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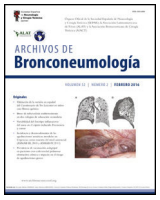

Editorial

Challenges in the Management of Lung Cancer in ILD

Pulmonary fibrosis constitutes the end stage of a broad range of heterogeneous fibrotic interstitial lung diseases (ILDs), characterized by progressive scarring of the lung. More than 500 causes of interstitial lung disease (ILD) have been identified so far including genetic disorders, autoimmune diseases, environmental exposures to toxins, drugs and radiation. Despite the emergence of two, relatively effective, antifibrotic drugs during the last decade, prognosis of fibrotic ILDs is still dismal as both drugs only slow down disease progression and thus leaving patients with major functional disability.[1] Except the functional decline per se, prognosis is also negatively affected by prevalent comorbidities including lung cancer.[2] Patients with pulmonary fibrosis belong to high-risk group for lung cancer development based on the recent US Preventive Services Task Force Recommendation Statement.[3] According to large epidemiological studies, approximately 10% of patients with PF will develop lung cancer which ultimately will be their major cause of death.[4]

The pathogenic association between lung scarring and fibrosis, called "scarcinoma" is not a new concept.[5] Nevertheless, both the incidence and prevalence of lung cancer within the context of pulmonary fibrosis were significantly low, the past few years, due to the short lifespan of patients with lung fibrosis. As we apply antifibrotic therapies and prolong survival, studies have demonstrated an accumulated incidence of lung cancer in patients with fibrotic ILDs that could reach up to 25%–50% of cases within 10 years of follow-up, that is achievable with current standard of care.[6] To this end, there is an imperative need to focus not only on ILD progression per se, but also on successful management of lethal comorbidities, such as lung cancer. The latter involves prevention, early detection and timely intervention within the context of multi-disciplinary approaches between pulmonologists, oncologists, radiologists and thoracic surgeons.

Despite abundant mechanistic links between pulmonary fibrosis and lung cancer, there is considerable lack of knowledge on the diagnostic and therapeutic management of patients diagnosed with both clinical entities, as has been also indicated by an international survey, named DIAMORFOSIS (DIAgnosis and Management Of lung canceR and FibrOSIS) survey where only five areas of interest reached consensus agreement among respondents while 28% of participants stated lack of awareness for the coexistence of these two entities.[7] The recent Japanese guideline on the management of IPF underlines the impact of comorbid lung cancer on patients' survival and quality of life and the need for large randomized controlled trials enrolling patients with fibrotic-(f)-ILDs and lung cancer.[8]

Currently, diagnostic and therapeutic approaches to lung cancer in patients with f-ILDs are a matter of debate since guideline-based,[9,10] stage-appropriate approaches to treat lung cancer may be associated with a significant progression of the f-ILD or significant complications such as acute exacerbations, infections, immune- and/or-irradiation-related pneumonitis which again associate with high morbidity and mortality.[11] Most recent evidence suggests safety and efficacy of platinum-doublets and immune-check point inhibitors in patients with f-ILD and lung cancer[12–14]; yet, studies are severely underpowered and rigid conclusions cannot be drawn. A large randomized controlled study (J-SONIC) investigating the efficacy of carboplatin plus nab-paclitaxel with or without nintedanib in patients with advanced non-small cell lung cancer and IPF highlighted the beneficial role of antifibrotics (nintedanib) in prolonging survival of fibrotic ILDs with concomitant lung cancer of non-squamous histology.[15,16] Important to say that epidemiological and therapeutic data in the field of f-LD and lung cancer are predominantly from Asian countries and there is major lack of evidence at a pan-European or North American level. In some countries patients with f-ILD and concomitant lung cancer are occasionally excluded from current antifibrotic standard of care.

In line with this European Respiratory Society has recently (2022) launched a Task Force (TF) to formulate a Clinical Practice Guideline (CPG) statement to harmonize management approaches, fuel future therapeutic trials, increase awareness for the coexistence of IPF and lung cancer, and standardize the implementation of preventive strategies potentially impacting on patients' survival and quality of life. Within this TF-CPG, PICO-based questions including: ways to monitor patients with IPF for lung cancer development, use of antifibrotics, role of surgery, targeted therapy, immunotherapy and radio-chemotherapy in patients with IPF and technically resectable, locally advanced or advanced lung cancer will be addressed.

Regarding those questions and considering the editorial nature of this manuscript our personal opinion state the following: patients with fibrotic ILDs should be closely (at least annually) monitored for lung cancer development with either HRCT or low dose CT scan. Antifibrotics should not be discontinued following lung cancer diagnosis considering the dual role of nintedanib as both anticancer and antifibrotic compound and the beneficial effects of pirfenidone in reducing post-operative mortality in patients with ILDs.[6] With regards to systemic chemotherapy, as stated above, platin based douplets present with acceptable safety and efficacy profile while the role of targeted therapy and immunotherapy being still debatable with nivolumab, durvalumab and pembrolizumab holding promise for future RCTs.[4] The concept of reduced or body-weight adjusted doses for ICIs such as pembrolizumab (2 mg/kg) could be considered in the context of RCTs based on experimental

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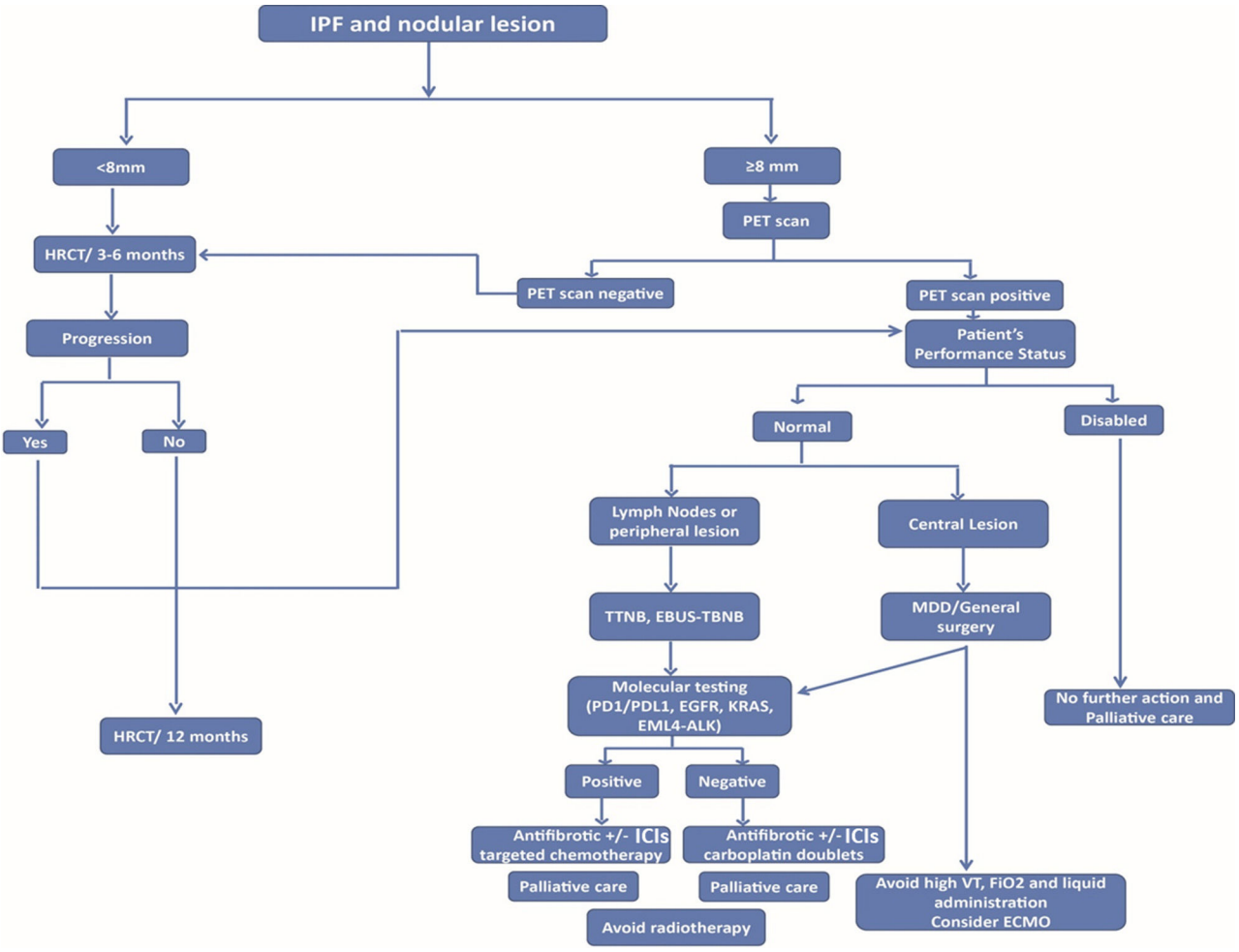

Fig. 1. Suggested management of patients with IPF and lung cancer lesion. *Abbreviations*: ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; HRCT: high resolution computed tomography; ICIs: immune-check point inhibitors; IPF: idiopathic pulmonary fibrosis; VT: tidal volume.

data from our group supporting an antifibrotic role of low doses of pembrolizumab in the experimental model of lung fibrosis with potentially less lung toxicity.[17] With regards to risks of radiation-induced pneumonitis and pneumothorax in patients with PF and lung cancer, data is conflicting and decisions should be made on a case-by-case basis taking into account the location of the cancer lesion whether is at the periphery of lung and close to fibrotic lesions or more centrally. Finally patients with f-ILDs of good performance status and technically resectable lung cancer should undergo surgical lung resection considering the 76% improved survival probability compared to no resection[4]; yet, results should be treated cautiously and rigid conclusions should not be drawn. Peri-operative safety precautions including avoidance of high FiO_2 and fluid overload, protective ventilation, reduced duration of single-lung ventilation, and minimal tissue manipulation (i.e. segmentectomy versus lobectomy) should be carefully discussed with thoracic surgeons and anesthesiologists as they are of paramount importance (Fig. 1).[4]

The issue of lung cancer management in f-ILDs is timely and a CPG is of critical importance in order to help advance this field as the therapeutic landscape in pulmonary fibrosis continues to evolve. A major clinical dilemma applies to patients with lung cancer and incidental findings of ILAs and whether ILAs have an impact on complications from cancer management. Recent data have demonstrated that this group of patients should be treated cautiously and thus radiologists, thoracic surgeons and oncologists should be aware of the presence of ILAs in patients diagnosed with lung cancer.

Conflicts of Interest

AT has received fees for speaking and/or organizing education from, Boehringer Ingelheim and Hoffmann-La Roche, Ltd., related to the content of this manuscript. PT and FS have no competing interests to declare.

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