

Patients with IPF and lung cancer: diagnosis and management



Alice S / RSPH / Science Photo Library

Idiopathic pulmonary fibrosis (IPF) is a debilitating fibrotic lung disease of unknown origin and pathogenesis with a steady increase in both incidence and mortality in recent years.¹ Despite encouraging efficacy data for pirfenidone and nintedanib,^{2,3} neither of these compounds has been tested prospectively in the context of IPF coexisting with lung cancer, a frequent comorbid condition of IPF.⁴ Indeed, epidemiological evidence suggests that up to 22% of patients with IPF develop lung cancer, with a risk nearly five times as high as that of the general population.⁵ Despite abundant epidemiological and mechanistic links between IPF and lung cancer,^{6,7} little is known about the diagnostic and therapeutic management of these patients. The most recent ATS/ERS/JRS/ALAT guidelines, updated in 2015, do not address this crucial issue.¹

Identifying a solitary nodule on chest high-resolution CT (HRCT) in patients with IPF represents a major diagnostic pitfall for physicians owing to problematic diagnostic approaches. The Fleischner Society's updated guidelines⁸ suggest a PET scan for nodules greater than 8 mm in diameter with low or moderate pre-test probability. When PET uptake is negative, CT surveillance or non-surgical lung biopsy is recommended. For moderate or high uptake, the guidelines⁸ recommend surgical lung biopsy and resection; however, this approach could be detrimental for patients with IPF, especially those with advanced disease, owing to the potential induction of acute exacerbation.⁹ Additionally, it is unknown whether patients undergoing pulmonary resection have a better prognosis than do those who do not undergo surgery and are simply monitored with low-dose HRCT. A large, retrospective analysis¹⁰ has shown that in patients with IPF with surgically treated non-small-cell lung cancer, surgery-related mortality was higher (7.1% vs 1.9%; $p=0.03$) and 5-year survival was lower (61.6% vs 83.0%; $p=0.019$) than in patients without IPF.¹⁰ CT-guided transthoracic needle biopsy (TTNB) might offer a fruitful diagnostic alternative, avoiding the complications of general anaesthesia, surgery, and mechanical ventilation; however, extra care should be taken in cases with concomitant emphysema owing to the increased risk of iatrogenic pneumothorax.

We suggest that patients with IPF should be considered at high risk for lung cancer. Close surveillance with yearly HRCT should be mandatory not only to monitor disease progression but also for early detection of malignancy.

Considering the relatively advanced age of most of these patients, the estimated radiological risk is low. The diagnostic approach of assessing the solitary nodule in patients with IPF should be applied on an individual basis, based on each patient's performance status and preferences. We suggest the following algorithm: HRCT once a year in all patients with IPF. For nodules of less than 8 mm diameter, we suggest close monitoring of patients with HRCT every 3–6 months. If HRCT shows progression of the nodule, we recommend a PET-CT scan. For nodules with diameter of at least 8 mm, PET-CT scan is highly recommended. If PET uptake indicates tumour lesion, we suggest minimally invasive diagnostic procedures, including TTNB for peripheral lesions or endobronchial ultrasound-guided transbronchial needle biopsy if pathological lymph nodes (≥ 8 mm) are also present. If the patient is not suitable for biopsy, we suggest multidisciplinary discussion for a personalised approach. For advanced tumour lesions, we recommend discussion on an individual basis regarding prognosis and management, which might include no further diagnostic procedures and mild therapeutic regimens (ie, antifibrotic agents and palliative care).

Data are scarce on the optimal chemotherapeutic regimen in patients with IPF and lung cancer. Studies have shown increased pulmonary toxicity in patients with interstitial lung disease who were treated with conventional chemotherapeutic regimens, except for with carboplatin.⁴ Case series have shown deleterious effects of radiotherapy on patients with established lung fibrosis,⁹ which should therefore be avoided unless life-threatening situations arise. Proton beam therapy, which can deliver a more concentrated dose of radiation than conventional approaches, has shown promising results.¹¹ Studies investigating the effects of new immunomodulatory agents including PD-L1 inhibitors would be of substantial interest for a selective number of cases, yet are associated with a high risk of drug-induced pneumonitis.¹² Standard molecular lung cancer testing could also be used for targeted treatments. We suggest that implementation of aggressive chemotherapeutic regimens should generally be avoided in patients with IPF and lung cancer because the risk for complications including acute exacerbations outweighs the benefits. The same applies to irradiation treatment, which is more detrimental than beneficial.

Lancet Respir Med 2017

Published Online
December 11, 2017
[http://dx.doi.org/10.1016/S2213-2600\(17\)30478-2](http://dx.doi.org/10.1016/S2213-2600(17)30478-2)

Another challenge of the real-world clinical practice is to establish whether antifibrotic agents can be combined or can even synergise with chemotherapy or radiotherapy. Nintedanib has been initially approved for treatment of non-small-cell lung cancer in combination with docetaxel-based second-line therapy.¹³ Retrospective data suggested a beneficial effect of preoperative pirfenidone on the incidence of postoperative acute exacerbations in patients with adenocarcinoma and IPF.¹⁴ We suggest that antifibrotic agents should not be discontinued during diagnostic or therapeutic work-up of lung cancer because benefits seem to outweigh the risk for unfavourable outcomes. The final decision should be based on a multidisciplinary discussion including oncologists and on a case-by-case basis.

Several patients with IPF and concomitant lung cancer have been excluded from existing antifibrotic standards of care including nintedanib and pirfenidone. A consensus statement on the diagnostic and therapeutic work-up of such patients is sorely needed. In the meantime, management of patients with IPF and lung cancer should follow the premise to first do no harm: aggressive diagnostic and therapeutic interventions should only be applied after careful consideration of IPF severity and the patient's performance status. Surgical lung interventions should be applied in a selective number of cases and under safety precautions including low-tidal volume ventilation strategies, avoidance of high fraction of inspired oxygen, and minimal perioperative administration of liquids. Alternative treatments such as proton beam therapy or radiofrequency ablation could be of therapeutic benefit with relatively minimal complications, particularly in patients who are not fit enough for surgical interventions. Implementation of palliative care might be appropriate and could improve patients' quality of life despite having no effect on survival.¹⁵ Preventative strategies for early diagnosis of lung cancer including HRCT and PET scans represent the cornerstone for timely therapeutic interventions. When lung cancer complicates IPF, the multidisciplinary team should also include oncologists, thoracic surgeons, and anaesthesiologists to establish the best therapeutic and management approach.

*Argyris Tzouvelekis, Paolo Spagnolo, Francesco Bonella, Carlo Vancheri, Vasilios Tzilas, Bruno Crestani, Michael Kreuter, Demosthenes Bouros
First Academic Department of Pneumology, Hospital for

Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece (AT, VT, DB); Division of Immunology, Biomedical Sciences Research Center "Alexander Fleming", Athens 16672, Greece (AT); Section of Respiratory Diseases, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy (PS); Interstitial and Rare Lung Disease Unit, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany (FB); Regional Referral Centre for Rare Lung Diseases, University Hospital "Policlinico", Department of Clinical and Respiratory Medicine, University of Catania, Catania, Italy (CV); Service de Pneumologie A, Hôpital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris, Paris, France (BC); and Center for Interstitial and Rare Lung Diseases, Thoraxklinik, Heidelberg University Hospital, Member of the German Center for Lung Research, Germany (MK)
argyrios.tzouvelekis@fleming.gr

AT holds a patent for aerosolised thyroid hormone for the treatment of fibrotic lung diseases, disclosed to Yale University. FB reports grants and non-financial support from Boehringer Ingelheim and Roche, outside of the submitted work; CV and MK report grants and personal fees from Boehringer Ingelheim and Roche, outside of the submitted work; BC reports personal fees and non-financial support from AstraZeneca and Sanofi; and grants, personal fees, and non-financial support from Boehringer Ingelheim and Roche, outside of the submitted work. All remaining authors declare no competing interests.

- 1 Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788–824.
- 2 Costabel U, Albera C, Lancaster LH, et al. An open-label study of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (RECAP). *Respiration* 2017; **94**: 408–15.
- 3 Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; **370**: 2071–82.
- 4 Karamitsakos T, Tzilas V, Tringidou R, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther* 2017; **45**: 1–10.
- 5 Ozawa Y, Suda T, Naito T, et al. Cumulative incidence of and predictive factors for lung cancer in IPF. *Respirology* 2009; **14**: 723–28.
- 6 Guyard A, Danel C, Theou-Anton N, et al. Morphologic and molecular study of lung cancers associated with idiopathic pulmonary fibrosis and other pulmonary fibroses. *Respir Res* 2017; **18**: 120.
- 7 Vancheri C. Common pathways in idiopathic pulmonary fibrosis and cancer. *Eur Respir Rev* 2013; **22**: 265–72.
- 8 Mets OM, de Jong PA, Chung K, Lammers JJ, van Ginneken B, Schaefer-Prokop CM. Fleischner recommendations for the management of subsolid pulmonary nodules: high awareness but limited conformance—a survey study. *Eur Radiol* 2016; **26**: 3840–49.
- 9 Kreuter M, Ehlers-Tenenbaum S, Schaaf M, et al. Treatment and outcome of lung cancer in idiopathic interstitial pneumonias. *Sarcoidosis Vasc Diffuse Lung Dis* 2015; **31**: 266–74.
- 10 Watanabe A, Miyajima M, Mishina T, et al. Surgical treatment for primary lung cancer combined with idiopathic pulmonary fibrosis. *Gen Thorac Cardiovasc Surg* 2013; **61**: 254–61.
- 11 Ono T, Hareyama M, Nakamura T, et al. The clinical results of proton beam therapy in patients with idiopathic pulmonary fibrosis: a single center experience. *Radiat Oncol* 2016; **11**: 56.
- 12 Kato T, Masuda N, Nakanishi Y, et al. Nivolumab-induced interstitial lung disease analysis of two phase II studies in patients with recurrent or advanced non-small-cell lung cancer. *Lung Cancer* 2017; **104**: 111–18.
- 13 Reck M, Kaiser R, Mellemaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014; **15**: 143–55.
- 14 Iwata T, Yoshida S, Fujiwara T, et al. Effect of perioperative pirfenidone treatment in lung cancer patients with idiopathic pulmonary fibrosis. *Ann Thorac Surg* 2016; **102**: 1905–10.
- 15 Kreuter M, Bendstrup E, Russell AM, et al. Palliative care in interstitial lung disease: living well. *Lancet Respir Med* 2017; **5**: 968–80.