Editorial

Treating lung cancer in patients with interstitial lung disease: what do we know?

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Management of interstitial lung disease (ILD) remains a challenge for patients and healthcare providers. While pirfenidone and nintedanib, so termed anti-fibrotic agents, have been shown to slow decline in pulmonary function, decrease all-cause mortality and the rate of acute exacerbations (AE-ILD) in idiopathic pulmonary fibrosis (IPF) (1-4), morbidity and mortality remain high for IPF, the most deadly ILD (5,6). In addition to progressive decline in lung function and AE-ILD, patients with IPF are at risk for pulmonary hypertension, venous thromboembolism, and lung cancer (6-8). Patients with co-existent ILD and lung cancer have a worse survival than patients with lung cancer alone (9).

The treatment options for lung cancer in patients with ILD remain severely limited. Surgical resection may be contraindicated due to reduced lung function or comorbidities including pulmonary hypertension. Surgery, radiation, chemotherapy, and immunotherapy are associated with an increased risk of AE-ILD in patients with IPF and other types of ILD (10-13). In a cohort of 1,763 patients with ILD who underwent resection of lung cancer at 61 centers in Japan, AE-ILD occurred in 9.3% of patients with a mortality of 43.9% (13). In this study, lobectomy and segmentectomy were associated with increased acute exacerbation as compared to wedge resection (OR =3.8) (13). Given these limited treatment options, there is a pressing need to investigate alternative therapies beyond the traditional three pillars of cancer care. Interventional Oncology, the fourth pillar of cancer care, includes percutaneous ablation, also known as image-guided thermal ablation. Percutaneous ablation includes radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, which are minimally invasive needle-directed therapies using either heat or cold to eradicate tumors (14). Percutaneous ablation has been shown to preserve lung function (15), a key advantage in patients with ILD who already have impaired lung function (6).

Most of the published data regarding treatment of thoracic neoplasms in patients with ILD relate to RFA. A systemic review found that rates of ILD-specific toxicity following RFA were similar to radiation therapy, but mortality associated with RFA was lower (16). In the general population, cryoablation has demonstrated the lowest rate of major complications compared to RFA and MWA (17), which suggests that it could be the safest thermal ablation modality for patients with ILD. However, data on percutaneous cryoablation in patients with ILD is limited to one institution (18-20).

A recently published retrospective single center cohort

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study by Kaseda *et al.* explores predictors of adverse events and mortality following the treatment of 609 tumors (median diameter 1.3 cm, range 0.2–10.2 cm) in 227 patients (24.7% with primary lung cancer) with 366 percutaneous cryoablation sessions from 2002 to 2016 (18). This study represents one of the largest cohorts to date on percutaneous lung cryoablation and includes 37 patients with interstitial lung disease, 15 of which had IPF. The Eastern Cooperative Oncology Group (ECOG) performance score was less than 2 for all patients. For all comers, mortality at 30- and 60-day was 0% and 0.5%, respectively, which compares favorably with surgical resection and radiation (21). The two fatalities at 60-days were attributed to AE-ILD, amounting to a 60-day mortality of 13.3% for the IPF subgroup and 5.4% for all ILD patients. The most common adverse event was a pneumothorax (18.0% of sessions) which required chest tube placement in 59.1%. Instances of pneumothorax without chest tube requirement are an expected outcome and no longer a complication as per the 2021 Society of Interventional Radiology guidelines (22). No general anesthesia was used for the ablation procedures.

A retrospective cohort study by Yamauchi from 2012 from the same institution includes 22 patients with 34 stage I primary lung cancers treated in 25 percutaneous cryoablation sessions between 2004 and 2010 (20). In this report, two fatalities were attributed to AE-ILD and the total number of patients with ILD was not specified. Lastly, a 2017 conference abstract by Ohtsuka from the same institution outlines a retrospective analysis of 11 patients with severe IPF and T1N0M0 non-small cell lung cancer who underwent percutaneous cryoablation between 2003 and 2016. Two fatalities at 90-day were attributed to AE-ILD, resulting in an 18.1% mortality for patients with IPF (19).

It is not uncommon for the same institution to publish multiple analyses on patients who underwent percutaneous thermal ablation of lung tumors since high-volume centers are still few and far between. In this setting, it is helpful to clearly define overlap between cohorts and reference prior work. The 2014 guideline on standardized reporting criteria of image-guided tumor ablation emphasizes the importance of providing a comprehensive description of the study population (23). Ideally, this would include information on overlap of the study cohort with other published studies. Without information regarding the overlap with other studies, it is unclear whether the two fatalities from AE-ILD reported in the three reports from the same institution refer to the same patients. As a result, reported mortality rates following percutaneous cryoablation in patients with IPF range from 13.3% to 18.1%, and this may have significant bearing on individual treatment decisions.

To improve the current knowledge in this area and better guide clinical decision-making, prospective studies are needed to further define risk factors for adverse events in patients with ILD, especially AE ILD. Factors such as ILD subtype, disease severity, or concurrent ILD treatments (i.e., use of antifibrotic therapy) may help inform the risk of complications with percutaneous ablation and other oncologic therapies. Biomarkers in peripheral blood may prove to be informative for predicting AE-ILD and other adverse events (24). Imaging biomarkers may identify patients with subclinical ILD (25). Also, functional evaluation is critical since functional impairment may or may not correlated with disease severity on imaging (25). To this end, a multidisciplinary approach involving specialized surgeons, pulmonologists, radiation oncologists, interventional oncologists, and radiologists is required. Interdisciplinary collaboration allows for the integration of clinical, radiologic, and pathologic information and stands to improve the management of patients with ILD. As therapeutic efficacy of ILD treatments improve over time, it is possible that lung cancer will become a significant driver of mortality in patients with ILD and further understanding of the risks of oncologic therapies in this population will be essential.

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