

## Lung surgery in interstitial lung disease—a safe and useful procedure?

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The group of interstitial lung diseases (ILD) includes a wide spectrum of disorders with variable clinical presentation, treatment response and prognosis. Idiopathic pulmonary fibrosis (IPF) is by far the most dismal disease in this group, with a median survival time of just 3-4 years (1). The diagnostic criteria for IPF are based on exclusion of any other cause for ILD by thorough clinical history, and a typical radiographic image revealing a so-called usual interstitial pneumonia (UIP) pattern in a high resolution computed tomography (HRCT) (2). Whenever a HRCT is slightly atypical, the clinical presentation or the age of the patient not supportive of IPF, surgical lung biopsy should be considered to establish a more definite diagnosis. As with any invasive procedure, the potential benefits of a lung biopsy have to be in balance with the risk of the surgery and the perioperative insults, including both anesthesia and mechanical ventilation (3).

When it is about the decision to biopsy or not, two important issues have to be addressed: (I) will the result of a biopsy affect the clinical management and (II) will the potential benefit from the biopsy justify the risk associated with surgery?

The first question, whether a biopsy alters the clinical management of patients with ILD was nicely addressed by the study of Qun Luo and colleagues (4). They report that lung biopsies by VATS can have a significant impact on the final diagnosis of ILD presenting with atypical or inconclusive HRCT images. This retrospective study included 32 patients who underwent VATS for ILD, 20 of them having undifferentiated ILD after review of the clinical history and the HRCT. In all these patients, the biopsy allowed to establish a definite pathological diagnosis. Another recent study of 103 patients undergoing

surgical lung biopsy in the United Kingdom for undefined ILD has also shown that a definite diagnosis can be obtained in a majority of these patients; however, the authors also cautioned that this approach impacted the clinical management in only half of the patients and had significant risk, including a 5% 30 day mortality (5). Luo *et al.* found non-specific interstitial pneumonia (NSIP) in 14 patients, UIP in 3 and connective tissue disease (CTD) associated ILD in 3 subjects. The differentiation between these three disorders is very relevant—NSIP has a substantially better prognosis than idiopathic UIP, and both NSIP and CTD-ILD are much more likely to respond to immunosuppressive therapy. In contrast, immunosuppressive treatment in IPF-UIP can increase mortality as recently shown by a randomized, placebo controlled trial sponsored by the NIH-IPF network (6). In this trial called “PANTHER” more deaths and hospital admissions was observed in the IPF patients treated with a combination of azathioprine, N-acetylcysteine, and prednisone compared to placebo. Of note, this therapy has been very widely used for treatment of IPF until then (7). IPF drug development is moving faster than ever before, and IPF may soon become a treatable disease (8). Pirfenidone is an antifibrotic therapy with some efficacy in IPF (9), and has recently been approved as first IPF specific therapy by many regulatory agencies in Japan, India, Korea, Europe and Canada. It is anticipated that more IPF therapies will follow this path over the next couple of years. While everyone welcomes the positive impact of new drug developments on the management of IPF, the potential side effects of these novel compounds and their socioeconomic impact on the health care systems cannot be neglected and warrant careful patient selection. Therefore, it is even more important to be as certain about the diagnosis of ILD as possible, and VATS biopsies will continue to play an important role in the decision making process in the future. Further, many of the compounds that are under investigation for IPF have very specific molecular targets and modes of action, such as inhibiting growth factors, blocking integrins, targeting membrane bound or cytoplasmic tyrosine kinases (10). Similar to the example of EGFR targeted cancer therapies (11), one could speculate that some of these novel treatments will only be successful in patients where these molecular mechanisms are active in the lung tissue,

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and only a biopsy would allow to determine this.

Even with a good rationale in favor of performing lung surgery in patients with unclear ILD, it is critical to address the safety and risks associated with the procedure. There were several publications addressing this question over the past decade, all of them retrospective cohorts and based on single center experiences. Kreider *et al.* reported 68 patients with ILD who had a mortality rate of 4.4% after 60 days due to exacerbation of the underlying lung disease (12). They also did a meta-analysis of 22 studies that had been published until 2007, including a total of 2,223 patients, showing an overall mortality of 4.5% after VATS in undifferentiated ILD. Poor pre-operative performance, documented by low DCO or FVC, supplemental oxygen, dependence on mechanical ventilation, and presence of pulmonary hypertension (PH) were associated with significantly higher risk of post-operative complications including death (3,12-14). Several studies also reported that patients with a final diagnosis of IPF-UIP after the biopsy had a higher risk of exacerbation (12,15). While there are no details related to presence of PH or need for pre-operative supplemental oxygen in the patients of the current study, their pulmonary function was relatively preserved, with mean FVC of 73%, and DLCO of 62%. This is perhaps contributing to the modest degree of serious complications post VATS seen in the study by Luo and colleagues (4). On the other hand, it shows how important it is to carefully select patients for VATS biopsies to avoid problems and reduce mortality associated with a surgical procedure, as manifested by the fact that while 51% of Luo *et al.* patients diagnosed with ILD underwent some kind of invasive examination, only 3.9% eventually underwent VATS lung biopsy. Additionally, video-assisted resection, typically requiring single lung ventilation, might not be feasible in the extremely sick patients who cannot tolerate one lung ventilation. In those cases, open biopsy is frequently required and the morbidity and mortality are typically higher.

Two more questions need to be discussed: (III) what is the underlying pathophysiology for acute exacerbations post lung biopsy and (IV) how can we modify the approach to VATS in order to reduce the exacerbations?

We have to speculate to address the question on the biology underlying the acute worsening or exacerbation of fibrotic and interstitial lung disease post-surgical biopsies. Many of the ILDs are a consequence of repetitive injury (e.g., asbestosis or hypersensitivity pneumonitis), followed by excessive repair, which in its chronic form results in fibrosis (16). In IPF, fibrosis occurs without apparent injury, although most of the current pathogenetic concepts postulate that recurrent alveolar micro-injuries may play an important role in the disease (1,17). It is reasonable to assume that any alveolar injury is able to trigger disease activity in all ILDs. During VATS, the lungs are affected by at least two major insults. The surgical procedure damages some tissue on the side of

biopsy, whereas the mechanical ventilation injures primarily the opposite lung during one sided ventilation. Interestingly, many reports state that acute exacerbation post VATS occurs more frequently on the non-operated lung (15). This is not only true for VATS biopsies, but also in cancer surgeries for pulmonary malignancies in patients who have underlying lung fibrosis. What may happen on a cell biology level during this period of one-sided lung ventilation, which can last between 1 to 4 hours? Alveolar epithelium and interstitial space are exposed to high oxygen levels, and to high inspiratory peak pressures. The FIO<sub>2</sub> levels that were used in patients suffering from and acute exacerbation of IPF post lung surgery were reported to be >0.6 (15). There is no published information on ventilation pressures in any of these reports. Anesthesia for thoracoscopic surgeries usually employs protective ventilator strategies with low tidal volumes of 6-8 mL/kg to avoid high inspiratory pressures (18). However, the fact that acute exacerbation of IPF can occur even with low tidal volume settings (4-6 mL/kg in the report of Sakamoto and colleagues) it is plausible that peak inspiratory pressures are still higher in IPF lungs than normally (15). These conditions probably injure epithelial cells, via oxidative stress and pressure forces. The disease-exaggerating role of abnormal mechanical stretch of the lung matrix in pulmonary fibrosis has just recently been recognized (19,20).

Regardless of the exact pathophysiology, it seems obvious that more gentle mechanical ventilation during lung surgery should help to reduce complications, particularly acute exacerbations of fibrotic disease. The study by Luo *et al.* did not report a single case of exacerbation, likely due to diligent selection of patients, who really needed the procedure (4). However, their cohort was relatively small and the findings of a single center study should not be generalized. Patients at higher risk for exacerbation, i.e., having low FVC, low DCO and being already on home oxygen therapy or under mechanical ventilation, should be extra carefully assessed, if not excluded from surgical lung procedures.

In summary, lung surgery by VATS is and will remain an important diagnostic tool for a significant number of patients with fibrotic lung disease. Clinicians and patients need to be aware of the benefits of the procedure, and have to be thoroughly informed about the associated risks. The overall mortality associated with VATS in fibrotic lung disease is significant. Careful selection of patients and avoiding patients with more advanced disease will help reduce peri-operative complications and acute exacerbations. There is a paucity of information on protective mechanical ventilation protocols in this specific setup and we suggest to study this important clinical question in prospective clinical trials in the near future.

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