Review

Mortality after surgical lung biopsy for the evaluation of interstitial lung diseases

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ABSTRACT

Interstitial lung diseases (ILD) represent a heterogeneous group of disorders in which the aetiology, not infrequently, remain unknown. Specific ILD requires a multi-disciplinary approach (MDD), in expert reference centers for diffuse parenchymal lung diseases (DPLD), using a stepwise approach which sometimes ends with the request of tissue sampling. The standard procedure to obtain histology in undefined ILD is the surgical lung biopsy (SLB) via video-thoracoscopy (VATS). However, SLB is associated with significant postoperative morbidity and mortality, and the physician must weigh carefully risks and benefits when a SLB is considered. VATS lung biopsy appears to be safer than open biopsy with an associated 90-day mortality that is somewhat lower, but not negligible, at approximately 3.4%. Last but not least, higher mortality risk may occur in patients whose ultimate diagnosis is idiopathic pulmonary fibrosis (IPF), as SLB in patients with IPF may trigger an acute exacerbation of IPF. Confirming the diagnosis and differentiating among specific forms of ILDs may though not be possible without performing SLB. Newer techniques, such as uniportal VATS under thoracic epidural anesthesia or intercostals block or transbronchial cryobiopsy may increase the safety of tissue sampling in undefined ILD patients.
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INTRODUCTION

Interstitial lung diseases (ILD) are numerous and represent a heterogeneous group of disorders, which range from acute inflammatory processes to progressive fibrotic conditions, with variable clinical presentation, treatment response and prognosis[1]. The gold standard ILD diagnosis is obtainable on the basis of a multi-disciplinary approach (MDD), in expert reference centers for diffuse parenchymal lung diseases (DPLD), using a stepwise approach which sometimes ends with the request of tissue sampling, as histopathology may serve as the only distinguishing feature between similar clinical-

radiologic presentations[1,2]. The standard procedure to obtain histology in undiagnosed/undetermined ILD is the surgical lung biopsy (SLB) via video-thoracoscopy (VATS)[1,2]. However, SLB is associated with postoperative morbidity and mortality[3]. The aim of this review is to summarize current knowledge regarding surgical lung biopsy morbidity and mortality in ILD patients.

THE CURRENT ROLE OF SLB IN THE DIAGNOSTIC APPROACH OF ILDS

In 2001, the American Thoracic Society (ATS)/European Respiratory Society (ESR) consensus panel proposed a useful classification scheme that divides DPLD into four categories: i) the DPLDs of known causes, ii) the idiopathic interstitial pneumonias (IIPs), iii) the granulomatous diseases, and iv) other forms of DPLD. The IIPs include seven entities, namely idiopathic pulmonary fibrosis (IPF) being the most frequent among them, nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP); classification scheme that was updated regarding the IIPs in 2013 and highlighted the presence of unclassifiable categories of IIPs, that is patients where a final diagnosis may not be achieved despite lengthy MDD[4,5]. Moreover, the advent of high-resolution computed tomography of the chest (HRCT), which allowed more detailed imaging of the lung parenchyma and refinements in the histopathologic classification, allowed differentiation of distinctive ILDs and led to the current, more restrictive, definition of IPF, which is crystallized in the new international statement on the diagnosis and treatment of IPF that defines new diagnostic criteria based principally on the combination of characteristic clinical, radiologic (HRCT), and eventually of histologic findings[2].

Despite the fact that aforementioned recent guidelines have been published, some issues concerning the practical evaluation of a patient with suspected DPLD remain unclear, thus the diagnosis and classification of the disease in an individual patient remain a challenge in real clinical practice[6,7]. An accurate diagnosis of DPLD is important to the management of these patients as prognosis, attention to extrapulmonary manifestations and comorbidities, choice of medication, and consideration for lung transplantation, all depend on the accurate diagnosis and staging of the underlying DPLD disease[1,2,8]. It is the task of the physician to distinguish which of the over 500 distinct entities is present in a particular patient. As such, the diagnostic route includes initially a well-performed patient history and physical examination, appropriate laboratory testing, imaging (HRCT), bronchoalveolar lavage (BAL) and, if needed, tissue biopsy to reach a confident ILD diagnosis[1,2] (Table 1). Typically for idiopathic pulmonary fibrosis (IPF), and for some other ILD entities, HRCT imaging may be sufficiently characteristic to avert the need for lung biopsy[2]; this is especially true in a clinical setting where all the suspected ILD cases are evaluated in an expert reference center for DPLD, and consensus is reached by an expert multidisciplinary team[2]. The recent ATS/ERS consensus statement reiterates that findings on transbronchial biopsy and BAL fluid are not reliable for establishing a diagnosis[2]. Surgical lung biopsy is currently considered the gold standard for accurate diagnosis of non-IPF/UIP disease, and when clinico-radiological data result in an uncertain ILD diagnosis[2].

SURGICAL LUNG BIOPSY IN ILDS: BASIC CONCEPTS

When surgical lung biopsy is deemed necessary in

TABLE 1. Characteristics determining need for SLB in patients with ILD[2,10]

- Age <50 years
- Duration of illness less than 3 months
- Systemic symptoms (fever, weight loss, sweats)
- No defined clinical or exposure history (e.g. drug, collagen vascular disease, occupational /environmental exposure)
- Unusual pulmonary/extrapulmonary manifestations (hemoptysis, unexplained PH, peripheral vasculitis)
- Recurrent pneumothorax
- Absent family history of ILD
- No characteristic HRCT patterns (e.g. no presence of UIP pattern)
- Discrepancy between clinical and radiographic features
- Rapid deterioration of lung function
- Normal or nonspecific BAL/TBB (e.g. infection, cancer, lipoid pneumonia, hemorrhage, eosinophilic pneumonia, asbestos bodies, positive lymphocyte transformation test, etc)
- Establishment of specific histological diagnosis may change therapy and/or prognosis
- Absence of contraindications for SLB
- Risk-benefit ratio

patients with suspected ILD, the approach of choice is by VATS, a minimally invasive technique that has largely substituted since the early 1990's biopsy by conventional limited thoracotomy[9]. VATS lung biopsy is performed under general anesthesia with one lung ventilated using a double-lumen endotracheal tube[10,11]. Nearly all patients tolerate single lung ventilation, unless they are severely hypoxic and require positive end-expiratory pressure (PEEP) to maintain oxygenation[12]. In addition, the VATS technique offers excellent view of the entire lung parenchyma, allowing to performing targeted biopsies. Only rarely the initial VATS approach needs to be converted to mini-thoracotomy, due to extensive pleural adhesions or stiff lung[13]. The location where the lung biopsy is taken should be guided by the most affected sites on HRCT[14,15], although areas with scarred or honeycombed lung, middle lobe and lingula must be avoided[15]. Obtaining biopsies from multiple lobes (at least two) is recommended[15-17]. Retrospective studies indicated that surgical lung biopsies yielded a pathological diagnosis in 37-100% of cases[17]. However, Nicholson *et al* quantified major observer variation among pathologists[18]. Thus, integrating histopathological data with HRCT scanning and clinical findings is highly recommended[18].

RISK FACTORS AND POSTOPERATIVE MORTALITY AFTER SLB FOR THE EVALUATION OF ILD

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; acute exacerbation of underlying fibrotic disease, persistent air leak, hemothorax, postoperative pneumonia and pneumothorax after discharge represent the most frequent postoperative complications[19-21] (Table 2). When it is about the decision to biopsy or not, two important issues have to be addressed: a) will the result of a biopsy affect the clinical management and, b) will the potential benefit from the biopsy justify the risk associated with surgery. 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[22]. There were several publications addressing this question over the past decade, all of them retrospective cohorts and based on single center experiences, that reported wide variation in effectiveness and complications. However, rigorous systematic evaluation was seldom performed because of the great variability of inclusion criteria, surgery expertise, and methodological quality of different studies[23].

TABLE 2. Complications of VATS lung biopsy in ILD[15,22,23,26,28,36]

Intra-operative
• Anesthesia related complications
• VATS –specific complications
Post-operative
• Mechanical ventilation dependence
• Prolonged air leak (> 5 days)
• Acute exacerbation of underlying interstitial pneumonia
• Post-op pneumonia/empyema
• Port-site infection
• Pneumothorax after discharge
• Broncho-pleural fistula
• Hemothorax
• Hematoma at incision site
• Persistent pain

To elucidate this, Han Q *et al* performed a systematic review and meta-analysis regarding the diagnostic yield and postoperative mortality rate of surgical lung biopsy in patients with suspected interstitial lung diseases[23]. They systemically searched for published studies between 2000 and 2014 and selected 23 studies. A total of 2148 patients with suspected ILD undergoing SLB were included. There were 5 prospective studies and 18 retrospective studies. Three studies were multicenter studies, including 1 retrospective study and 2 prospective studies; others were studies from a single institution. The mean age of patients ranged from 36.1 to 62.0 years, and 1124 (52.3%) were male. All patients had suspected ILD yet remained undefined or unclassified with thorough clinical and radiologic information. There were 1632 patients undergoing VATS (76.0%) and 268 patients undergoing open lung biopsy (OLB) (12.5%) in 21 studies reporting SLB techniques. The median diagnostic yield was 95% (range, 42%-100%), with idiopathic pulmonary fibrosis as the most frequent diagnosis (618, 33.5%). Surgical lung biopsy was mainly guided by HRCT findings. Biopsy site, biopsy number, and the surgical lung biopsy method may not be associated with the diagnostic accuracy. Regarding the distribution of 1847 specific diagnoses made by SLB, IPF accounted for most cases (618, 33.5%), followed by nonspecific interstitial pneumonia (NSIP) (219, 11.9%), HP (178, 9.6%), cryptogenic organizing pneumonia (139, 7.5%), sarcoidosis (126, 6.8%), and connective tissue

disease-related ILD (73, 4.0%). The pooled 30- and 90-day mortality rates were 2.2% and 3.4%, respectively. The composite postoperative mortality was 3.6%. Significant heterogeneity was observed among individual studies therefore, subgroup analyses were applied to explore the possible source of heterogeneity[23].

Subgroup analysis revealed that exclusion criteria based on immunocompromised status, mechanical ventilation (MV), and severe respiratory dysfunction (diffusing capacity of lung for carbon monoxide (DL_{CO}) <35% or forced vital capacity (FVC) <55% predicted), age (patients aged more than 70 years), surgical lung biopsy technique and underlying ILD subtype, may be possible sources of heterogeneity. It is of note that only 3 studies evaluated the mortality rate on the basis of underlying ILD subtypes[23]. Bando et al and Kreider et al found all deaths were observed in IPF cases. Instead, Lettieri et al demonstrated that the mortality rate was not related to the underlying ILD, although more deaths were observed in those with IPF compared with those without IPF[3,20,24].

In order to develop a practical risk score for 90-day mortality following SLB for ILD, Fibla et al from Mayo Clinic conducted a retrospective study on 311 consecutive patients undergoing SLB for ILD between 2002 and 2009[25]. They found that postoperative complication, 30-day and 90-day mortality rates were 11.5%, 9% and 10.6%, respectively. The most frequent diagnosis was IPF (39%). Univariable and multivariable analyses were used to identify factors associated with 90-day mortality. Therefore, a scoring system was developed by proportionally weighting the regression coefficients of the significant predictors of 90-day mortality: age >67 (P <0.0001, weighted score 1.5), preoperative intensive care unit (ICU) admission (P = 0.006, weighted score 2), immunosuppressive treatment (P = 0.004, weighted score 1.5) and open surgery (P = 0.03, weighted score 1). Patients were grouped in four classes showing incremental risk of death at 90 days: class A, score 0 (2%); class B, score 1-2 (12%); class C, score 2.5-3 (40%); class D, score >3 (86%). They concluded that SLB entails a considerable surgical risk with an overall 90-day mortality around 10%, and they were able to develop a practical risk score which, if validated by other independent prospective studies, can be easily used to stratify the risk of SLB candidates and assess the cost-effectiveness of this procedure[25] (Table 3).

Kreider et al also described their experience with VATS lung biopsies in 68 patients with ILD and they reported a mortality rate of 4.4% after 60 days due to exacerbation of the underlying lung disease[20]. They also performed

TABLE 3. Proposed practical risk score for SLB in ILD[25]

Predictor	Score	Class	Mortality risk
		I	
Age > 67 years	1.5	Score 0	2%
Preoperative ICU admission	2	**II** Score 1-2	12%
Immunosuppressive treatment	1.5	**III** Score 2.5-3	40%
		IV	
Open surgery	1	Score >3	86%

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 undefined ILD. Poor preoperative performance, documented by low DL_{CO} 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[20].

Several published studies have drawn attention recently to unexpected, apparently irreversible episodes of acute exacerbation experienced by patients who underwent VATS lung biopsy that revealed an underlying UIP/IPF[21,24,26-29]. These observations raise two important questions: a) what is the underlying pathophysiology for acute exacerbations post lung biopsy and b) how can we modify the approach to VATS in order to eventually reduce the exacerbations.

Regarding the first question we may speculate that during VATS the lungs are affected by at least two major insults[22]. 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[21,27]. This is not only true for VATS biopsies, but also in surgeries for pulmonary malignancies in patients who have underlying lung fibrosis[30,31]. Probably, alveolar epithelium and interstitial space are exposed to high oxygen levels, and to high inspiratory peak pressures. Anesthesia for thoracoscopic surgeries usually employs protective ventilator strategies with low tidal volumes of 6-8 mL/kg to avoid high inspiratory pressures[32]. 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[21]. These conditions probably injure epithelial cells, via oxidative stress and pressure forces. It seems obvious that more gentle mechanical ventilation during lung surgery should help to reduce complications, particularly acute exacerbations of fibrotic disease[33]. Diligent selection of patients (Table 4), who really need the procedure and the application of new surgical techniques such as uniportal VATS biopsies under thoracic epidural anesthesia or intercostal block can provide better intraoperative and postoperative outcomes, avoiding invasive ventilation, thus increasing the safety of VATS biopsy in ILD patients[23,33-35].

WHAT IS NEW

Recently, transbronchial lung biopsy using the flexible cryoprobe (cryo-transbronchial lung biopsy, cTBLB) has also been reported in the diagnosis of DPLD[36-38], representing a safe, and minimal invasive diagnostic tool for the histological diagnosis of ILD[39,40]. In a recent systematic review and meta-analysis that included 14 studies with 1183 patients, Dhooria S *et al* found a diagnostic yield of 76.9%, with the size of samples obtained with cTBLB significantly bigger compared with flexible forceps biopsy (20.4 vs 4.3 mm^2)[41]. The complications of cTBLB included pneumothorax (6.8%), severe bleeding (0.3%), and death (0.1%), likely representing a promising and an 'innovative' way to obtain lung samples for the diagnosis of ILD avoiding VATS[41]. Despite the presence of only one study comparing TBL cryobiopsies to the gold standard SLB, the evidence published recently triggers new questions[40,42]. In the presence of an ILD, should cTBLB be performed in the first place, instead of SLB, for a histologic diagnosis? Maybe it is time to consider to include the cTBLB as an option for a histological diagnosis of ILD, when histology is appropriately requested and indicated after a multidisciplinary assessment in the setting of an expert reference center for diffuse parenchymal lung diseases[40,41,43]. Therefore, we suggest the establishment of national reference centres in Greece that may have not only important diagnostic and therapeutic implications but will also boost the research for this heterogeneous group of disorders.

TABLE 4. Risk factors for postoperative complications of VATS lung biopsy in ILD[15,18,22,23,26,28,36]

- Supplemental oxygen preoperatively
- Age (>70 years)
- DL_{CO} <40%
- FVC <55%
- UIP pattern on HRCT
- Immunodepression
- Mechanical ventilation
- Preoperative intensive care unit (ICU) stay
- Open lung biopsy
- Pulmonary hypertension

CONCLUSION

Surgical lung biopsy by VATS is a valuable and important tool in the diagnostic work-up of undefined ILD, enabling an accurate diagnosis, although 90-day mortality is approximately 3.4% with significant heterogeneity across studies principally due to underlying UIP/IPF, age, immunocompromised status, mechanical ventilation and severe respiratory dysfunction. Clinicians and patients need to be aware of the benefits of the procedure, and have to be thoroughly informed about the associated risks. The institution of expert centers and the multidisciplinary approach will delineate circumstances in which SLB will be more informative than HRCT and when a surgical lung biopsy is not necessary, and ultimate, may cultivate the growth of new diagnostic modalities such as TBL cryobiopsy.

COMPETING INTERESTS

All the authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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