Idiopathic pulmonary fibrosis and lung cancer: future directions and challenges

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive disease of pulmonary scarring. New treatments slow disease progression and allow pulmonary fibrosis patients to live longer. Persistent pulmonary fibrosis increases a patient's risk of developing lung cancer. Lung cancer in patients with IPF differs from cancers that develop in the non-fibrotic lung. Peripherally located adenocarcinoma is the most frequent cell type in smokers who develop lung cancer, while squamous cell carcinoma is the most frequent in pulmonary fibrosis. Increased fibroblast foci in IPF are associated with more aggressive cancer behaviour and shorter doubling times. Treatment of lung cancer in fibrosis is challenging because of the risk of inducing an exacerbation of fibrosis.

In order to improve patient outcomes, modifications of current lung cancer screening guidelines in patients with pulmonary fibrosis will be necessary to avoid delays in treatment. 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) computed tomography (CT) imaging can help identify cancer earlier and more reliably than CT alone. Increased use of wedge resections, proton therapy and immunotherapy may increase survival by decreasing the risk of exacerbation, but further research will be necessary.

Introduction

Pulmonary fibrosis is scarring of the lung parenchyma that causes difficulty breathing. It is occurring more frequently as the population is living longer [1]. Fibrosis is even more devastating because it is associated with an increased risk for lung cancer [2]. A large Korean population study reported that 1.2% of the overall population developed lung cancer; however, the percentage increased to 5% in patients with emphysema and to nearly 6% in those with fibrosis. Moreover, in patients who had emphysema and fibrosis combined, the risk of lung cancer increased to 12% [3]. Smoking alone could not explain why Ozawa *et al*. [4] found the cumulative incidence of lung cancer to be 15% and 55% when Japanese patients lived with IPF for 5 years and 10 years, respectively. Yoon *et al*. [5] showed a nearly five-fold increased rate of lung cancer in those with an autoimmune disease but were unsure if it was attributable to fibrosis or immunosuppression. With the cumulative risk of cancer in these patients increasing over time, and with more pulmonary fibrosis patients living longer, owing to the new approved anti-fibrotic treatments, the percentage of these patients developing lung cancers is expected to increase [6–8].

The prevalence of lung cancer in pulmonary fibrosis patients ranges from 4.4% to 13%, but is as high as 48% in autopsy studies [9–13]. Even the earliest findings of pulmonary fibrosis, called interstitial lung abnormalities, increased the risk of cancer in the National Lung Screening Trial, with an adjusted incidence rate ratio of 1.33 [14]. Lung cancer in idiopathic pulmonary fibrosis (IPF) patients is linked to a

worse prognosis and decreased survival [5, 15, 16]. Also, patients with IPF who have had a single lung transplantation have over 20 times increased risk of developing lung cancer compared to the general population [17]. In a retrospective study by Brett *et al*. [18] in 900 patients with a lung cancer diagnosis, one in three patients were found to have pulmonary fibrosis.

Why does lung cancer occur in pulmonary fibrosis?

Fibrosis is a condition inherently related to relentless transforming growth factor (TGF)-β action that regulates many intracellular mediators and pathways recognised in the oncology literature, including cell growth, organ development, the immune system, metastasis and progression of cancer [19]. TGF-β promotes cellular growth in cancer cells, and has the opposite effect in benign cells, a phenomenon coined the "TGF-β paradox" [19]. Zhang *et al*. [19] proposed that the TGF-β paradox is due to extracellular signal-regulated kinase (ERK) pathway activation in malignant cells and inactivation in non-cancer cells. Benign cells activate their proliferation cycle *via* ERK upregulation after TGF-β stimulation, in the same way as their oncogenic counterpart, but respond to homeostatic mechanisms or autoregulation [20]. In healthy cells, when natural TGF-β receptors (types I and II) are abundant and activated by TGF-β, there is a downstream activation of ERK proteins and co-activation of protein phosphatase 2A-α, which acts as an intrinsic safety control [21]. Downregulation of TGF-β receptors is the pivotal event that changes cellular behaviour. Low TGF-β receptor levels promote metastasis and cancer progression and are crucial for early carcinogenesis [20]. Pirfenidone inhibits TGF-β, preventing the activation of downstream signalling pathways that lead to the production of collagen and other extracellular matrix (ECM) proteins [22]. In a study of patients with IPF, researchers found that those with shorter telomeres had a faster rate of lung function decline than those with longer telomeres [23]. This suggests that telomere biology may play a role in the development and progression of IPF [23].

Programmed cell death-ligand 1 (PD-L1) expression is increased in IPF and lung cancer [24]. PD-L1 is a protein that is expressed on the cell's surface and binds to the PD1 receptor on T-cells [25]. This interaction leads to the suppression of the immune response, which contributes to the pathogenesis of these diseases [24]. The MET signalling pathway (a receptor tyrosine kinase whose ligand is hepatocyte growth factor) is a major regulator of cell growth and proliferation and is activated in both IPF and lung cancer in response to hypoxia [2, 26]. Its activation in different cancers leads to increased cell proliferation and tumour growth and increased expression of a number of genes involved in cell proliferation [27]. In addition, the MET signalling pathway activates the Akt signalling pathway (a serine-threonine protein kinase), which results in increased growth and promotion of cell survival [28, 29]. In IPF, the MET signalling pathway is upregulated in fibroblasts and myofibroblasts that are responsible for the excessive collagen deposition and tissue fibrosis that characterises the disease [30].

Pulmonary fibrosis provides a microenvironment where cancer can thrive [15]. Lung cancer in pulmonary fibrosis patients is more aggressive. The reason behind this is multifactorial. TGF-β is produced by fibroblasts in pulmonary fibrosis and cancer-derived epithelial cells [31]. It increases myofibroblast employment at the cancer margins, protecting them from apoptosis and allowing them to invade basement membranes [31].

Fibrosis causes the ECM to undergo extensive remodelling, with collagen deposition and fibre degradation. The effect of stiff matrices in cancers is profound [32]. The fibrotic ECM alters mechanotransductive signalling, redefining cell-to-cell communication [33]. The tropism of cancer towards stiffened cells was coined "durotaxis" by Lo *et al.* [34], for the cellular preference for hardened substrates. A stiff ECM not only provides a two-way communication system between the interstitium and cancer cells [35], but also promotes macrophages and fibroblasts to undergo differentiation into their malignant counterparts, known as tumour-associated macrophages and cancer-associated fibroblasts [36, 37]. Epithelial-to-mesenchymal transition (EMT) is a vital process for fibrosis and cancer [38].

Is lung fibrosis a precancerous condition?

The association between pulmonary fibrosis and lung cancer is not a new topic. Papers have been written about this since the 1960s [2, 39, 40]. Hyperplasia and metaplasia seen in IPF may lead to additional transformation and cancer development [41]. Some have proposed that the unrelenting bronchial regeneration may lead to cancer formation [18]. There are vast similarities between fibroblasts in IPF and cancer cells [42]. Both multiply rapidly, evade immune response and growth suppressors, resist apoptosis, have persistent activation of proliferative signalling pathways and utilise the Warburg effect [42, 43]. The Warburg effect refers to increased glucose uptake by malignant cells and fibroblasts of IPF [7, 44]. This glucose is later anaerobically processed, yielding by-products to be used in biosynthesis of molecules needed for the uncontrolled proliferation of cells [44]. Fibroblasts in IPF differ from normal lung

TABLE 1 Idiopathic pulmonary fibrosis (IPF) fulfils the five criteria set forth by the National Cancer Institute [45] and therefore qualifies as a precancerous condition

Premalignant criteria	IPF
Associated with an increased risk of cancer	IPF has an increased risk of lung cancer
When a precancer progresses to cancer, the resulting cancer arises from cells within the precancer	Lung cancer arises from cells within the precancer in IPF
Differs from the normal tissue from which it arises	IPF differs from normal tissue from which it arises
Differs from the cancer into which it develops	IPF differs from the cancer into which it develops
There is a method by which the precancer can be diagnosed	IPF can be diagnosed by a combination of clinical, radiological and pathological features

fibroblasts with their ability to disrupt basement membranes [43]. In IPF, TGF-β causes EMT and alveolar epithelial type 2 cells are transformed to myofibroblasts. Activated myofibroblasts secrete ECM including collagen and alpha smooth muscle actin. In lung cancer, cancer-associated fibroblasts are present at the site of tumour initiation and responsible for endothelial–mesenchymal transformation leading to tumour angiogenesis [40]. The National Cancer Institute in the USA defines precancer as conditions meeting five criteria: 1) the condition must have a higher likelihood of cancer, 2) the cancer develops from the precancerous condition, 3) the precancer is distinct from its native tissue, 4) the condition is not cancer but can have some characteristics of cancers, and finally 5) there must be techniques available for the condition to be identified [45]. IPF fulfils the five criteria set forth by the National Cancer Institute and therefore qualifies as a precancerous condition (table 1).

Difference between lung cancers in fibrotic *versus* non-fibrotic lung

Nonsmall cell lung cancer (NSCLC) is the most prevalent histological type of lung cancer in the overall population. Among NSCLCs, squamous cell carcinoma (SCC) and adenocarcinoma are the most common subtypes. Since 1990, adenocarcinoma has remained the most common histological subtype in men and women irrespective of smoking status [46] Some studies found that the most common subtype of NSCLC found in patients with fibrosis is SCC [47–50].

Most SCCs (60–80%) in non-IPF patients arise in the proximal portions of the tracheobronchial tree. However, in IPF patients, the lesions are mainly peripheral, in the lower lobes, and near areas of honeycombing [51]. Lee *et al*. [52] published a matched case–control study of surgically treated lung cancer patients with and without pulmonary fibrosis and discovered that patients with IPF plus lung cancer (IPF-LC) were more likely to have a higher ratio of forced expiratory volume in 1 s to forced vital capacity (FVC), lower FVC, lower diffusing capacity of the lung for carbon monoxide and higher carcinoembryonic antigen levels than those with lung cancer only ($p<0.01$). Post-operative survival was notably lower in patients with IPF-LC than in those with lung cancer only (5-year survival rate 37.5% *versus* 72.5%, $p=0.001$). Additionally, IPF-LC patients had worse respiratory outcomes, worse symptoms and higher rates of respiratory deaths and post-operative deaths than non-IPF lung cancer patients ($p<0.001$) [52]. Furthermore, cancer that occurs in fibrotic lung progresses more rapidly because of the tumour microenvironment, which is less likely to control tumour growth and dissemination [15]. Fibroblast proliferation is related to disease progression [53]. The study by Khan *et al*. [53] from 2015 showed that most patients with fibrosis and lung cancer had some amount of SCC in their tumours. This is not surprising given that, within pathology specimens of patients with lung cancer and fibrosis, there are atypical epithelial cells adjacent to squamous metaplasia, which is next to carcinoma *in situ* and invasive SCC, demonstrating evolution of the neoplasm [53]. Due to the distinct features of cancers in pulmonary fibrosis patients and lung cancer in the general population, some have labelled these cancers as "scar-cinoma" [43, 54].

Lung cancer screening in patients with pulmonary fibrosis

The National Comprehensive Cancer Network in the USA considers pulmonary fibrosis a risk factor for lung cancer. Nonetheless, the main indication for a yearly low-dose chest computed tomography (CT) screening remains a strong smoking history (⩾20 pack-years) [55]. Tzouvelekis *et al*. [56] suggested an annual high-resolution CT as a lung cancer screening method for IPF patients and proposed that nodules <8 mm should be followed-up every 3–6 months. Nodules >8 mm should undergo 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)-CT. Patients with imaging findings suggesting a neoplastic lesion should have a minimally invasive biopsy [56]. It should be noted that patients with fibrosis undergoing CT-guided biopsy could be at higher risk of complications from peri-procedural pneumothorax [57]. In addition, pneumothoraces in patients with fibrosis have an increased risk of reoccurring [58].

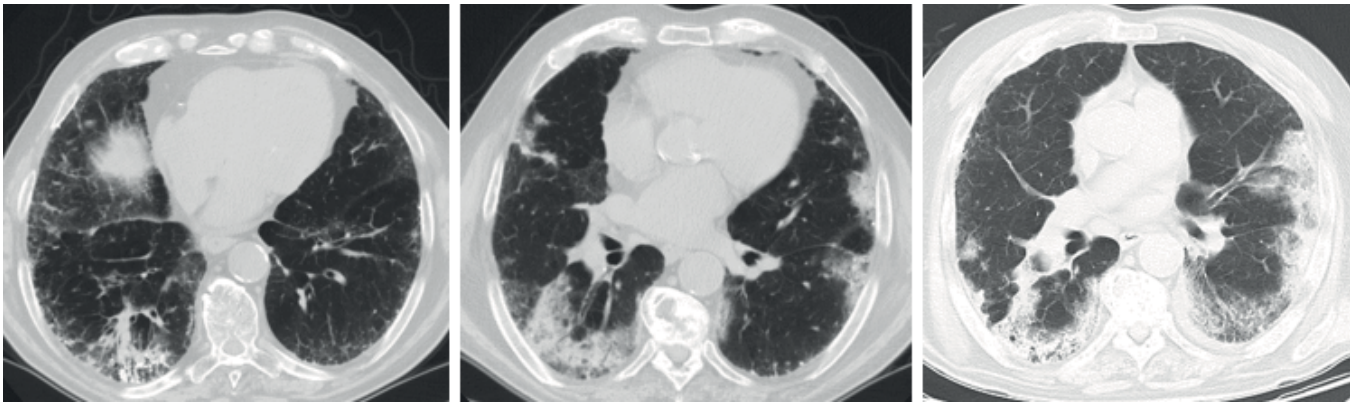

FIGURE 1 Evolution over 6 months of mucinous adenocarcinoma in a background of usual interstitial pneumonia on chest computed tomography. The cancer looks like consolidation, making early diagnosis challenging.

The low rate of detection of lung cancer among living subjects with pulmonary fibrosis, when compared to *post mortem* diagnosis, highlights the need for standardised lung cancer screening guidelines for patients with pulmonary fibrosis to allow early detection. If the majority of lung cancers in patients with fibrosis are SCC, which tends to have shorter doubling times than adenocarcinoma, follow-up of nodules identified on chest CT may need modification.

Lung cancer is challenging to detect in fibrotic lung tissue where the leading edge of fibrosis often has a mass-like configuration confounding timely diagnosis. Some cancers in patients with IPF can mimic lung infection, delaying diagnosis (figure 1). FDG PET-CT scanning could be useful for evaluation of fibrotic lung. Low-grade FDG PET-CT uptake occurs in areas of fibrosis, while cancers are distinguished from fibrosis with their very high standardised uptake value (figure 2).

Treatment of lung cancer in patients with pulmonary fibrosis

The lung cancers found in patients with fibrosis are typically early-stage like those found in lung cancer screening, because chest CT scans are frequently performed to evaluate the progression of fibrosis. Early-stage lung cancer in the absence of fibrosis is usually treated with surgery for cure, but surgery may not be possible in those with fibrosis due to respiratory compromise in this population or fear of exacerbation of fibrosis [59]. Therefore, patients with fibrosis and lung cancer may be referred for radiation and chemotherapy more than their counterparts without fibrosis. Treatment of lung cancer in fibrosis patients is complicated: surgery, chemotherapy and radiation can cause exacerbations of fibrosis and increase the likelihood of a poor outcome [60]. Supportive care may offer the same outcomes as traditional

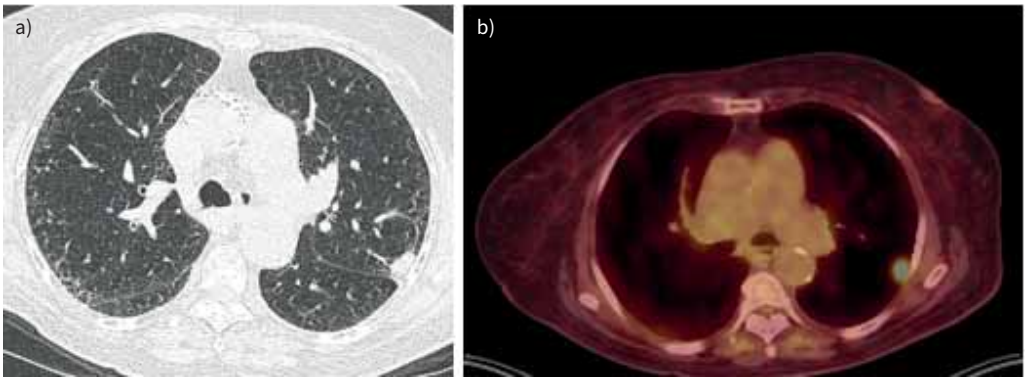

FIGURE 2 a) An axial chest computed tomography (CT) image and b) a fused axial 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)-CT image demonstrate peripheral squamous cell cancer occurring in a patient with a "probable usual interstitial pneumonia" pattern. There is low maximum standardised uptake value (SUV_{max}) in fibrotic lung parenchyma compared to tumour SUV_{max} of 12.5.

treatments in this group of patients. Diminished survival for patients with lung cancer and fibrosis is an opportunity for more effective therapeutic interventions.

Surgery

Surgical excision is the mainstay for treatment of early-stage lung cancer in non-fibrotic patients. Since patients with fibrosis typically have early-stage lung cancer, surgery would seem to be the best option. Lung cancers accompanied with a histopathological diagnosis of IPF carry worse post-operative mortality when compared to lung cancer in non-IPF patients [61]. Saito *et al.* [62] reported that the 5-year post-operative survival rates were 61.6% in IPF-LC patients with cancer stage IA (⩽1.0 cm) and 83.0% in those without IPF ($p<0.0001$). Multivariate analysis showed that for lung tumours measuring 1.1–2.0 cm, lobectomy and segmentectomy have similar survival rates; however, patients experienced better outcomes with wedge resection, supporting the concept that for lung cancers in fibrosis, smaller surgical procedures are better. For tumours measuring 2.1–3.0 cm, lobectomy remains the standard surgical technique. Nevertheless, for patients in whom lobectomy is not advisable, segmentectomy and wedge resection show comparable survival rates [63]. Any resection will cause a reduction in pulmonary function. Larger procedures cause more complications, including acute exacerbation, acute lung injury/acute respiratory distress syndrome, and higher post-operative mortality [63]. The risk of post-operative exacerbation was less with pirfenidone prior to surgery [64].

Chemotherapy

In the non-IPF NSCLC population, chemotherapy combined with immunotherapy is typically chosen as the main alternative to surgery for those with tumour PD-L1 expression >50%. For patients with squamous cancers, a combination of pembrolizumab (anti-PD-L1 antibody), carboplatin and either paclitaxel or nab-paclitaxel can be used. In NSCLC patients with non-squamous cancer, the currently most used combination consists of carboplatin and pemetrexed with pembrolizumab [65–67].

The use of combined regimens or sole immunotherapy alone has not been broadly tested in IPF-LC patients. Ide *et al.* [68] reported a case of a 62-year-old patient with adenocarcinoma and IPF who showed a complete response to nivolumab (a BRAF inhibitor) for >1 year without any sign of exacerbation of IPF. Conversely, Yamaguchi *et al.* [69] recognised pulmonary fibrosis as a significant risk factor for the incidence of drug-induced pneumonitis secondary to pembrolizumab use in patients with NSCLC ($p=0.0008$).

Watanabe *et al.* [70] studied the efficacy of chemotherapy on patients with lung cancer and pulmonary fibrosis, specifically in advanced NSCLC-IPF patients. In such a study, a carboplatin and etoposide combination demonstrated mortality benefits in patients with stage III NSCLC-IPF comparable to those obtained in NSCLC patients without IPF. Minegishi *et al.* [71] studied the effects of carboplatin and etoposide (or paclitaxel) in lung cancer in patients with fibrosis. Lung cancer patients with fibrosis had a similar median progression-free survival rate but worse overall survival rate to lung cancer patients without fibrosis. They reported a small incidence of treatment-related acute exacerbations (5.8%) and a variable rate of toxicities. Nevertheless, most patients tolerated five complete cycles of both drugs.

New clinical trials testing specific monoclonal antibodies and tyrosine kinase inhibitors for the treatment of NSCLCs are in progress. A phase I/II clinical trial studying the efficacy and side-effects of a combination of stereotactic body radiation therapy (SBRT) and an anti-TGF-β antibody (fresolimumab) for patients with NSCLC is underway (ClinicalTrials.gov identifier NCT02581787). Fresolimumab therapy has been shown to decrease the clinical progression of systemic sclerosis [72]. More studies concerning the use of other inhibitors (for ALK, EGFR, ROS1 and BRAF) in patients with pulmonary fibrosis and lung cancer are necessary.

Shared signalling pathways for IPF and lung cancer could be exploited as common targets for the treatment of both. Yamamoto *et al.* [73] studied the combination of pirfenidone added to immune checkpoint inhibitors or carboplatin-based chemotherapy for the treatment of NSCLC in patients with IPF and found that no patients developed acute exacerbations of their pulmonary fibrosis. Furthermore, cancer-associated fibroblasts promote cancer progression and pirfenidone inhibits fibroblasts and crosstalk between fibroblasts and cancer cells [74]. Nintedanib, a tyrosine kinase inhibitor, has been used successfully in combination with docetaxel for treatment of advanced NSCLC [75].

Radiation therapy

Patients considered unsuitable for surgery may be referred for definitive radiation therapy. SBRT is an effective, noninvasive modality for patients with early-stage NSCLC who cannot endure surgical resection

due to comorbidities [76–78]. Only a few studies have outlined the outcomes of SBRT in patients with fibrosis. YAMASHITA *et al*. [79] demonstrated that SBRT caused severe pulmonary toxicity in nine out of 13 patients with IPF, and seven of these cases were fatal. Pulmonary toxicity is one of the most prevalent complications after radiation therapy for the treatment of lung cancer. Severe pulmonary toxicity arises in 1.5–20% of patients who receive SBRT and in 5.0–25% of those who receive standard fractionated radiation therapy [80].

Proton therapy is a new treatment for patients with NSCLC, especially for those with early-stage disease and centrally located lesions. The main advantage of proton therapy over other forms of external beam radiation therapy is its lower quantity of scattered radiation [80]. HATA *et al*. [81] suggested that proton beams might contribute to greater efficacy and lower toxicity in the management of patients with stage I NSCLC and pulmonary fibrosis. The hypothetical efficacy of proton therapy in comparison with SBRT for the treatment of lung cancer in IPF patients needs further investigation. One might predict improved outcomes because, like with wedge resection, less lung is compromised.

Conclusion

Guidelines are well established for the screening, diagnosis and management of lung cancer in patients with a history of smoking, but not for patients with lung cancer associated with pulmonary fibrosis. Prospective studies in patients with fibrosis are needed to learn how to diagnose lung cancer early and treat it more effectively to limit morbidity and mortality. FDG PET-CT scanning may play a role in early diagnosis. Sub-lobar surgical resections, immunotherapy and proton therapy show potential, but further investigation is necessary regarding survival and quality of life for the patients who already have a significant respiratory compromise. Further research is necessary when current treatments add little more than palliative care.

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