrotic therapy than in those who were not (2.2% vs. 6.7% at 3 years and 3.3% vs. 9.7% at 5 years, respectively). To date, only one study by Miura *et al*. showed that antifibrotics decreased the risk of LC development [8]. In 261 patients with IPF, (83 treated with pirfenidone and 178 not treated), pirfenidone treatment was a significantly independent low-risk factor for LC development in multivariate Cox proportional hazard analysis. These results are largely

consistent with our observations. However, Cox proportional hazard model used in Miura's study is thought to be inappropriate for these analyses, because this model does not consider competent events. Collectively, our results indicated that antifibrotic therapy was associated with reduced LC development in IPF.

LC has a significant negative impact on the survival of patients with IPF [4 5 9 10] and accounts for 8.0%–17.3% of IPF mortality prior to antifibrotic therapy initiation [4 5]. However, data about whether antifibrotic therapy affects LC-related mortality in patients with IPF are limited. In this regard, the present study clearly showed that antifibrotic therapy significantly reduced the LC-proportional mortality by approximately a tenth in this study (1.6% vs. 15.2%, respectively). Collectively, these data suggest that antifibrotic therapy can reduce LC-related mortality in patients with IPF.

Currently, an aberrant wound-healing process is believed to involve in the pathogenesis of both IPF and LC. Indeed, shared genetic and epigenetic mechanisms and signalling pathways including epithelial-mesenchymal transition process have been reported[5 9] . The mechanisms by which antifibrotic therapy reduces the risk of LC development in IPF are not fully elucidated [8]. Pirfenidone can inhibit tumour progression in vivo [3 5]. Further, nintedanib was originally developed as an anti-cancer drug and approved for non-small cell lung carcinoma [3 5]. However, it should be noted that this study does not provide direct evidence of the anticancer activity of the antifibrotics in IPF patients. Importantly, our results did not support a direct anti-cancer role for antifibrotics in IPF patients. Further research is required to elucidate the actual mechanisms for our findings.

This study had several limitations. First, it was a retrospective and single-cohort study, and may have had bias including immortal bias and selection bias for initiating antifibrotic therapy. There was the possibility that the indications for antifibrotic therapy might affect the results. Additionally, the smoking status was not matched between the

groups. Second, although the total number of IPF patients included was large, the number of patients who developed LC during antifibrotic therapy was relatively small. To overcome these biases, a larger study must be performed.

In conclusion, patients with IPF who received antifibrotic therapy showed a lower incidence and prevalence of LC in IPF than those did not. Therefore, antifibrotic therapy may be beneficial in preventing LC development and reducing LC-related mortality rates, which may be partly associated with the survival benefit of antifibrotic therapy.

**Abbreviations:**

LC: lung cancer

IPF: idiopathic pulmonary fibrosis

FVC: forced vital capacity

**Ethics approval and consent to participate**: The study protocol was approved by the ethical committee of Hamamatsu University School of Medicine (17-196) and was performed in accordance with the approved guidelines. The need for patient approval and/or informed consent was waived due to the retrospective nature of the study.

**Consent for publication**: Not applicable.

**Data availability statement:** Data supporting the findings of this study are available from the corresponding authors upon reasonable request.

**Conflicts of interest**: None declared.

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**Author contributions:** HN and YS: Conception and design, data collection, data analysis and interpretation, manuscript writing and final approval of the manuscript. KM: Statistical analysis, data collection and data analysis. YA, KM, HH and KY: Conception and design, data collection and data analysis. HN, HH, MK, KF, NE, TF, YN, NI and HN: Data collection, data analysis and supervision. TS: Conception and design, manuscript writing and administrative support.

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**FIGURE LEGENDS**

**Figure 1. Cumulative incidence of lung cancer in patients with IPF with or without antifibrotic therapy.**

Kaplan–Meier curves of the cumulative incidences of lung cancer development in patients with IPF with or without antifibrotic therapy (A). Kaplan–Meier curves of the cumulative incidences of lung cancer development in patients with IPF according to the use of antifibrotics, nintedanib (B) and pirfenidone (C). To calculate the cumulative incidences of LC development, as antifibrotic therapy initiation is a time-dependent event, all 345 patients (both IPF-antifibrotic therapy (+) and IPF-antifibrotic therapy (-)) were initially categorised as "without antifibrotic therapy" at the time of IPF diagnosis. Then, patients who initiated AFT (189 IPF-antifibrotic therapy (+)) were distributed into "with antifibrotic therapy" at the time of antifibrotic therapy initiation. The 156 patients with IPF-antifibrotic therapy (-) were categorised as "without antifibrotic therapy" consistently. Any death before LC development was considered as a competing risk in these analyses. P values were determined via Gray's analyses.

Abbreviations: IPF, idiopathic pulmonary fibrosis;

***Table 1. Clinical characteristics of 345 patients with IPF***

| | All patients (n = 345) | IPF-antifibrotic therapy (+) patients (n = 189) | IPF-antifibrotic therapy (-) patients (n = 156) | p-value† |
|---|---|---|---|---|
| Age, years | 70.0 (64.0–75.0) | 70.0 (64.0–74.0) | 71.0 (64.8–78.0) | 0.033 |
| Sex, male | 293 (84.9%) | 157 (83.1%) | 136 (87.2%) | 0.364 |
| Clinical IPF/biopsy-proven IPF | 276 (80.0%)/69 (20.0%) | 154 (81.5%)/35 (18.5%) | 122 (78.2%)/34 (21.8%) | 0.500 |
| Observation period, months | 49.1 (25.7–81.5) | 52.1 (34.0–83.5) | 41.8 (17.3–80.1) | 0.022 |
| Duration of AFT administration, months | | 23.6 (9.2–38.5) | | |
| Pirfenidone/nintedanib | | 137 (72.5%)/52 (27.5%) | | |
| Smoking status at IPF diagnosis current / former / never | 15/267/63 | 4/144/41 | 11/123/22 | 0.02 |
| Smoking status at start of antifibrotic therapy current / former / never | | 1/147/41 | | 0.07 |
| Smoking status after IPF diagnosis current / former / never | | | 4/130/22 | |
| Smoking pack-year | 39.4 (27.2–54.0) | 40.0 (28.0–53.3) | 38.0 (25.5–55.0) | 0.620 |
| Family history of LC | 28 (8.1%) | 16 (8.5%) | 12 (7.7%) | 0.845 |
| BMI, $kg/m^2$ | 23.4 (21.2–25.2) | 23.8 (21.5–25.5) | 23.0 (20.6–24.6) | 0.020 |

| | | | | |
|---|---|---|---|---|
| **Pulmonary function test** | | | | |
| FVC, %-pred | 78.2 (65.8–91.9) | 77.8 (67.2–89.7) | 78.9 (64.0–93.4) | 0.961 |
| $FEV_1$, %-pred | 84.0 (70.4–90.2) | 84.7 (71.3–94.5) | 82.7 (69.3–93.3) | 0.327 |
| $FEV_1$/FVC, % | 84.6 (79.5–88.3) | 84.7 (80.4–88.6) | 84.5 (77.0–87.6) | 0.227 |
| DLCO, % | 67.8 (54.3–82.9), n = 226 | 67.8 (53.6–80.5), n = 146 | 68.6 (57.3–87.3), n = 80 | 0.318 |
| **6-Minute walk test** | | | | |
| Distances, m | 448 (385–515), n = 123 | 458 (386–515), n = 82 | 440 (385–500), n = 41 | 0.836 |
| Minimum $SpO_2$, <90% | 61/123 (49.6%) | 42/82 (51.2%) | 19/41 (46.3%) | 0.703 |
| **Laboratory parameters** | | | | |
| KL-6 level, U/mL | 890 (620–1370) | 893 (659–1353) | 881 (597–1380) | 0.497 |
| SP-D level, ng/mL | 203 (121–313) | 211 (133–318) | 182 (114–293) | 0.101 |

† IPF-antifibrotic therapy (+) vs. IPF-antifibrotic therapy (-)

IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; LC, lung cancer; BMI, body mass index; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; DLCO, lung diffusion capacity for carbon monoxide; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D

***Table 2. Incidence and prevalence of LC, and rate of LC-related mortality in patients with IPF treated with or without antifibrotic therapy***

| | All patients (n = 345) | IPF-antifibrotic therapy (+) patients (n = 189) | IPF-antifibrotic therapy (-) patients (n = 156) | Risk ratio† |
|---|---|---|---|---|
| LC cases, n | 35 | 5 | 30 | |
| Incidence, per 100 person-year (95% CI) | 2.14 (1.50–2.96) | 1.07 (0.35–2.47) | 4.53 (3.08–6.41) | 0.235 (0.092–0.602) |
| Prevalence, % (95% CI) | 10.1 (7.2–13.8) | 2.65 (0.86–6.07) | 19.2 (13.4–26.3) | 0.138 (0.055–0.346) |
| LC-related mortality, % (95% CI) | 7.9 (4.7-12.1) | 1.61 (0.20-5.70) | 15.2 (9.0-23.6) | 0.106 (0.025-0.450) |

† IPF antifibrotic therapy (+) patients vs. IPF antifibrotic therapy (-) patients

IPF, idiopathic pulmonary fibrosis; LC, lung cancer; CI, confidence interval

# SUPPLEMENTARY FILE

**Impact of antifibrotic therapy on lung cancer development in idiopathic pulmonary fibrosis**

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# METHODS

## Study design and patients

This retrospective study reviewed the medical records of 378 consecutive patients with IPF who were admitted to Hamamatsu University of School of Medicine, Seirei Hamamatsu Hospital and Seirei Mikatahara Hospital from January 1991 to July 2019. In total, 27 patients were concomitantly diagnosed with LC and IPF, and six patients who had a previous history of LC before IPF diagnosis were excluded from this study. The remaining 345 patients with IPF were included and further classified according to antifibrotic therapy initiation. IPF patients who received antifibrotic drugs for at least 1 month were defined as the IPF-antifibrotic therapy (+) group, and those who never received antifibrotic drugs during the observation period, or who received less than 1 month were defined as the IPF-antifibrotic therapy (-) group. Then, 189 patients who received antifibrotics were classified under the IPF-antifibrotic therapy (+) group, and 156 patients who did not receive antifibrotics under the IPF-antifibrotic therapy (-) group (**Supplementary Figure S1**).

Because this study was retrospectively conducted, the indications for antifibrotic therapy were not properly pre-defined in all patients. However, there were two major situations in which antifibrotic therapy was initiated: one was that antifibrotic therapy was started immediately after IPF diagnosis, and the other was that antifibrotic therapy was started when disease progression was confirmed during observation (**Supplementary Table S4**). Disease progression was broadly defined as: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis on high-resolution CT [1]. In 48 (25.4%) of 189 patients, treatment with antifibrotics was

discontinued during the observation period, with a median exposure time of 8.6 months. The reasons for the discontinuations of antifibrotic therapy was presented in **Supplementary Table S5**.

IPF diagnosis was based on the ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association criteria [2-4]. The outcome of this study was LC development. LC was staged according to the 8th edition of the IASLC staging criteria [5]. The time of LC diagnosis was defined as the date of establishing histological diagnosis. Patients were followed up at least every 2-3 months, confirming survival and developing lung cancer as outcomes.

The study protocol was approved by the ethics committee of Hamamatsu University School of Medicine (17-196) and was conducted according to the approved guidelines. The need for patient approval and/or informed consent was waived due to the retrospective nature of the study.

## Data collection

Data about clinical data, laboratory findings, pulmonary function test results and outcomes were obtained from the medical records. Baseline data were collected at the time of IPF diagnosis.

## Statistical analysis

Discrete variables were expressed as counts and percentages, and continuous variables were expressed as median [interquartile range], unless otherwise specified. In the comparison between the patients with IPF-antifibrotic therapy (+) and those with IPF-

antifibrotic therapy (-), the Mann–Whitney U and Fisher's exact tests were used to compare continuous variables and categorical variables, respectively.

The incidence of LC development in 189 IPF-antifibrotic therapy (+) was estimated from the date of antifibrotic therapy initiation, as initiating antifibrotic therapy is a time-dependent event, and to estimate the incidence of LC development from the date of diagnosis in these patients may result in immortal bias and the underestimation of the incidence of LC development. Meanwhile, the incidence of LC development in 156 IPF-antifibrotic therapy (-) patients was estimated from the date of IPF diagnosis. The incidence of LC was calculated by person–years of follow-up. The prevalence was assessed by dividing number of LC cases by the number of patients. LC-related mortality was calculated based on the proportion of LC-associated deaths among all deaths (**Table 2**).

For assessing the cumulative incidence of LC, all of 345 patients (both 189 IPF-antifibrotic therapy (+) and 156 IPF-antifibrotic therapy (-) patients) were first categorised as "without antifibrotic therapy" at the time of IPF diagnosis. Then, when patients started antifibrotic therapy, the patients were censored and transitioned into "with antifibrotic therapy" at the time of antifibrotic therapy initiation. The cumulative incidence of these patients was calculated from the start of antifibrotic therapy. The 156 patients with IPF-antifibrotic therapy (-) were categorised as "without antifibrotic therapy" consistently. The cumulative incidences of LC were calculated using the Kaplan–Meier method, and differences were evaluated using Gray's test (**Figure 1**). Fine–Gray proportional hazard analyses were performed to identify predictive factors associated with LC development. Any death before LC development was considered as a competing risk in these analyses. The variables of Fine–Gray proportional hazard analyses that were considered clinically important factors and known risk factors for LC development in IPF were selected.

The risk of development of LC with or without antifibrotic therapy was also evaluated using Markov multistate model to describe the transitions risk of LC development with or without antifibrotic therapy. The Markov multistate models have traditionally been used to study the effect of transitory state of illness (or interventions such as transplantation) on outcomes. The transient states were defined as follows: individuals diagnosed with IPF ("without antifibrotic therapy"; state 1), those who initiated antifibrotic therapy ("with antifibrotic therapy"; state 2), LC development (state 3), and death before LC development (state 4). The transition time from state 1 to state 2 was defined as the difference between the date of IPF diagnosis and date of antifibrotic therapy initiation. Similarly, LC development (transition to state 3) was taken as the date from the last entry into either state 1 or state 2 till the date of LC diagnosis. Estimates for both transition intensities and probabilities from one state to another were obtained from the Markov model. The former summarises the instantaneous risk of transition between any two states and is analogous to a hazard rate, whereas the latter is an estimate of the probability of transitioning to a different state or time.

Statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphical user interface for R software program (version 2.13.0, The R Foundation for Statistical Computing, Vienna, Austria) [6]. A p-value of $< 0.05$ was considered as the level of statistical significance for all analyses.

## RESULTS

### *Clinical characteristic*

We compared smoking status between patients receiving antifibrotic therapy at the start of the therapy and those not receiving after IPF diagnosis. There was no significant difference in smoking status between them (**Table 1)**.

### *Incidence, prevalence, LC-related mortality, and cumulative incidence of LC development according to the indication or timing for antifibrotic therapy.*

According to the indications or timing for antifibrotic therapy, the incidence, prevalence, and LC-proportional mortality were also examined. Eighty-four patients started antifibrotic therapy immediately after IPF diagnosis, and 99 patients started subsequent to disease progression (**Supplementary Table S4**). The cumulative incidences of LC development were similar between the groups (**Supplementary Figure S3A**). The incidence, prevalence, and LC-proportional mortality were also equivalent between the groups (**Supplementary Table S6**).

### *Incidence, prevalence, LC-related mortality, and cumulative incidence of LC development between antifibrotic therapy-continued and -discontinued cases.*

The incidences, prevalence, and LC-proportional mortality are shown in **Supplementary Table S7**. There were no significant differences between the patients continuing antifibrotic therapy over the observation period and those discontinuing antifibrotic therapy. The cumulative incidence of LC development did not also differ between them (**Supplementary Figure S3B**).

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**Supplementary FIGURE LEGENDS**

**Figure S1. Flow diagram of the study.**

Abbreviations: IPF, idiopathic pulmonary fibrosis; LC, lung cancer;

**Figure S2. Fitted probabilities of LC development with or without antifibrotic therapy.**

Diagram showing the multistate model used for modelling the impact of antifibrotic therapy on LC development in patients with IPF (A). Fitted probability of LC development curves based on transition intensities from states 1 to 3 (i.e., transitioning to death without antifibrotics) and state 2 to 3 (i.e., transitioning to LC development after antifibrotic therapy) in the unadjusted multistate model (B).

**Figure S3. Cumulative incidence of LC in patients with IPF according to indications of antifibrotic therapy, and IPF-antifibrotic therapy-continued cases and antifibrotic therapy-discontinued cases.**

Kaplan–Meier curves of the cumulative incidence of LC according to indications of antifibrotic therapy (A). Kaplan–Meier curves of the cumulative incidence of LC in IPF-antifibrotic therapy-continued cases and antifibrotic therapy-discontinued cases (B). The cumulative incidence of LC development was estimated from antifibrotic therapy initiation. Any death before LC development was considered as a competing risk in these analyses. P values were determined via Gray's analyses.

Abbreviations: IPF, idiopathic pulmonary fibrosis;

***Supplementary Table S1. Incidence and prevalence of LC, and rate of LC-related mortality in patients with IPF treated with nintedanib or pirfenidone***

| | IPF patients receiving nintedanib (n=52) | IPF patients receiving pirfenidone (n=137) |
|---|---|---|
| LC cases, n | 0 | 5 |
| Incidence, per 100 person-year (95% CI) | 0 (0–0) | 1.44 (0.47–3.32) |
| Prevalence, % (95% CI) | 0 (0–0) | 3.65 (1.20–8.31) |
| LC-related mortality, % (95% CI) | 0 (0-0) | 2.02 (0.25-7.11) |

IPF, idiopathic pulmonary fibrosis; LC, lung cancer; CI, confidence interval

***Supplementary Table S2. Clinical characteristics of 35 patients who developed LC***

| | LC in all patients (n = 35) | LC among IPF-antifibrotic therapy (+) patients (n = 5) | LC among IPF- antifibrotic therapy (-) patients (n = 30) | p-value |
|---|---|---|---|---|
| Age, years | 72.0 (65.0–77.5) | 73.0 (65.0–74.0) | 70.5 (65.3–77.8) | 0.869 |
| Sex, male | 35 (100%) | 5 (100%) | 30 (100%) | 1.000 |
| Duration from IPF to LC diagnosis, months | 25.4 (8.6–59.0) | 33.7 (12.8–34.3) | 23.7 (8.6–62.2) | 1.000 |
| Duration from antifibrotic therapy initiation to LC diagnosis, months | | 10.0 (7.1-10.1) | | |
| Smoking; current / former / never | 5/29/1 | 0/4/1 | 5/25/0 | 0.156 |
| Smoking pack-year | 50.0 (35.5–79.5) | 44.0 (32.3–63.8) | 50.0 (37.0–79.5) | 0.574 |
| LC detecting | | | | |
| Asymptomatic (screening) / symptomatic | 27 (77.1%) / 8 (22.9%) | 4 (80.0%) / 1 (20.0%) | 23 (76.7%)/ 7 (23.3%) | 1.000 |
| **Histology** | | | | |
| Adenocarcinoma | 11/29 (37.9%) | 3/5 (60%) | 8/24 (33.3%) | 0.424 |
| Squamous cell carcinoma | 11/29 (37.9%) | 1/5 (20%) | 10/24 (41.7%) | |
| Small cell carcinoma | 4/29 (13.8%) | 0/5 (0%) | 4/24 (16.7%) | |
| Other types | 3/29 (10.3%) | 1/5 (20%) | 2/24 (8.3%) | |
| **Staging** | | | | |
| Stage I | 19/35 (54.3%) | 3/5 (60%) | 16/30 (53.3%) | 1.000 |
| Stage II | 3/35 (8.6%) | 0/5 (0%) | 3/30 (10.0%) | |

| | | | | |
|---|---|---|---|---|
| Stage III | 1/35 (2.9%) | 0/5 (0%) | 1/30 (3.3%) | |
| Stage IV | 12/35 (34.3%) | 2/5 (40%) | 10/30 (33.3%) | |
| **Cancer location** | | | | |
| Peripheral and nearby reticulation | 28/35 (80.0%) | 5/5 (100%) | 23/30 (76.7%) | |
| Peripheral and apart from reticulation | 3/35 (8.6%) | 0/5 (0%) | 3/30 (10.0%) | 1.000 |
| Central | 4/35 (11.4%) | 0/5 (0%) | 4/30 (13.3%) | |
| **Treatment** | | | | |
| Surgery | 13/35 (37.1%) | 2/5 (40.0%) | 11/30 (36.7%) | |
| Chemotherapy | 10/35 (28.6%) | 2/5 (40.0%) | 8/30 (26.7%) | 0.868 |
| Radiotherapy | 1/35 (2.9%) | 0/5 (0%) | 1/30 (3.3%) | |
| Best supportive care | 11/35 (31.4%) | 1/5 (20.0%) | 10/30 (33.3%) | |

IPF, idiopathic pulmonary fibrosis; LC, lung cancer

***Supplementary Table S3. Risk factors for the development of LC based on the univariate and multivariate Fine–Gray analyses***

| Predictors | HR | 95% CI | p-value | | HR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| **Univariate analysis** | | | | **Multivariate analysis** | | | |
| Age, years | 0.987 | 0.955–1.020 | 0.44 | Age, years | 1.007 | 0.973–1.044 | 0.68 |
| Sex, male | 28570 | 18860–43270 | <0.0001 | Sex, male | 13610 | 3286–56340 | <0.0001 |
| BMI, $kg/m^2$ | 1.058 | 0.951–1.178 | 0.30 | Smoking history | 2.641 | 0.338–20.660 | 0.35 |
| Smoking history | 8.652 | 1.174–63.770 | 0.03 | Antifibrotic therapy, yes | 0.298 | 0.106–0.835 | 0.021 |
| FVC, % | 1.028 | 1.010–1.046 | 0.0018 | FVC, % | 1.018 | 0.997–1.040 | 0.093 |
| $FEV_1$, % | 1.008 | 0.995–1.022 | 0.21 | | | | |
| $FEV_1$/FVC, % | 0.966 | 0.935–0.999 | 0.04 | | | | |
| DLCO, % | 1.001 | 0.986–1.016 | 0.90 | | | | |
| TP level, g/dL | 0.968 | 0.667–1.406 | 0.87 | | | | |
| Alb level, g/dL | 0.952 | 0.357–2.541 | 0.92 | | | | |
| LDH level, U/L | 0.9985 | 0.9939–1.003 | 0.53 | | | | |
| CRP level, mg/dL | 1.049 | 0.878–1.254 | 0.60 | | | | |
| KL-6 level, U/mL | 1.000 | 0.9995–1.000 | 0.92 | | | | |
| SP-D level, ng/mL | 1.000 | 0.998–1.001 | 0.66 | | | | |
| Antifibrotic therapy, yes | 0.234 | 0.090–0.606 | 0.0028 | | | | |

IPF, idiopathic pulmonary fibrosis; LC, lung cancer; CI, confidence interval; BMI, body mass index; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; DLCO, lung diffusion capacity for carbon monoxide; TP, total protein; Alb, albumin; LDH, lactate dehydrogenase; CRP, C-reactive protein; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D

***Supplementary Table S4. Indications or timing of antifibrotic therapy***

| Patients receiving antifibrotic therapy (n=189) | |
|---|---|
| Starting immediately after IPF diagnosis | 84 (44.4%) |
| Starting subsequent to disease progression | 99 (52.4%) |
| A relative decline in FVC of 10% or more of predicted value | 53 (28.0%) |
| A relative decline in FVC of 5% to less than 10% of predicted value and worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT | 24 (12.7%) |
| Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT | 22 (11.6%) |
| Others* | 6 (3.2%) |

*, Starting at the time of approval of antifibrotic therapy in Japan, or patients had initially refused antifibrotic therapy, but then his/her will changed.

IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity

***Supplementary Table S5. Reasons for discontinuation of antifibrotics in 48 patients with IPF***

| Causes for antifibrotic therapy discontinuation (n=48) | |
|---|---|
| Adverse drug reactions | 32 (66.7%) |
| Gastrointestinal disorders | 21 (43.8%) |
| Liver enzyme elevation | 7 (14.6%) |
| Photosensitivity | 2 (4.2%) |
| Rash | 1 (2.1%) |
| Visual impairment | 1 (2.1%) |
| Disease progression | 10 (20.8%) |
| Patients' will | 2 (4.2%) |
| Others | 4 (8.3%) |

IPF, idiopathic pulmonary fibrosis

***Supplementary Table S6. Incidence and prevalence of LC, and LC-related mortality according to the indications or timing of antifibrotic therapy.***

| | IPF-antifibrotic therapy (+) patients (n = 189) | Starting immediately after IPF diagnosis (n = 84) | Starting subsequent to disease progression (n=99) | Others* (n=6) | Risk ratio † |
|---|---|---|---|---|---|
| LC cases, n | 5 | 2 | 3 | 0 | 0.78 (0.13-4.64) |
| Incidence, per 100 person-year (95% CI) | 1.07 (0.35–2.47) | 0.94 (0.11-3.37) | 1.20 (0.25-3.48) | 0 (0–0) | 0.79 (0.13-4.59) |
| Prevalence, % (95% CI) | 2.65 (0.86–6.07) | 2.38 (0.29-8.34) | 3.03 (0.63-8.6) | 0 (0–0) | 1.50 (0.10-23.41) |
| LC-proportional mortality, % (95% CI) | 1.61 (0.20-5.70) | 2.08 (0.05-11.1) | 1.39 (0.04-7.5) | 0 (0–0) | 0.78 (0.13-4.64) |

*, Starting at the time of approval of antifibrotic therapy in Japan, or patients had initially refused antifibrotic therapy, but then his/her will changed.

† Starting immediately after IPF diagnosis vs. Starting subsequent to disease progression

LC, lung cancer; CI, confidence interval; IPF, idiopathic pulmonary fibrosis;

***Supplementary Table S7. Incidence and prevalence of LC, and LC-related mortality between antifibrotic therapy-continued cases and -discontinued cases.***

| | IPF-antifibrotic therapy (+) patients (n = 189) | Antifibrotic therapy-continued cases (n = 141) | Antifibrotic therapy-discontinued cases (n = 48) | Risk ratio |
|---|---|---|---|---|
| LC, cases | 5 | 4 | 1 | |
| Incidence, per 100 person-year (95% CI) | 1.07 (0.35–2.47) | 1.15 (0.31–2.91) | 0.83 (0.02–4.55) | 1.376 (0.16–12.2) |
| Prevalence, % (95% CI) | 2.65 (0.86–6.07) | 2.84 (0.78–7.10) | 2.08 (0.53–11.07) | 1.36 (0.16–11.9) |
| LC-proportional mortality, % (95% CI) | 1.61 (0.20-5.70) | 1.12 (0.03-6.10) | 2.86 (0.07-14.9) | 0.39 (0.03-6.12) |

LC, lung cancer; CI, confidence interval; IPF, idiopathic pulmonary fibrosis