

Lung cancer and interstitial lung disease: a literature review

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Abstract: The association between lung cancer (LC) and interstitial lung disease (ILD) can be explained by the shared risk factors like smoking and physiopathology of fibrogenesis and cancerogenesis. The relative LC risk is shown to be 3.5- to 7.3-times higher in ILD, with LC occurrence estimated at 10–20% in ILD, with >15% of ILD patients likely to die from LC. ILD incidence upon LC diagnosis varied from 2.4–10.9%. Primary radiological presentations consist of peripheral lesions, mostly in the inferior pulmonary lobes, either close to or within the ILD areas. There is a trend towards inverted proportion of adenocarcinomas and squamous-cell carcinomas, with EGFR mutations very rarely found. ILD negatively impacted LC prognosis, with surgery associated with increased morbidity-mortality, particularly due to acute exacerbation (AE) of ILD. Limited resection reduced this risk, whilst increasing that of cancer mortality. Studies on radiotherapy that can induce AE-ILD are scarce. Chemotherapy was associated with similar response rates to those in LC patients without ILD, yet worse survival. This difference may be accounted for by ILD patients' poorer health and higher risk of drug-induced pneumonitis. Further studies are warranted to better understand cancer physiopathology within the fibrotic areas, along with the therapeutic strategies required.

Keywords: Lung cancer (LC); pulmonary fibrosis; interstitial lung disease (ILD)

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Introduction

The first literature reviews on the association between lung cancer (LC) and interstitial lung disease (ILD) date back to over 10 years. Primarily focused on epidemiology (1,2), these reviews reported increased LC risk in ILD. Published in 2017, the last review focused on LC associated with idiopathic pulmonary fibrosis (IPF) (3). Our current review sought to further enhance our understanding of LC-ILD, considering recently published data.

Sharing common risk factors with LC like smoking or exposure to chemicals (4,5), IPF must be distinguished from other ILDs. Like carcinogenesis, IPF physiopathology is primarily based on epithelial damage, repair abnormalities, and epithelial mesenchymal transition, whereas for the other ILD subtypes, inflammation and immunosuppression are paramount features. These last displays a better prognosis than IPF.

The review has several limitations we wish to highlight upfront. Most data were derived from retrospective Asian cohorts, with ILD diagnoses based on surgical samples or

retrospective pre-operative CTs. While nearly all studies focused on IPF, only few concerned all ILDs.

Methods

Literature review

A systematic Medline search through PubMed was performed from inception to January 2018 for published reports restricted to human subjects and English or French language. Bibliographies from selected articles were screened for relevant publications.

Selection of studies

The inclusion criteria were: (I) ILD or IPF; (II) LC. Studies reporting ILD secondary to LC therapy or LC secondary to ILD therapy were excluded.

ILD classification

The commonly-affected area in ILD is the pulmonary interstitium. Pulmonary damage weakens alveolar wall integrity, causing epithelial cell lesions, inflammation, and myofibroblast infiltration, with extracellular matrix accumulation. This results in diminished pulmonary compliance and altered gas exchanges, with eventually pulmonary insufficiency.

In the early 2000's, a new ILD classification was proposed, recently updated (6). IPF is the most serious ILD, occurring in male smokers aged ≥ 60 , with a median survival of 2–3 years. Other ILDs essentially involve inflammatory processes, with better prognosis.

Common features of ILD and LC

The two leading hypotheses regarding LC-ILD are the shared risk factors and common physiopathology (*Figure 1*).

Common risk factors

As smoking and exposure to occupational hazards are common risk factors for LC and ILD especially IPF, both may account for their concomitant occurrence (4,5). However, smoking is not always preponderant, since LC risk in scleroderma patients is no higher in smokers than non-smokers (7).

Common pathophysiology

The pathophysiology of ILDs, particularly IPF, resembles that of cancer development, including epithelial cell anomalies ranging from metaplasia to carcinomatous transformation, cellular bioenergetics, soluble mediator release, gene alterations, and aging with telomere attrition and aberrant recapitulation of developmental pathways.

Cellular abnormalities and cell-to-cell interactions

Epithelial layer abnormalities like hyperplasia of pulmonary cells, cuboidal cells, and mucous cells, along with epithelial metaplasia within fibrotic regions, were demonstrated in IPF (8). Epithelial metaplasia appears linked to cancerogenesis, with transition zones from metaplasia to invasive cancer located close to fibrosis areas (9,10). Histone deacetylase enzyme (HDAC) overexpression was recently demonstrated in aberrant bronchial cells populating fibrotic regions, with HDACs exhibiting anti-apoptotic activity via *p53* inhibition or cMyc stimulation observed in cancer cells (11).

The metabolic perturbation in cancer cells is known as the Warburg effect, meaning that glycolysis is preferred over oxidative phosphorylation, even in the presence of oxygen. The Warburg effect has also been observed upon myofibroblast differentiation, a distinct physiopathological step in pulmonary fibrosis (12).

In LC, interactions between stroma and tumor influence tumor progression and metastatic diffusion. Peritumoral stroma shares common features with pulmonary fibrosis, and several authors have reported that this stroma facilitates mesenchymatous phenotype development in tumor cells, along with their invasive capability (13–15). Inflammatory cells are involved in carcinogenesis in smokers via oxygen-free radical production (16), with decreased tumor immune surveillance. A diminished T lymphocyte response was demonstrated in chronic obstructive pulmonary disease, contributing to enhanced LC risk (17).

Soluble mediators and gene alterations

The carcinomatous transformation of epithelial cells during fibrogenesis is likely facilitated by cytokine or nitrous derivative secretion (18,19) into the microenvironment, enhancing acquired genetic anomalies like *p53* mutations.

Tumor growth factor beta (TGF β) appears involved in fibrogenesis. In normal conditions, TGF β exerts an anti-proliferative action on epithelial cells and stimulates the Wnt/ β -catenin signalization pathway, transforming fibroblasts into myofibroblasts (20,21). Using cDNA arrays,

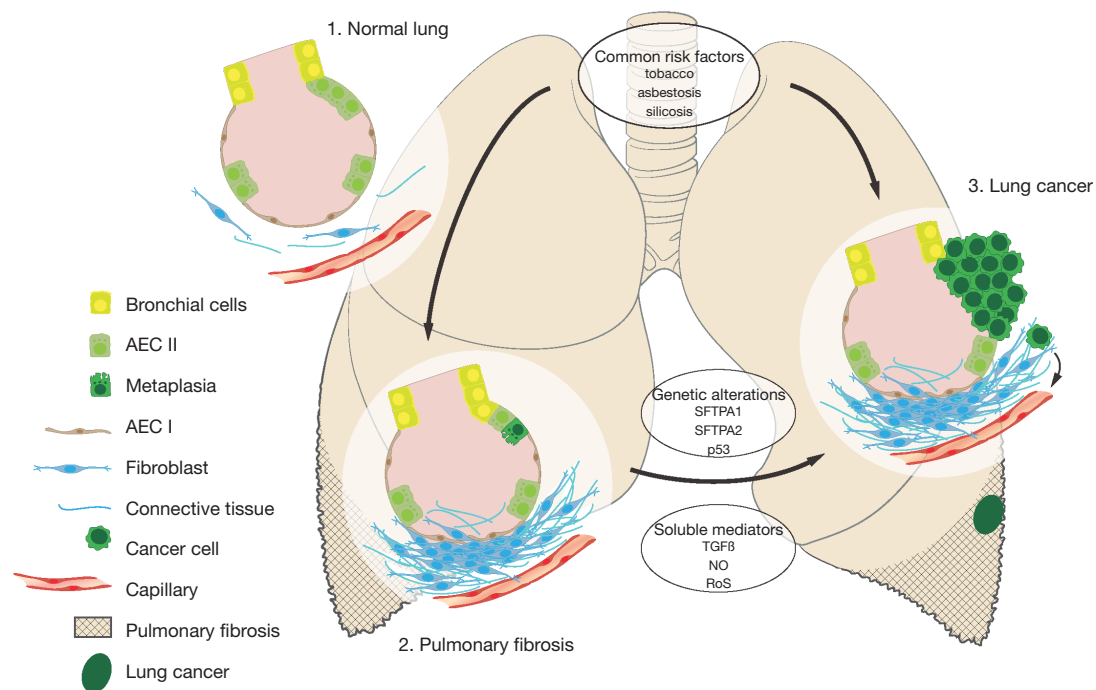


Figure 1 Pathobiological paradigm for LC in ILD. Evidence suggests that the pathobiology of LC in ILD involves both common risk factors (e.g., tobacco and asbestos) and common pathophysiology (e.g., cellular abnormalities). In ILD, a combination of genetic, environmental, and behavioral factors are believed to contribute to the development of a fibrotic phenotype characterized by extracellular matrix deposition, parenchymal scar formation, and lung remodeling. LC in ILD is most likely favored by genetic alterations (e.g., SFTPA, p53) and soluble mediators' secretions (TGFβ, NO, RoS). TGFβ, transforming growth factor β; NO, nitric oxygen; RoS, reactive oxygen species; LC, lung cancer; ILD, interstitial lung disease.

a study revealed Smad4 expression, involved in TGFβ signaling, to be diminished in LC patients with concomitant IPF compared to those without, promoting diminished growth inhibitory response to TGFβ (22). TGFβ decreased cancer immune surveillance, inhibiting effector T lymphocytes while stimulating regulator T lymphocytes. In a tumor xenograft transplant model, TGFβ instillation increased regulator T lymphocyte levels, with significant tumor growth, increased lung metastasis, and decreased overall survival (OS). Naringenin, an antifibrotic agent, reduced TGFβ pro-tumoral activity in animals (23).

TGFβ's role regarding LC-ILD association was evoked while investigating families with both conditions. Mutations in genes encoding surfactant proteins A2 (SFTPA2) that induce TGFβ secretion promoted pulmonary fibrosis, with associations found between cancer and ILD and SFTPA2 mutations (24,25). One study reported a family with 10 ILD patients, three exhibiting concomitant LC, while three others displayed LC without ILD, all patients exhibiting SFTPA2 mutations (25). Another study described a family

including 10 patients exhibiting ILD and three others LC, with six of the patients exhibiting SFTPA1 mutations (26).

Nitric oxygen (NO) produced in stressed epithelial cells caused guanine nitrification in cellular DNA. NO overexpression, along with guanine nitrification, was more common in pulmonary tissues from IPF and squamous-cell carcinoma patients versus healthy subjects, regardless of smoking status (27).

Oncogene and tumor-suppressor gene mutations induce genomic instability within epithelial cells. The p53 gene is the most-frequently mutated gene in LC. Kawasaki *et al.*, analyzing p53 gene mutations and expression in tumoral tissues from 19 LC-IPF patients, detected p53 mutations in cancer cells and squamous metaplasia cells in 57% and 26% of patients, respectively (8). Another study focused on expired air and blood samples from IPF patients revealed genetic alterations within tumor suppressor genes (28). Searching for common anomalies between IPF and LC in the AKT/MAPK and TLR signaling pathways proved inconclusive (29).

Most genetic hallmarks that characterize the ageing

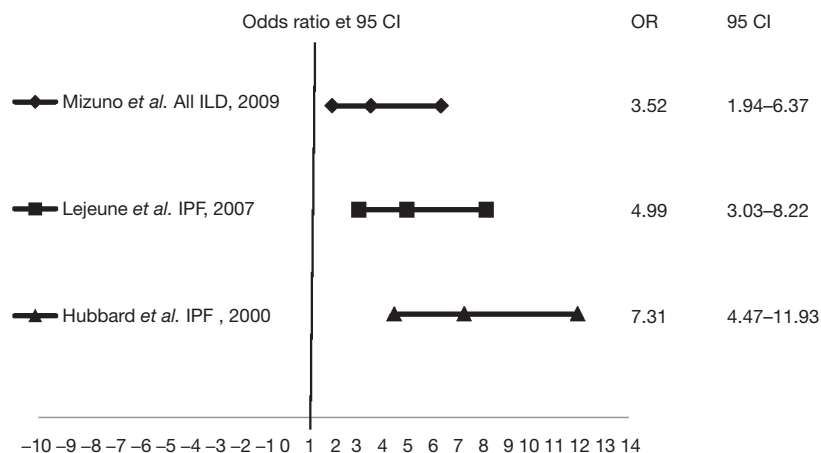


Figure 2 LC risk in ILD patients (see text). LC, lung cancer; ILD, interstitial lung disease.

process were identified in both IPF and LC like abnormal telomere shortening, aberrant recapitulation of developmental pathways, and cellular senescence (30-32).

Contrasting LC risk between IPF and other ILDs

Increased LC risk in ILD

Increased LC risk in ILD was assessed in three studies (Figure 2). A Japanese case-control study comparing LC patients to healthy subjects participating in a CT screening program found the proportion of smokers to be higher in the LC group (88.5% vs. 45%) and LC risk to be 3.5 times superior in patients with fibrotic lesions, regardless of smoking status (33). Two IPF studies reported 4.99 and 7.3 times higher LC risk with this disease, respectively (34,35).

LC diagnosis is usually established in male smokers in their sixties (9,36,37). Concerning IPF patients, multivariate analysis demonstrated age >60 years, male gender, and tobacco smoking to be associated with relative LC risks of 2.41, 11.04, and 2.71, respectively (38). Two series found a significantly higher proportion of males with LC-IPF versus LC patients without ILD (92% vs. 62%; 94% vs. 74%, respectively) (39-41).

LC incidence and prevalence in IPF and other ILDs

Idiopathic ILD

Figure 3 lists published series reporting on LC frequency in IPF, combining pulmonary fibrosis and emphysema (CPFE). The first, a retrospective Japanese study involving 103 IPF patients, reported 20.5% of patients having

developed LC over a mean 52±44.8 months follow-up (36). In the second involving 205 cryptogenic fibrosing alveolitis (CFA) patients, LC frequency was 9.8% over a 4±21-year follow-up (42). An Italian cohort involving 181 IPF patients reported a 13% LC frequency (n=23) (37).

Analyzing CPFE populations, LC incidence was 46.8% (22/47) over a 3-year follow-up in a Japanese series and 14.6% (47/322) over a 10-year follow-up in the French GERM“O”P (Groupe d’Etude et de Recherche des Maladies Orphelines Pulmonaires) registry (43,44). Data on other idiopathic ILDs like non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), and lymphocytic interstitial pneumonia (LIP) are quasi-inexistent.

Other ILDs

Data concerning LC risk in other ILDs are difficult to interpret, as certain ILDs are strongly associated with smoking or exposure to carcinogens. Moreover, myositis and dermatomyositis can manifest as a paraneoplastic syndrome complicating LC.

Connective tissue disease (CTD)-associated ILD

A retrospective study reported a 5.5% (7/127) LC incidence in CTD-related ILDs over a median 67.4-month follow-up, with 1-, 3-, and 5-year cumulative incidences of 0, 1.8%, and 2.9%. In univariate analysis, heavy smoking and emphysema on CT were LC risk factors (45).

In cohort studies, scleroderma was proven an LC risk factor, with LC being the most common scleroderma-associated cancer with an incidence of 4.9% in Sweden versus 5.7% in Japan and 5.9% in Australia (46-48).

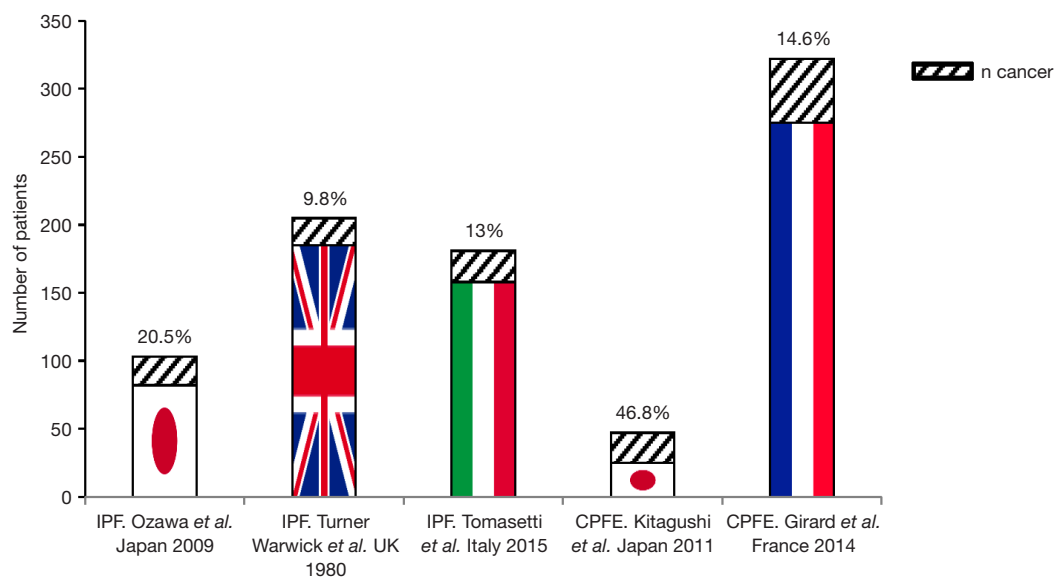


Figure 3 Cancer rates in IPF and CPFE patients (see text). IPF, idiopathic pulmonary fibrosis; CPFE, combining pulmonary fibrosis and emphysema.

A meta-analysis assessing cancer incidence in RA revealed increased cancer risk with a standardized incidence ratio (SIR) of 1.63 (49). Likewise, several cohort studies demonstrated an increased LC risk in systemic lupus erythematosus with an SIR of 1.37–3.1 (50). In these two CTD, no link was reported between LC and ILD.

Idiopathic inflammatory myopathies like polymyositis (PM) and dermatomyositis (DM) can manifest as paraneoplastic syndromes. ILD appears to diminish the LC cancer risk, especially among Asians (51–53).

Silicosis and asbestosis

In a meta-analysis, silicosis was an LC risk factor with a 2.37 RR, in contrast to silica exposure without silicosis (54). Smoking markedly increased LC risk in silicosis patients, with a 4.47 RR.

Concerning asbestos exposure, most patients who develop LC in this setting are also smokers. The association between asbestos exposure and LC proves difficult, with roughly 33% of such cancers presumably caused by double exposure (55). Asbestosis, an ILD secondary to asbestos fiber inhalation, increases LC risk (55,56).

Hypersensitivity pneumonia (HP)

HP refers to ILDs secondary to organic antigen exposure, the best known being bird fancier's or farmer's lung. A Japanese study identified 11 cancer cases among 104 (10.4%) HP patients, most exhibiting bird fancier's lung ($n=93$), and all involving smokers. Seven patients underwent lung

biopsy, revealing a pattern of usual interstitial pneumonia (UIP) similar to IPF (57).

Sarcoidosis

Data on sarcoidosis are controversial. In a meta-analysis, sarcoidosis was initially not associated with increased LC risk, though an increased risk was observed at 5 years post-diagnosis, followed by risk decrease, and ending with a diminished risk at 10 years (58).

Langerhans cell granulomatosis

Langerhans cell granulomatosis is strongly associated with smoking. Two series reported links between LC and Langerhans cell granulomatosis, suggesting increased LC risk (59,60).

LC mortality in IPF

A paper reviewed the published series on LC-related mortality in IPF, reporting a mean mortality of 17.3% (61). In a 1990–1992 UK cohort survey, IPF diagnosis was initially established in 588 patients; of these, 488 died, 46 due to LC (9.4%). A more recent German study revealed that of 272 IPF-diagnosed patients, 171 died, 13 (7.3%) from LC (62).

LC in ILD or ILD in LC?

Another means of investigating LC-ILD is to assess ILD

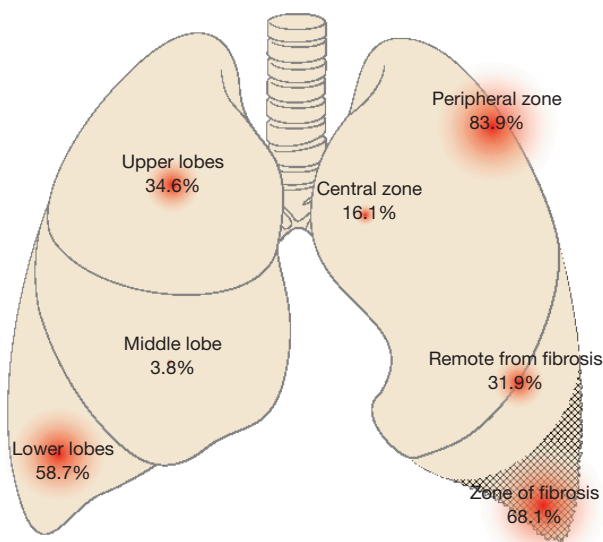


Figure 4 CT scan presentation of LC associated with ILD (see text). LC, lung cancer; ILD, interstitial lung disease; CT, computed tomography.

frequency in LC populations (Table S1). Most series pertaining to IPF reported a frequency of 2.4–10.9% (10,38,41,63-70), with only three from Japan exhibiting higher rates of 16.8% and 24.3% (71,72). In the first study, IPF diagnosis was based on histological analysis (71), potentially including infra-radiological IPFs, which may explain the differences.

Clinical presentation

Cancer detection mode and stage at diagnosis

LC is mostly diagnosed after ILD, with numerous LCs fortuitously detected upon CT ILD-surveillance (73). So far, 4,672 patients concomitantly exhibiting non-small cell lung cancer (NSCLC) were reported, with stage I, II, III, and IV in 42.7%, 14.9%, 22.5%, and 13.3% of cases, respectively. A recent surgery series comparing 104 patients with ILD-LC to 1,160 LC-alone patients revealed a higher proportion of the former exhibiting pleural invasion (69). Concerning small-cell LC, 209 cases were reported, 39.7% of whom were localized.

CT-scan presentation and PET-scan requirement

In ILD, LCs mostly manifests as peripheral tumors (83.9% of 503 patients) developing within/near fibrotic areas

(68.1% of 474), in the inferior lung lobes (58.7% of 2,877) (Figures 4,S1,S2). Their limits are distinct, with spiculated contours and possibly an air bronchogram (73,74).

In a series of 66 peripheral T1N0 cancers, 64% occurred in the inferior lobes, 53% at the fibrosis/healthy tissue interface, and 31.8% in fibrotic areas. Most tumors consisted of solid, round or oval lesions, with a median doubling time of 77 days (75). In another study (76), tumors were more commonly found in areas with more fibrosis (12/16 patients). A South Korean study reported contrasting results involving 63 LC-IPF patients. While peripheral (56%), most lesions predominantly affected the superior lobes (51%), far from fibrotic areas (63%). One possible explanation was that 19% of patients exhibited small-cell LCs, more centrally located (38).

Assessing tumor size on CT proved difficult. In a study involving 1,357 surgical patients, 136 exhibiting ILD, tumor size was underestimated in 10.3% of ILD patients versus 3.2% of controls (77).

Mediastinal analysis of LC-ILD is more difficult, owing to reactively-increased mediastinal lymph node sizes in 55–93% ILD cases (78). CT specificity for mediastinal staging is diminished in IPF (47% vs. 84%). PET revealed similar sensitivity and specificity rates in patients with or without ILD (78). Comparing LC-IPF patients to those without ILD, the authors demonstrated that PET versus CT alone increased diagnostic accuracy from 14% to 33%.

Histology and molecular analysis

Obtaining histological cancer diagnosis can prove challenging owing to patient frailty. In the GERM“O”P study, histological diagnosis was impossible in 9 (19%) patients (43). Thirteen series, including six surgical ones, assessed LC histology distribution in ILD cases versus ILD-free controls. Seven revealed statistically different histological distribution in ILD from controls, with less adenocarcinoma (ADC) (24–40% vs. 42–80%) and more squamous-cell carcinoma (SCC) (29–68% vs. 13–26%) cases, the other six revealing similar distributions (9,38,41,64,65,67,68,72,79-83) (Figures S3,S4).

Synchronous cancers were more frequently described in IPF patients versus ILD-free in two series, one based on autopsy data (17% vs. 5%; 21.9% vs. 3.4%) (9,41). A retrospective Japanese study reported higher frequency of combined small-cell LC with NSCLC (7/22; 33%) versus single cancers (17/119; 14%) (79).

Activating mutations in epidermal growth factor receptor

(EGFR) gene were rarely detected in LC-ILD, owing to high frequencies of smokers and SCC histology (Table S2). Five Japanese series compared *EGFR* gene mutation frequencies in NSCLC patients with and without ILD. EGFR mutations were detected in 0–5.8% of tumors in ILD patients versus 24.3–47% in those without (72,84–87). A multivariate analysis revealed EGFR mutations to be independently associated with absent ILD (86). In another study involving ADC patients, those with histologically-confirmed ILD were more commonly Kras-mutation carriers (87). Guyard *et al.* reported NGS performed using an amplicon panel to analyze hotspots and targeted regions in 22 cancer-associated genes in 27 samples from patients with LC-ILD (88). They authors found several alterations in *MET*, *FGFR3*, *ERBB4*, *DDR2*, *EGFR*, *BRAF*, and *PI3KCA* genes in 25 samples. There were neither EGFR mutations nor ALK or ROS rearrangements found. Surprisingly, only one tumor was considered Kras-mutated, whereas PDL1 expression ($\geq 1\%$) was reported in 10 cases (61%), with only one tumor $>50\%$ PD-L1 expression.

Lung cancer diagnostic approach in ILD

Due to the frailty of ILD patients with increased LC risk, the optimal LC diagnostic approach must be carefully assessed. In a recent letter, Tzouveleakis *et al.* proposed an algorithm, with HRCT to be performed once a year in all IPF patients for LC screening purposes (89). Yet, the benefit/risk of this approach has never been evaluated in IPF patients, with 90% of positive CTs eventually considered false-positive in the National Lung Screening Trial. For nodules with a diameter ≥ 8 mm, PET-CT scan appears highly recommended. If FDG uptake is indicative of tumor lesions, the authors suggested proceeding first to minimally-invasive diagnostics, including transthoracic needle biopsy (TTNB) for peripheral lesions or endobronchial ultrasound-guided trans-bronchial needle biopsy in the presence of pathological lymph nodes. Concerning the risk of pneumothorax, radial probe endobronchial ultrasound-guided transbronchial biopsy should be employed instead of TTNB in specific settings, such as emphysema and larger lesions with a bronchial sign within (90).

The role of liquid biopsy as non-invasive diagnostic tool for LC-ILD must still be defined, considering the technique's specificity $<60\%$ for a pre-specified alteration, namely EGFR mutation in advanced NSCLC, being even lower in early-stage disease. Moreover, the molecular

alterations to be tested probably differ from NSCLC cases without IPF (see above) (88).

Treating LC while reducing the risk of ILD exacerbation

Treating LC in ILD raises the issue as to which standards of care should be applied for these elderly patients with diminished respiratory reserve. In the GERM“O”P registry, 20/47 (43%) LC patients with combined pulmonary fibrosis and emphysema (CPFE) did not receive the standards of care, 8 (17%) on account of CPFE (43), while in the Miyazaki series involving stage I–IIIA patients, 67.6% ILDs (n=34) underwent surgery *vs.* 82.6% ILD-free (n=1,089) (40). In another study, 10/34 (29%) LC patients with IPF received only best supportive care (10).

Operable NSCLC

Tables S3,S4 display published series on operated LC in association with IPF or other ILDs, respectively.

Prognosis of operated NSCLCs

The survival of operated LC patients with concomitant ILD was inferior to that of those without ILD. A large Japanese surgical cohort compared the prognosis of 1,763 LC-ILD to that of LC registry patients (91,92). The 5-year survival rates for stage IA, IB, IIA, IIB, IIIA, IIIB, and IV were: 59% *vs.* 86.8%; 42% *vs.* 73.9%; 43% *vs.* 61.6%; 29% *vs.* 49.8%; 25% *vs.* 40.9%; 17% *vs.* 27.8%; 17% *vs.* 27.9%, respectively. Other authors compared 5-year survival rates of patients with and without ILD in three series for stage IA (65,69) and I (93), as follows: 54.2% *vs.* 88.3%, 70.3% *vs.* 93.9%, 61.6% *vs.* 83% (65,93), respectively. In three other studies not differentiating LC staging, 5-year survival rates were: 52% *vs.* 63%; 35.6% *vs.* 62.5%; 37.5% *vs.* 72.5% (67,68,94).

Mortality attributable to ILD-related complications (see below)

Postoperative complication rates were in the 6.2–32% range, respiratory-related mortality being higher in patients with ILD. A Korean study comparing 33 LC-IPF to 66 LC patients reported respiratory mortality rates of 21% *vs.* 3% (94).

Cancer-related mortality

In 1,763 Japanese LC-ILD patients, 50.2% of deaths were related to cancer, 26.8% to respiratory aggravation, and 23% to another cause (91). In the Saito study comparing 28

Table 1 Risk factors for postoperative exacerbation

| |
|------------------------------|
| Patient-related |
| Gender, age |
| FVC |
| UIP on radiography |
| History of AE |
| Preop. corticosteroids |
| KL-6 |
| Surgery-related |
| Resection volume |
| Duration of surgery |
| O ₂ concentration |
| Fluid intake/loss balance |

FVC, forced vital capacity; UIP, usual interstitial pneumonia; AE, acute exacerbation.

LC-ILD to 322 LC patients, deaths were cancer-related in 17.9% *vs.* 3.7% in controls (65).

Second cancer after first intervention was more common, affecting 36% of cases in one series (95). In the Yano study, limited resections for small-sized tumors were associated with a 2.78-times higher recurrence risk in ILD (96). Of the aforementioned 1,763 operated LC-ILD cases, 425 (24.1%) were treated using infra-lobar resection. AE-related death risk was significantly inferior in patients treated using wedge surgery than those undergoing lobectomy, yet with cancer-related death risk significantly increased (91).

Post-operative complications and AE

NSCLC surgery causes prolonged hospitalization and increased morbidity due to pneumopathy, prolonged drainage, and postoperative AEs (65-67). In the Sato study, CPFE (n=55) was associated with more cardio-pulmonary complications compared to IPF without emphysema (n=45), without between-group mortality differences (97).

Postoperative AEs consisted of respiratory deterioration and parenchymal opacities, without infectious or cardiac causes. In the operated Japanese LC-ILD series (n=1,763), the AE rate was 9.3%, with 43.9% mortality. AEs mainly occurred on day 10 post-surgery (98), in line with previously reported data (99). AEs may also occur in infra-clinical or infra-radiological ILD (63,100), with several risk factors identified (*Table 1*).

Patient-related risk factor

Age >75 years (101), IPF versus other ILDs (65,98,102), honeycomb pattern on CT (103,104), fibrosis in the non-operated lung (105), and functional limitation were risk factors for post-operative AEs (66,68,98). In the Voltolini study, patients with FVC >90% did not exhibit post-operative acute respiratory insufficiency (68). A Japanese study described no early AEs among 21 operated LC-IPF patients, possibly due to highly-selected patients (95).

The other risk factors included elevated KL6 or CRP levels, preoperative corticosteroids in IPF, and hyperfixation on PET (98,106-108).

Surgery-related risk factor

Increased post-operative AE risk was associated with >4-hour-long operations, high pre-operative oxygen concentrations (104), parenchyma resection extent (66,98), and relevant volemia variations (107).

Risk scoring

Using a risk scoring system should enable surgery to be performed more often in LC-ILD (109), with patients classed as low-risk if a <10% AE probability, intermediate risk if 10–25%, and high-risk if >25%.

AE prevention

Iwata *et al.* retrospectively compared 31 patients receiving preoperative pirfenidone versus 19 untreated, reporting one AE with pirfenidone versus four without (110). A phase II study assessed pirfenidone's pre-operative efficacy in 43 LC patients, 39 exhibiting IPF (111,112), with AEs observed in two IPF cases (5.1%). Potential benefits of systematic post-operative corticotherapy were suggested from 22 operated patients, with 3/4 patients without corticotherapy exhibiting AEs versus 2/18 corticoid-treated subjects (101).

Pooled data analysis in INPULSIS studies demonstrated a decrease in AEs under nintedanib (7.7% *vs.* 14.9%) in patients IPF with FVC <70% (113). Perioperative CT could enable both infra-clinical AE detection and early treatment (105).

Inoperable localized NSCLC

Radiotherapy is contra-indicated in severe ILD, producing radiation pneumonitis (RP) rates of up to 43% (95). Ozawa *et al.* reported RP in 9/651 patients undergoing radiotherapy, extended ILD affecting >10% of lung parenchyma identified as sole independent risk factor (82).

Radiotherapy in infra-clinical ILD

Infraclinical ILD is considered an RP risk factor. Evaluating

thoracic radiotherapy for LC (n=40) or esophageal cancer (n=19), Yamaguchi *et al.* reported RP in 36% of cases with infraclinical ILD versus 13% without (114), as confirmed by another study (115).

Stereotaxic radiotherapy

Stereotaxic radiotherapy spares healthy tissues surrounding the tumor, with yet isolated fatal RP cases reported (116,117). Yamaguchi *et al.* assessed RP risk in 100 patients, 16 with infraclinical ILD (118). Though grade 2–5 RP risk was not enhanced, 3/16 infraclinical ILD patients versus 0/84 controls displayed extensive pneumonitis beyond the radiation field. In another study involving stage I NSCLC patients, ILD on CT (n=20/157) was an independent grade >2 RP risk factor (119).

Proton therapy

Proton therapy was evaluated in 16 ILD patients, with disappointing results (120).

Stage IV NSCLC

Like for surgery, some patients with ILD seem to be too frail to receive chemotherapy. In four published series, 20–25% patients were deemed unable to undergo chemotherapy (37,121–123). Kashiwabara *et al.*, however, reported that patients solely receiving comfort care exhibited poorer median OS than those undergoing chemotherapy (2.6 *vs.* 10.9 months) (83).

Efficacy of first-line therapies

All studies assessing first-line therapy efficacy in LC-IPF/ILD are listed in *Tables S5,S6*. A recent meta-analysis covered seven studies involving 251 patients with stage IIIA, IIIB, or IV LC-ILD. Response and control rates were 41.3% and 77.7%, respectively, with a PFS of 4.4 months and OS of 8.5 months (124).

Few studies compared chemotherapy efficacy and prognosis of LC-ILD versus LC. ILD seems to be an independent poor prognostic factor, with HRs of 2.33 for PFS and 2.87 for OS (123).

Carboplatin-paclitaxel is the most common regimen (*Tables S5,S7*), with bevacizumab at times employed in combination with carboplatin-paclitaxel (125), offering similar efficacy without more toxicity (126).

Several hypotheses could explain the poorer survival in ILD despite similar response rates, such as poor prognostic factors (i.e., age, male predominance), lower proportion

of ADC, lower oncogenic addictions, and increased risk of chemotherapy-induced AE-ILD.

Second-line chemotherapy

In published series, 31.6–72.2% received second-line chemotherapy (*Tables S5,S7*). In Kashiwabara's study, LC-ILD patients underwent a median of one line versus two for LC patients (83). Investigating second-line docetaxel therapy in stage IIIB–IV (n=35) patients, Watanabe reported an 8.6% response rate, 37.5% control rate, 1.6-month PFS, and 5.1-month OS (127). Choi *et al.* reported a 1.2-month PFS and 4-month OS following second-line chemotherapy (128). Nintedanib, a tyrosine kinase inhibitor (TKI), was demonstrated efficient in both IPF and NSCLC progressing after first-line therapy (129,130). In this last setting, a subgroup analysis revealed that nintedanib's benefits on OS were limited to the ADC subgroup (130).

Chemotherapy-induced ILD or chemotherapy-induced increased AE-ILD risk?

Chemotherapies may provoke drug-induced interstitial pneumonitis, with pre-existing ILD as known risk factor. Two retrospective studies revealed drug-induced ILD to be more common with underlying ILD, 29% *vs.* 10% and 22.4% *vs.* 4.6%, respectively (82,131). Sakurada *et al.* reporting a 5.38 OR in pre-existing ILD (n=161) (131).

Drug-induced ILD responsible for aggravating pre-existing ILD could be considered as chemotherapy-induced AE, one meta-analysis reporting an 8.47% AE incidence.

Patient-related risk factors

The ILD subtype appears paramount, with IPF and radiological UIP pattern identified as risk factors. In two series, AE incidence was 22% *vs.* 8% and 50% *vs.* 18% (132) in patients with radiological UIP pattern versus without, respectively. The Minegishi cohort reported a 3.19 RR of AE (P=0.13) in patients with IPF versus other ILDs (133,134), with decreased FVC as an independent risk factor for drug-induced ILD (135).

Treatment-related risk factors

In Kenmotsu's series, vinorelbine and paclitaxel were rarely responsible drug-induced ILDs. Patients receiving cisplatin or carboplatin exhibited similar AE incidence (10% *vs.* 13%), which was higher for docetaxel (28%) and etoposide (24%), whilst lower for paclitaxel (3%) (132). A trial is currently ongoing evaluating nintedanib's role in preventing AEs induced by carboplatin plus Nab-paclitaxel regimens (136).

Similar results were reported with another series (72) involving 53 LC-ILD patients undergoing 96

chemotherapies: docetaxel caused more AEs than others (18.4% vs. 5.2%), while AEs were similar with or without pemetrexed (13.3% vs. 9.9%), whereas paclitaxel caused no aggravation. Pemetrexed/cisplatin is the preferred first-line regime for extended ADC treatment versus gemcitabine for SCC, with little data available for LC-ILD. In 459 consecutive patients, Sakurada *et al.* reported 33 chemotherapy-induced ILDs, 11 with underlying ILD. Of 88 pemetrexed-treated patients, no drug-induced ILD occurred (131). For stage IV NSCLC-ILD, of 39 patients receiving first-line cisplatin/gemcitabine, one AE was noted, versus two in 13 receiving cisplatin/pemetrexed (128).

TKI gefitinib, erlotinib, and afatinib are indicated after detecting activating *EGFR* gene mutations. In the general population, TKI-EGFR carries the risk of drug-induced ILD, especially for gefitinib versus erlotinib (137). Underlying LC-ILD is an independent risk factor of drug-induced ILD (OR: 2.89) (138).

Crizotinib, a TKI used in LC patients with ALK rearrangements, was responsible for drug-induced ILD in 2.4% of cases, with one fatal AE on preexisting ILD reported (139,140). Nivolumab, a novel agent that binds to the PD1 receptor, is used in LC, and particularly SCC. Two studies (phase I and II) reported 7% and 5% drug-induced ILD, respectively (141,142), while a retrospective study revealed nivolumab-induced ILD in 43/915 (5%) (143). A pilot trial of nivolumab in six mild ILD patients did not reveal any pulmonary complication (144).

Small-cell LC

Table S6 lists data from three series comprising 80 patients with small-cell LC-ILD, 27 localized-stage (133,145,146). Carboplatin-etoposide chemotherapy was administered to 47 patients, cisplatin-etoposide to 33. Tumor response and control rates were 62.5%, 88.2%, 75% and 94%, respectively, with 4.5–5.5-month PFS, 7–9-month OS. Grade 3 and 4 hematological complication rates from two studies were 72.7% and 88.2% (133,145).

Concerning second-line chemotherapy, the Fujimoto series comprised 23 patients receiving paclitaxel-carboplatin, paclitaxel alone, or topotecan (147), resulting in response and control rates of 22% and 52%, respectively, with a median PFS and OS of 2.1- and 7.1-month, comparable to ILD-free patients, with an AE rate of 13%. Enomoto *et al.* evaluated topotecan safety as second-line in 11 patients and third-line in 12, with 5 (21.7%) exhibiting AEs after last topotecan injection (148).

Conclusions

LC-ILD association is common in clinical practice. While patient prognosis appears poorer than with LC alone, most therapeutic regimens can be applied, with therapeutic management properly adapted taking AE-ILD risk into account.

Our review emphasizes the multidisciplinary relevance of LC-ILD management. Surgery and radiotherapy decisions must consider patients' limited respiratory function and risk of post-operative/-radiotherapy acute exacerbation (AE)-ILD. Risk/benefit assessments of early AE-induced mortality versus late LC-recurrence must be performed case-by-case. Chemotherapy for advanced-disease raises the issue of feasibility and AE-ILD risk, with the exact role of ILD and LC therapies better defined.

Studies are warranted to further our understanding of underlying cancer development in the fibrotic areas, with prospective clinical studies conducted to better define the optimal therapeutic strategies.

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Footnote

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Supplementary

Table S1 Frequency of interstitial lung diseases in lung cancers

| Series | Country | Recruitment | n cancers | n ILDs | % of ILD | ILD type |
|------------------------------|---------|-----------------|-----------|--------|----------|--|
| Park <i>et al.</i> 2001 | Korea | All stages | 2,660 | 63 | 2.4 | IPF |
| Khan <i>et al.</i> 2015 | Ireland | All stages | 637 | 34 | 5.3 | IPF |
| Kawasaki <i>et al.</i> 2002 | Japan | Surgical series | 711 | 53 | 5.3 | IPF |
| Chida <i>et al.</i> 2008 | Japan | Surgical series | 834 | 91 | 10.9 | IPF |
| Watanabee <i>et al.</i> 2008 | Japan | Surgical series | 858 | 56 | 6.5 | IPF |
| Saito <i>et al.</i> 2011 | Japan | Surgical series | 350 | 28 | 8 | IPF |
| Goto <i>et al.</i> 2014 | Japan | Surgical series | 387 | 65 | 16.8 | IPF |
| Kumar <i>et al.</i> 2003 | England | Surgical series | 951 | 22 | 2.3 | 16 IPF, 6 NSIP |
| Chiyo <i>et al.</i> 2003 | Japan | Surgical series | 931 | 36 | 3.9 | 26 IPF, 10? |
| Voltolini <i>et al.</i> 2013 | Italy | Surgical series | 775 | 37 | 4.8 | 11 IPF, 26? |
| Kanaji <i>et al.</i> 2016 | Japan | Stage IIIB, IV | 218 | 53 | 24.3 | 34 IPF, 19? |
| Usui <i>et al.</i> 2011 | Japan | All stages | 1,148 | 102 | 8.9 | CPFE |
| Hata <i>et al.</i> 2016 | Japan | Surgical series | 1,264 | 104 | 8.2 | 77 IPF, 10 CTD, 2 NSIP, 1 OP, 2 smoker ILD, 12? |
| Tao <i>et al.</i> 2017 | Japan | Surgical series | 257 | 60 | 23.3 | 25 UIP, 35 non UIP* |
| Sekihara <i>et al.</i> 2017 | Japan | Surgical series | 2054 | 106 | 5 | 79 UIP, 27 non UIP* |
| Personal data, 2016 | France | All stages | 907 | 48 | 5.3 | ILD |

*, CT pattern; ILD, interstitial lung disease; ILF, idiopathic lung fibrosis; NSIP, nonspecific interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; OP, organizing pneumonia; ?, unknown cause of ILD.

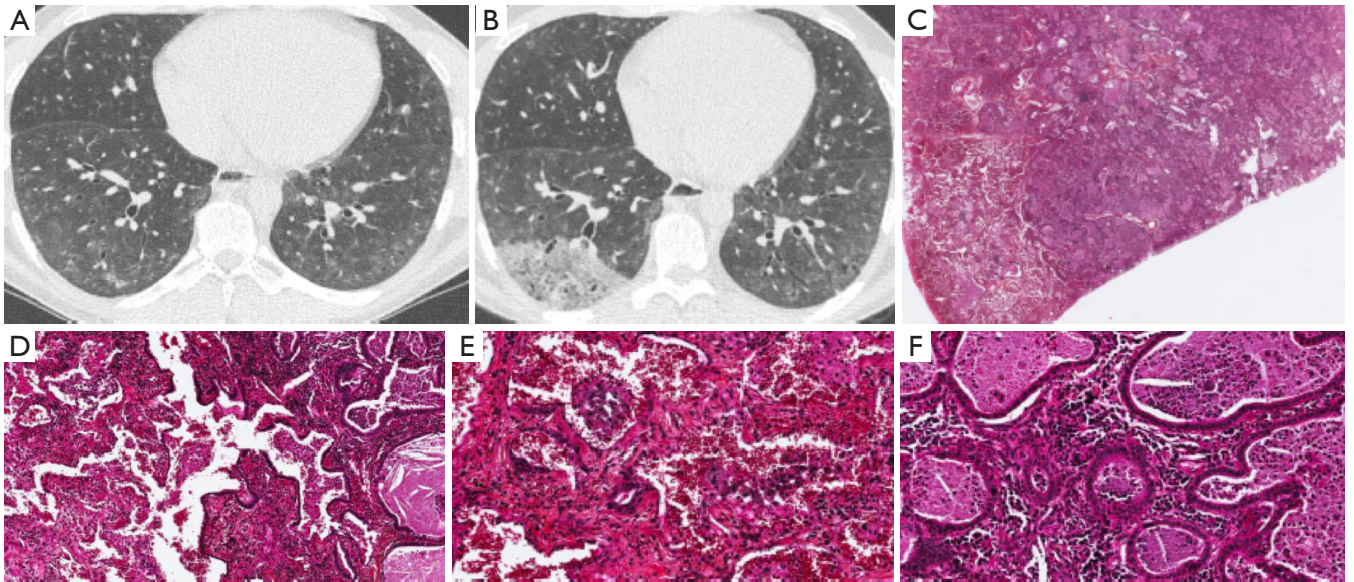


Figure S1 (A) CT scan of a 34-year-old man with ILD in a context of scleroderma in 2015; (B) CT scan of the same patient in 2017 showing a new right lower lobe opacity; (C) presence of a tumoural nodule of adenocarcinoma in a case of pulmonary involvement by scleroderma. $\times 1$, HES; (D) adenocarcinoma is present in the right of the field and non tumoural lung parenchyma on the left, with NSIP. $\times 10$, HES; (E) lung parenchyma with NSIP. The witness of the parietal wall is increased and there is inflammatory cells and alveolar hemorrhage. $\times 20$, HES; (F) invasive acinous adenocarcinoma with inflammatory cells. $\times 20$, HES. NSIP, non-specific interstitial pneumonia; ILD, interstitial lung disease; CT, computed tomography.

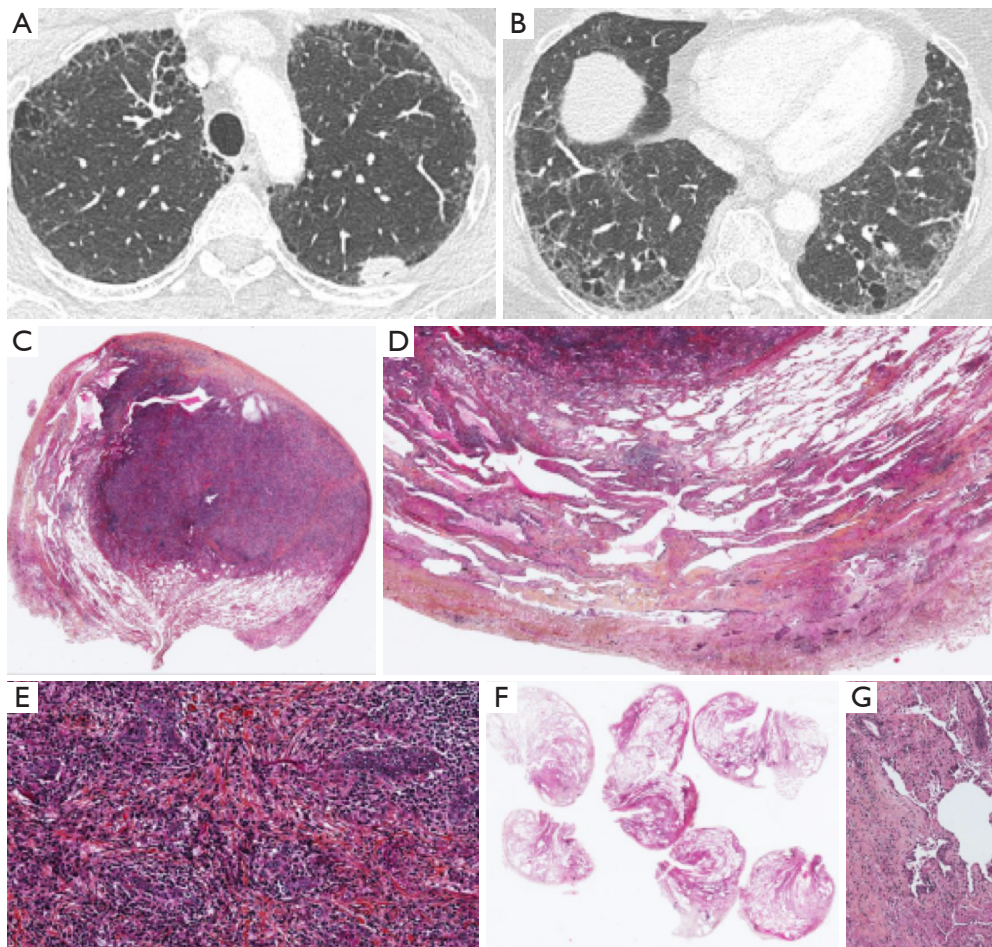
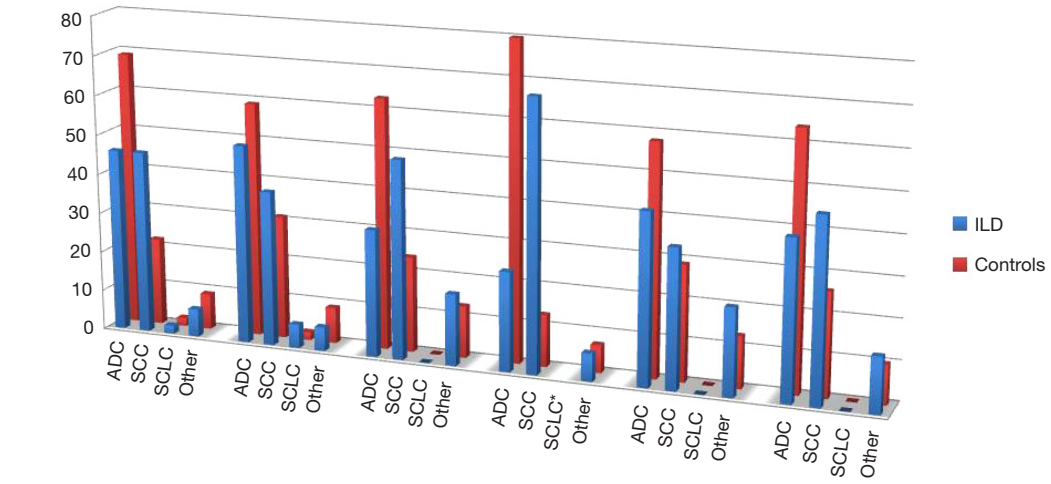


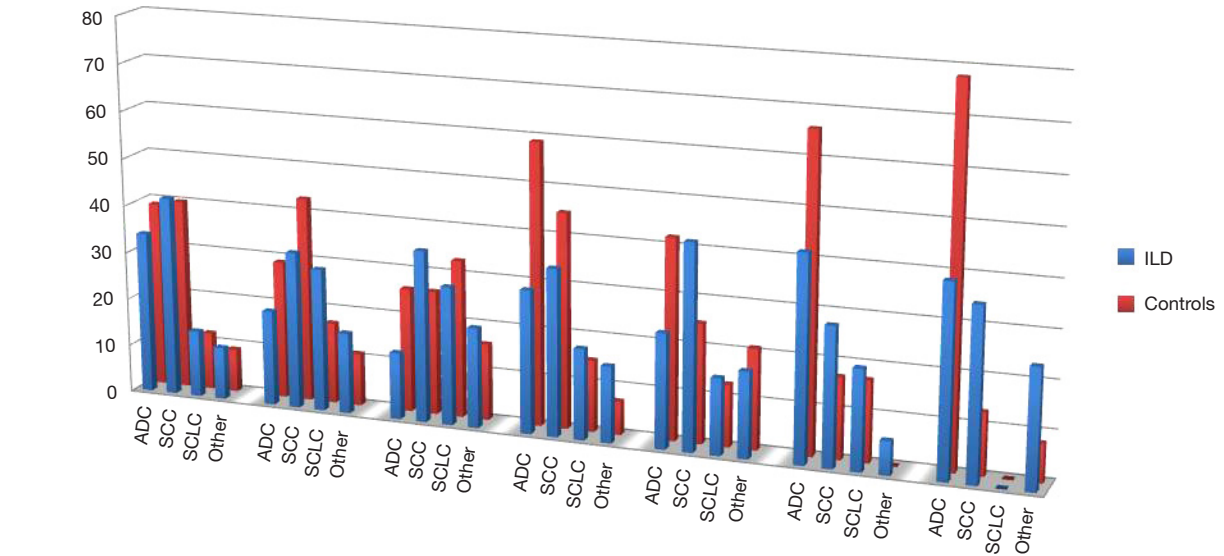
Figure S2 (A) CT scan of a 52-year-old tobacco smoker woman with a left upper lobe nodule. Presence of subpleural reticulation and paraseptal emphysema; (B) CT scan of the lower lobes showing a predominance of peripheral and basal predominance of reticular abnormalities with emphysema. The radiological pattern is possible UIP; (C) lymphoepithelial carcinoma in a case of UIP. $\times 1$, HES; (D) lung parenchyma surrounding the nodule with peripheral subpleural heterogeneous fibrosis. $\times 10$, HES; (E) lymphoepithelial carcinoma with carcinomatous islands associated with fibrosis and a lot of inflammatory cells. $\times 20$, HES; (F) heterogeneous fibrosis with subpleural and peripheral predominance; (G) fibroblastic focus. CT, computed tomography; UIP, usual interstitial pneumonia.



| | Kawasaki 2002** | Chiyo 2003 | Watanabe 2008** | Saito 2011** | Voltolini 2012 | Goto 2013** |
|-------------|--------------------|---------------|--------------------|-----------------|-------------------|----------------|
| ILD, n | 53 | 36 | 56 | 28 | 37 | 65 |
| Controls, n | 658 | 895 | 802 | 322 | 738 | 322 |

ADC: adenocarcinoma; SCC: squamous cell cancer; SCLC: small cell lung cancer; **, P<0,05; * unavailable data

Figure S3 Histological analysis of LC-ILD vs. LC: surgical series. LC: lung cancer; ILD, interstitial lung disease.



| | Mizushima,1995 | Hironaka,1999 | Oshikawa,2000 | Park,2001 | Ozawa,2015** | Kashiwabara,2015** | Kanaji,2016** |
|-------------|----------------|---------------|---------------|-----------|--------------|--------------------|---------------|
| ILD, n | 131 | 32 | 14 | 63 | 84 | 28 | 53 |
| Controls, n | 4,931 | 380 | 98 | 2,660 | 567 | 145 | 165 |

ADC: adenocarcinoma; SCC: squamous cell cancer; SCLC: small cell lung cancer; **, P<0,05

Figure S4 Histological analysis of LC-ILD vs. LC: all stages. LC: lung cancer; ILD, interstitial lung disease.

Table S2 EGFR mutations

| Author | n | Stage | ADC % | Smoker % | ILD % | ILD+ | | EGFR % | |
|--------------------------------|-------|---------|-------|----------|-------|-------|----------|--------|--------|
| | | | | | | ADC % | Smoker % | ILD | No ILD |
| Fujimoto <i>et al.</i> 2013 | 555 | I–IV | 100 | 52 | 6 | 100 | 87 | 3 | 47 |
| Usui <i>et al.</i> 2011 | 198 | I–IV | 85.4 | 62.6 | 8.5 | nd | nd | 5.8 | 28.7 |
| Sekine <i>et al.</i> 2013 | 88 | I–IV | 91 | 100 | 11.3 | nd | 100 | 0 | 24.3 |
| Kanaji <i>et al.</i> 2016 | 218 | IIIB–IV | 69 | 73 | 24.3 | 40 | 96 | 2 | 32 |
| Masai <i>et al.</i> , JTO 2016 | 2,309 | I–IV | 100 | 46.4 | 1.9 | 100 | 90.9 | 2.3 | 45.6 |

ILD, interstitial lung disease; ADC, adenocarcinoma; EGFR, epidermal growth factor receptor; nd, not done.

Table S3 Surgical series on idiopathic pulmonary fibrosis

| Citations | n* | Stage | ILD type | Surgery (pneumonectomy/ lobectomy/< lobe) | Survival | AE |
|---|--------|---|----------|---|--|-------|
| Kawasaki, <i>J Surg Oncol</i> 2002 | 53/711 | I, n=21; II, n=12; III, n=14; IV, n=6; | IPF | 0/52/1 | 5-year survival; 43% vs. 64.2% | ND |
| Fujimoto, <i>Ann Thor Surg</i> 2003 | 21 | I–II, n=14; III–IV, n=7 | IPF | 0/17/4 | 2-year survival; all stages: 52%; N0 and N1: 58%; N2: 25% | ? |
| Watanabee, <i>J Thorac Cardiovasc Surg</i> 2008 | 56/858 | I, n=28; II, n=5; III, n=14; IV, n=3; ND, n=6; | IPF | 0/44φ/12 | 5-year survival; stage I: 61.6% vs. 83%; stage II: 40% vs. 72.5%; stage III: 31.8% vs. 38%; stage IV: 0% vs. 15.4% | 7.1% |
| Saito, <i>Ann Thor Surg</i> 2011 | 28/350 | IA | IPF | 0/23/5 | 5-year survival; 54.2% vs. 88.3% | 10.7% |
| Suzuki, <i>Surg Today</i> 2011:914 | 28 | I–II, n=14; III–IV, n=14 | IPF | ND | 3-year survival; with AE: 42.5%; without AE: 55.2% | 32% |
| Mizuno, <i>Eur J Cardio Thor Surg</i> 2012 | 52 | I, n=32; II, n=13; III, n=17; | IPF | 0/47δ/5 | ND | 13.5% |
| Song, <i>Korean J Patho</i> 2014 | 43 | I, n=19; II, n=12; III, n=11; ND, n=1 | IPF | 3/37/3 | 1-year survival; 60% | ND |
| Goto, <i>Int J Clin Oncol</i> 2014 | 65/387 | IA, n=11; IB, n=17; IIB, n=10; IIIA, n=16; IIIB, n=8; IV, n=3 | IPF | 3/53/3 | ND | 6.2% |
| Lee, <i>Resp Med</i> 2014 | 33/66¶ | I, n=23; II, n=8; IIIA, n=2 | IPF | ?/?β/11 | 5-year survival; 37.5% vs. 72.5% | ND |
| Iwata, <i>Surg Today</i> 2014 | 28 | ND | IPF | 0/19/9 | 5-year survival; 62.8% | 25% |

n*, cancer associated with interstitial lung disease/cancer without interstitial lung disease; ¶, matched controls; φ, including 1 bilobectomy; δ, including 3 bilobectomies; β, 22 supralobar resections; ILD, interstitial lung disease; AE, acute exacerbation; ILF, idiopathic lung fibrosis; IPF, idiopathic pulmonary fibrosis.

Table S4 Surgical series on various interstitial lung diseases

| Citations | n* | Stage | ILD type | Surgery (pneumonectomy/ lobectomy/< lobe) | Survival | AE |
|---|-----------|---|---|---|--|---|
| Kumar, <i>Gen Thor Cardio Surg</i> 2003 | 22/951 | ND | Histology: UIP, n=16 NSIP, n=6 (including 3 CTD γ) | 6/17/1 | 3-year survival: 54% | θ : 21% vs. 3.7%; Pneumonectomy: 33%; Lobectomy: 17% |
| Chiyo, <i>J Thoracic Cardiovasc Surg</i> 2003 | 36/931 | I, n=10; II, n=4; III, n=18; IV, n=3 | IPF, n=26; Pneumoconiosis, n=5; CTD, n=5 | ND | 5-year survival: 35.6% vs. 62.5% | θ : 25% vs. 2% |
| Iyoda, <i>Exp Therapeutic Med</i> 2011 | 22 | I, n=19; II, n=2; III, n=1 | ND | 0/17/5 | ? | 22.7% |
| Chida, <i>Ann Thor Cardiovasc Surg</i> 2012 | 52/443 | ND | ND | ND | ND | 11.5% |
| Yano, <i>Inter Cardiovasc Thor Surg</i> 2012 | 62 | IA, n=24 IB, n=13; IIA, n=7; IIB, n=9; IIIA, n=8; IV, n=1 | CT-scan: IPF, n=7; NSIPf, n=25 NSIPc, n=16; Unclassifiable, n=14 | 0/44/18 | 1-year survival: 83.8%; 3-year survival: 60.3%; 5-year survival: 55.7% | 9.7% |
| Voltolini, <i>Eur J Cardio Thoracic Surg</i> 2013 | 37/775 | I, n=16; II, n=10; III, n=7; IV, n=3; | Histology: Pneumoconiosis, n=18; IPF, n=11; NSIP, n=8 (including 4 CTD) | 4/30/3 | 5-year survival: 52% vs. 63%; overall survival: 29 \pm 5.4 vs. 47 \pm 4.2 months | θ : 13.5% vs. 2.3% |
| Sato, <i>J Thorac Cardiovasc Surg</i> 2014 | 1,763 | I, n=1,028; II, n=311; III, n=358; IV, n=34 | CT-scan: UIP, n=1,300; Non-UIP, n=463 | 33/1,297 γ /425 | | 9.3% |
| Sato, <i>J Thorac Cardiovasc Surg</i> 2015 | 1,763 | idem | idem | | 5-year survival; FVC >80%: 43.8%; FVC \leq 80%: 20.8%; stage IA: 59%; FVC >80%: 64.3%; FVC \leq 80%: 20%; wedge: 33.2%; segment: 61%; lobe: 68.4%; stage IB: 42%; stage IIA: 43%; stage IIB: 29%; stage IIIA: 25%; stage IIIB: 17%; stage IV: 17% | |
| Omori, <i>Ann Thor Surg</i> 2015 | 103 | I, n=51; II, n=27; III, n=25 | IPF, n=46; non-IPF, n=57 | 2/79/22 | 5-year survival: IPF: 22.1%; non-IPF: 53.2% | IPF: 17.5%; Non-IPF: 8.7% |
| Sato, <i>Ann Thorac Cardiovasc Surg</i> 2016 | 100 | I, n=59; II, n=16; III, n=20; IV, n=5 | IPF, n=45; CPFE, n=55 | 0/62/38 | 5-year survival: CPFE: 24.9%; IPF: 36.8% | CPFE: 5.5%; IPF: 6.7% |
| Hata, <i>Ann Thor Surg</i> 2016 | 104/1,160 | IA, n=22; IB, n=41; IIA, n=13; IIB, n=8; IIIA, n=12; IV, n=8 | IPF, n=77; CTD-ILD, n=10; NSIP, n=2; OP, n=1; Smoker ILD, n=2; NA, n=12 | 1/73/30 | 5-year survival; stage IA: 70.3% vs. 93.9% | NA |
| Sekihara, <i>Interact Cardiovasc Thorac Surg</i> 2017 | 106/1,948 | I, n=62; II, n=31; III, n=13 | CT-scan: UIP, n=79; non-UIP, n=27 | 3/89/14 | 5-year survival: 40.4% vs. 72%; stage I: 44% vs. 84.6% | 4% |

n*, cancer associated with interstitial lung disease/cancer without interstitial lung disease; γ , including 61 bilobectomies; θ , all-cause acute respiratory failure; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; CTD, connective tissue disease; ILF, idiopathic lung fibrosis; NSIPf, fibrotic nonspecific interstitial pneumonia; NSIPc, cellular nonspecific interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; CTD-ILD, connective tissue disease-related interstitial lung disease; OP, organizing pneumonia; NA, not assessed; FVC, forced vital capacity; AE, acute exacerbation.

Table S5 Efficacy of chemotherapy in various interstitial lung diseases

| Citations | n | Histology, n | | | Stage | Chemotherapy | ILD | Response, % | Control, % | PFS, months | Survival, months | 1-year survival, % | AE, n (1st line) | Hematological complications | 2nd line (n) |
|--|--------|--------------|-----|-------|-----------------------------------|--|--|-------------------|--------------|----------------|------------------|--------------------|--|-----------------------------|--------------|
| | | AD | SCC | Other | | | | | | | | | | | |
| Shukuya, <i>Anticancer Res</i> 2010 | 15 | 10 | 5 | | IIIA/IIIB/IV/ POR: 1/5/7/2 | Carbo (AUC5)-Pacli, n=7; Carbo (AUC2)-Pacli, n=8 | IPF, n=4; NSIP, n=9; DIP, n=1; CTD, n=1 | 33 | 53 | 2.5 | 7 | 29 | 4 | ND | |
| Minegishi, <i>Lung Cancer</i> 2011 | 18 | 6 | 7 | | IIIA/IIIB/IV/ POR: 2/3/13 | Carbo-Pacli | IPF, n=6; Non-IPF, n=12 | 61 | 83 | 5.3 | 10.6 | 22 | 4 [1] | 33% | 13 |
| Okuda, <i>Anticancer Res</i> 2012 | 19 | 10 | 7 | 2 | IIIA/IIIB/IV/ POR: 4/6/9/5 | Carbo-Vino, n=9; CDDP-Vino, n=10 | IPF, n=16; Other, n=3 | 42.1 | 73.7 | 4.4 | 7.4 | 36.8 | 15.8 [15.8] | 63.2 | 6 |
| Kinoshita, <i>Oncol Lett</i> 2012 | 22 | 11 | 7 | 4 | IIIA/IIIB/IV/ POR: 1/6/15 | Carbo-Pacli, n=19; CDDP-Vino, n=2 CDDP-Doce, n=1 | IPF and NSIPi | 36.4 | 77.3 | 3.2 | 5.4 | ND | 3 [3] | ND | ND |
| Choi, <i>Cancer Chemoth Pharm</i> 2014 | 52 | 32 | 13 | 8 | ND | Carbo, n=33; CDDP, n=19; GEM, n=39; PEM, n=13 | IILD, n=42; Pneumoconiosis, n=5; CTD, n=5 | 42.3 | 78.8 | 5.4 | 7.9 | | 7 [3] | ND | 35 |
| Shimizu, <i>Cancer Chemoth Pharm</i> 2014¶ | 21 | 21 | | | IIIA/IIIB/IV: 3/2/16 | Carbo-Pacli, n=11; Carbo-Pacli-Beva, n=10 | CT-scan: UIP, n=5; Non-UIP, n=16 | 27 vs. 40 (ns) | 90 vs. 82 | 4.4 vs. 5.5 | 9.7 vs. 16.1 | | 1 (placebo group) | ND | ? |
| Enomoto, <i>Anticancer Res</i> 2015 | 25 | 21 | 0 | 4 | IIIA/IIIB/ IV/POR: 1/3/16/5 | Carbo-Pacli-Beva | IPF, n=13; Non-IPF, n=12 | 72 | | 7.2 | 8.5 | 40 | 3 including 1 during maintenance Beva | 72% | |
| Watanabee, <i>Anticancer Res</i> 2015 | 67 | 26 | 21 | 20 | IIIB/IV/POR: 20/42/5 | CDDP-Vino | ND | 34.3 | 73.1 | 3.7 | 7.4 | 22.4 | 7 [7] | 60% | 34 |
| Kenmotsu, <i>Cancer Chemoth Pharm</i> 2015 | 104 | 50 | 47 | 7 | III A and B/IV/ POR: 41/55/5 | Carbo-, n=85; (Pacli, n=63; Pacli- Beva, n=5; S1, n=7; GEM, n=6; other, n=4); CDDP-, n=19 (Vino, n=6; Doce, n=4; S1, n=3; Eto, n=3; other, n=3) | CT-scan: confirmed UIP, n=70; poss. or incompat. UIP, n=34 | 38 | 80 | 4.8 | 9.9 | | 26 (9 including 2 deaths) | | 57 (55%) |
| Kashiwabara, <i>anticancer Research</i> 2015 | 14/109 | ND | ND | ND | ? | ND | ND | ND | ND | ND | 10.6 vs. 27.9 | | | ND | |

¶, Comparison of both treatment arms; AD, adenocarcinoma; SCC, squamous-cell carcinoma; ILD, interstitial lung disease; PFS, progression-free survival; AE, acute exacerbation; POR, postoperative recurrence; Carbo, carboplatin; Pacli, paclitaxel; Doce, docetaxel; Vino, vinorelbine; CDDP, cisplatin; GEM, gemcitabine; PEM, pemetrexed; Beva, bevacizumab; Eto, etoposide; ILF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; NSIPi, idiopathic nonspecific interstitial pneumonia; DIP, desquamative interstitial pneumonia; CTD, connective tissue disease; IILD, idiopathic interstitial lung disease; UIP, usual interstitial pneumonia.

Table S6 Small-cell lung cancers treated with chemotherapy

| Citations | n | Localized | Disseminated | Chemotherapy | IPF/other | Response, % | Control, % | PFS, months | Survival, months | AE, n (1st line) | Hematological complications | 2nd line (n) |
|---|----|-----------|--------------|---------------------------------|-----------|-------------|------------|-------------|------------------|------------------|-----------------------------|--------------|
| Minegishi, <i>JTO</i> 2011 | 17 | 8 | 9 | Carbo/Eto, n=17 | 8/9 | 88.2 | 94 | 5.5 | 8.7 | 3 [1] | 88.2 | 8 |
| Watanabee, <i>Int J Clin Oncol</i> 2013 | 11 | | 11 | Carbo/Eto, n= 8; CDDP/Eto, n=3 | 11/0 | 62.5 | 75 | 4.7 | 7 | 4 [3] | 72.7 | 5 |
| Yoshida, <i>Anticancer Res</i> 2013 | 52 | 29 | 23 | Carbo/Eto, n=22; CDDP/Eto, n=30 | ND | 69 | ND | 4.5 | 9.4 | 6 [1] | ND | 33 |

IPF, idiopathic pulmonary fibrosis; PFS, progression-free survival; AE, acute exacerbation; Carbo, carboplatin; Eto, etoposide; CDDP, cisplatin.

Table S7 Efficacy of chemotherapy in idiopathic pulmonary fibrosis

| Citations | n | Histology, n | | | Stage | Chemo-therapy | ILD | Response, % | Control, % | PFS, months | Survival, months | 1-year survival, % | AE, n (1st line) | Hematological complications | 2nd line (n) |
|--|--------|--------------|-----|-------|----------------|--|-----|-------------|------------|-----------------|------------------|--------------------|------------------|-----------------------------|--------------|
| | | AD | SCC | Other | | | | | | | | | | | |
| Watanabee, <i>Respiration</i> 2012 or 2013 | 21 | ND | ND | ND | IIIB/IV: 11/10 | Carbo+Pacli, n=16; Carbo+Doce, n=3; VINO, n=2 | IPF | 42.9 | 80.9 | 5.4 | 11.4 | 28.6 | 10 [9] | 38.1% | |
| Kanaji, <i>J Cancer Res Clin Oncol</i> 2016¶ | 34/218 | 12 | 12 | 10 | IIIB/IV: 3/31 | ND | IPF | 31 vs. 55 | 53 vs. 87 | 92 vs. 196 days | 223 vs. 539 days | ND | 6 [6] (17.6%) | ND | ND |

¶, comparison between patients with and without idiopathic lung fibrosis; AD, adenocarcinoma; SCC, squamous-cell carcinoma; ILD, interstitial lung disease; ILF, idiopathic lung fibrosis; Carbo, carboplatin; Pacli, paclitaxel; Doce, docetaxel; VINO, vinorelbine; PFS, progression-free survival; AE, acute exacerbation.