The role of surgical lung biopsy in the management of interstitial lung disease: experience from a single institution in the UK

Vivienne Blackhall, Mohammed Asif, Alessandra Renieri, Serenella Civitelli, Alan Kirk, Ali Jilaihawi and Felice Granato

**OBJECTIVES:** Interstitial lung disease (ILD) includes a wide spectrum of pulmonary pathologies. The role of surgical lung biopsy (SLB) in the diagnosis of ILD is still controversial. The purpose of this study was to ascertain whether SLB is worthwhile in the management of ILD.

**METHODS:** One hundred and three patients underwent SLB for ILD from April 2008 to March 2010 at a single institution. Outcomes included patient demographics, preoperative investigations, preoperative diagnosis and treatment, surgical approach, number and site of biopsies, complications, length of postoperative stay and postoperative pathological diagnosis and treatment.

**RESULTS:** Fifty-one (49.6%) patients were male and 52 (50.4%) were female. The median age was 58 (range 26–78). Major complications were seen in 7 patients (6.8%). Five patients (4.9%) died within 30 days following surgery. Definitive pathological diagnosis (DPD) was achieved in 72 (69.9%) patients, whereas no DPD was achieved in 31 (30.1%). Within the group of patients who received DPD, this differed from the clinical diagnosis in 53 patients (51.5%), and was concordant in 19 (18.4%). The DPD was helpful in guiding the management of 47 patients (45.6%), who had a change in their treatment following the procedure. The median hospital stay was 4 days (range 2–42 days).

**CONCLUSIONS:** SLB is a well-recognized procedure. Although it provides a diagnosis for the majority of patients, in our series SLB was inconclusive in a considerable number of cases and did not lead to a therapeutic change for more than half of all patients. Furthermore, SLB is not without risk and can be associated with a prolonged hospital stay. We believe that SLB should be performed in a select group of patients with ILD after discussion by a multidisciplinary panel.

**Keywords:** Interstitial lung disease • Video-assisted thoracic surgery • Biopsy

**INTRODUCTION**

Interstitial lung diseases (ILDs) encompass a heterogeneous group of pulmonary pathologies with different aetiologies, ranging from acute inflammatory disorders to progressive fibrotic conditions [1]. Although the ILDs include a wide spectrum of diseases, their clinical features are often very similar and basic investigations such as spirometry, Chest X-ray and computer tomography (CT) scan may be non-specific, particularly in the absence of a clear environmental cause. Despite the development of sophisticated diagnostic methods, including positron emission tomography (PET), high-resolution computer tomography (HRCT) and bronchoscopic techniques [2–4], one-third of patients with ILD still require surgical lung biopsy (SLB) to achieve a definitive diagnosis [4, 5]. The role of SLB is, however, controversial because it can be associated with significant mortality and morbidity [6, 7].

The purpose of this study was to evaluate the efficacy of SLB in achieving a definitive pathological diagnosis (DPD) in a series of 103 consecutive patients with ILD and to examine whether the pathological diagnosis resulted in a change in patient management. An evaluation of mortality and morbidity following SLB was also performed.

**MATERIALS AND METHODS**

All patients undergoing SLB for ILD at our institution between April 2008 and March 2010 were included in the study. Patients with suspected metastatic disease or those with pulmonary nodules (defined as one or more discrete spherical lesions ≤ 3 cm in diameter, surrounded by normal lung, in the absence of associated lymphadenopathy and atelectasis) were excluded from the study. Inclusion criteria were the presence of either unilateral or bilateral ILD with no clear pathological diagnosis.

Information was retrospectively gathered from the clinical case notes and included: demographic data (age and sex), preoperative diagnosis and treatment, pulmonary function tests (PFTs) and transthoracic echocardiogram (TTE), surgical approach to biopsy, number of biopsies taken, side of biopsy, morbidity, mortality at...
SLB was performed under general anaesthesia, utilizing double lumen intubation and single-lung ventilation. All patients were placed in a lateral decubitus position. Surgical approach was via three port video-assisted thoracoscopic surgery (VATS) or by limited open thoracotomy in those patients in whom severe adhesions were encountered at endoscopic exploration. The site and side of biopsy were chosen after careful clinical evaluation and by the assessment of the distribution of disease and signs of possible pleural obliteration on CT scan. For the presence of three different lobar targets, in the presence of homogenous bilateral disease, the right side was chosen preferentially. For biopsy, a triangular wedge of pulmonary tissue was taken using an EndoGIA stapler (Auto Suture Company Division US Surgical, Norwalk, CT, USA). When feasible, specimens were obtained from each lobe. The specimen included a margin of normal lung tissue surrounding the target area. The samples were injected with formalin and sent for pathological examination.

We evaluated the number of patients in whom a pathological diagnosis was successfully achieved and subsequently compared this with the preoperative clinical diagnosis. Where no DPD was made, a second opinion from another pathologist was sought. We also examined whether biopsy altered the therapeutic management of patients. This was determined by review of case note entries of the follow-up carried out by chest physicians at intervals.

Statistical analysis was performed using basic statistical analysis and two-tailed Fisher’s exact test.

### RESULTS

Results are summarized in Table 1. One hundred and three consecutive patients were included in the study. Fifty-two patients were female (49.6%) and 51 were male (50.4%). The median age was 58 years (range 26–78 years). The median follow-up time was 25 months (range 1–44 months).

PFTs were performed in 85 (82.5%) patients. Forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), total lung capacity (TLC), FEV₁/FVC ratio and diffusing capacity of the lung for carbon monoxide (DLCO) were recorded in all cases. About half of patients with ILD have a normal DLCO adjusted per alveolar volume (DLCO/VA) [8], this was deliberately not included to avoid incorrect interpretations of the results.

Seventy-seven patients (74.8%) presented a restrictive pattern. The median values of predicted normal observed were: FVC = 64.3% (range 43–78), FEV₁ = 55.2% (range 35–75), TLC = 63.4% (range 45–75) and DLCO = 55.1% (range 35–87). The median FEV₁/FVC ratio was 0.85 (range 0.73–0.93).

Eight patients (7.8%) showed a non-specific pattern with reduced FVC but normal TLC and FEV₁/FVC ratio. The median results of predicted normal in this group were: FVC = 62.3% (range 55–73), TLC = 85.2% (range 82–93) and DLCO = 63.1% (range 45–76). The median FEV₁/FVC ratio in this group was 0.83 (range 0.71–0.92).

TTE was carried out in 25 patients (24.3%). Four patients (3.9%) demonstrated pulmonary hypertension and dilated right ventricle with preserved systolic function; in 2 cases (1.9%) mild aortic stenosis was found.

Eighty-one cases were performed using VATS techniques (78.6%), and 22 (21.4%) that were initially approached through VATS were converted to open because of extensive adhesions. The median number of biopsies taken was 2 (range 1–3); 63 (61.2%) patients had two biopsies, 38 (36.9%) had 1, 2 (1.9%) had three. The right lung was biopsied in 64 (62.1%) patients and the left lung was biopsied in 39 (37.9%).

The median hospital stay was 4.0 days (range 2–42 days). Major complications were seen in 7 patients (6.8%). These included respiratory failure in 4 (3.9%), ischaemic bowel in 1 (1.0%) upper gastrointestinal bleeding requiring blood transfusion in 1 (1.0%), postoperative effusion requiring re-admission in 1 (1.0%) and acute renal failure in 1 (1.0%). Five patients (4.9%) died within 30 days following surgery. Causes of death were respiratory failure in 4 and ischaemic bowel in 1. Of those patients who died in the first 30 days following surgery, 4 underwent VATS lung biopsy and one open lung biopsy. There was no significant difference between mortality rates between patient undergoing VATS or open procedures (P = 1.0).

Minor complications were seen in 7 patients (6.8%). These included wound infection in 1 (1.0%), urinary retention in 1 (1.0%), hypotension in 1 (1.0%), pneumothorax in 1 (1.0%) persistent air leak in 2 (1.9%) and atrial fibrillation in 1 (1.0%). There was no significant difference in morbidity rates between VATS SLB and open SLB (P = 0.677).

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<th>Table 1: Demographics and results</th>
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<td><strong>Total number of patients</strong></td>
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A DPD was achieved in 72 (69.9%) patients. Thirty-one (30.1%) patients received no clear DPD. There was no significant difference between VATS and open techniques in achieving a DPD ($P = 0.812$).

Of the 72 patients who received a diagnosis, the DPD differed from the clinical diagnosis in 53 patients (51.4%), and confirmed the clinical diagnosis in 19 (18.4%).

The most common pathological diagnosis was non-specific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP), which were seen in 32 patients (31.1%). Extrinsic allergic alveolitis accounted for 7 (6.8%), sarcoidosis accounted for 5 (4.9%) patients and Langerhans cell histiocytosis also for 5 (4.9%). Malignancy was seen in 2 (1.9%). Other diagnoses included emphysema, cryptogenic organizing pneumonia and drug-associated changes (Fig. 1).

Forty-seven (45.6%) patients had a change in their treatment following the procedure. Of these, 41 (39.8%) patients were commenced on a therapy having had no previous treatment. Twenty-nine (28.2%) patients were commenced on steroids, 2 (1.9%) were started on chemotherapy, 4 (3.9%) on inhalers, 2 (1.9%) on immunomodulators, 2 (1.9%) on antibiotics, 1 (1%) on anti-fungals and 1 (1%) on anti-tuberculosis chemotherapy. Following biopsy, statins were discontinued in 2 patients (1.9%). Other changes included a change of therapy from steroid inhalers to systemic steroids in 3 patients (2.9%).

Twenty-five (24.3%) patients received no change in therapy following biopsy.

The remaining 31 (30.1%) patients either received no clear diagnosis or died soon after the procedure meaning that a change in therapy was not applicable.

**DISCUSSION**

SLB is required in 30% of patients with ILD in order to obtain a DPD [4, 5]. Although imaging investigations, such as CT, PET and minimally invasive procedures including transbronchial biopsy (TBB) can be effective in the diagnosis of ILD [2, 3], they still have some limitations. The results of imaging studies often reveal non-specific changes, and minimally invasive biopsy frequently yields tissue volume that is insufficient for complete assessment [9, 10]. Transthoracic needle biopsy (TTNB) and TBB have important limitations: there may be inadequate specimen selection, with damaged or small quantities of tissue leading to difficult pathological interpretation [11–14]. Furthermore, for TBB the sampling comes from peri-bronchial areas where pathologic changes are often non-specific or not significant [11–13].

TTNB allows sampling of limited parenchymal tissue, resulting in poor diagnostic accuracy (63–75%) and is associated with high morbidity (42–44%) and mortality rates (0.5–1.1%) [14].

TBB has a variable diagnostic accuracy of 37.7–70%. This procedure is also associated with a complication rate of 15% (iatrogenic pneumothorax: 1–5%, haemothorax: 2–9%) [12, 13].

Research suggests that the commonest type of ILD includes UIP and NSIP [10], which is reflected in our results with ~30% of patients receiving these diagnoses. In this retrospective study, we analysed the diagnostic role of SLB in evaluating ILDs identified on the basis of clinical and radiological findings in the absence of an established diagnosis.

An analysis of the current literature has been carried out and summarized in Table 2.

Previous studies reported mortality rates between 0 and 17% [1, 5, 6, 10, 15–20] associated with SLB. Patient factors associated with an increased risk of mortality include mechanical ventilation at the time of SLB, an immunocompromised status and emergency biopsy [1, 15]. Open lung biopsy is associated with a greater risk of mortality compared with VATS techniques [1, 16, 17]. Lettieri described 30- and 60-day mortality rates of 4.8 and 6.0%, respectively, in a cohort of 88 patients undergoing either VATS or open biopsy [1]. LoCicero described an overall mortality rate as high as 17% in open lung biopsy in a series of 48 patients [16]. A meta-analysis of 22 studies performed by Kreider et al. [17] reported an aggregated mortality rate of 4.5% in individuals undergoing SLB for ILD. In an analysis of 196 patients undergoing either VATS biopsy or minithoracotomy, Lee et al. [18] observed no surgical mortality directly related to surgery.

In our series, we observed a 30-day mortality rate of 4.9%, consistent with these findings. Four patients (3.9%) who died as a result of respiratory failure presented preoperative restrictive syndrome with lower values of DLCO. In 1 case (0.9%), there was associated pulmonary hypertension. There was no significant difference in mortality rates between open and VATS procedures.

Lee et al. [18] described a 6.6% morbidity rate in the aforementioned study. The most common complication was prolonged air leak (6%, or 11 patients). One patient (0.5%) developed a haemothorax and one (0.5%) had an acute myocardial infarction. Qureshi et al. observed an overall morbidity rate of 13% in a series of 100 patients; of these 17.6% developed wound infections, 11% atelectasis and 1.4% respiratory failure [19]. We observed a similar morbidity rate of 13.6%, including both major and minor complications. Interestingly, in contrast to previous literature, our most common complication was that of respiratory failure (3.9%), followed by persistent air leak (1.9%) while only 1.0% of patients developed wound infection.

SLB does not always yield a definitive tissue diagnosis. Only a few previous studies have addressed this issue [5, 16, 18, 19]. Previous research by Qureshi et al. [19] demonstrated that a specific diagnosis was only achieved in 42% of patients; leaving 58% without a diagnosis. Our results are, however, more encouraging, with 69.9% of patients receiving a DPD following SLB. There was no significant difference between open and VATS techniques in successfully achieving a diagnosis ($P = 0.81$).
The median number of lung biopsies in those patients who received a diagnosis was 2, while the median number of biopsies in those patients who did not receive a diagnosis was 1, suggesting an advantage in taking several tissue biopsies. Interestingly, the research by Chechani et al. [20] concluded that there was no benefit in taking multiple biopsy specimens when a region of lung representative of the disease was biopsied. In our experience, at least two biopsies should be taken from the lung tissue in order to improve the likelihood of obtaining a diagnosis [4].

Three patients (2.9%) received a DPD of emphysema. As previously described by Wright et al. [21], when ILD (most commonly UIP) occurs in patients with emphysema, this may lead to unusual appearances at biopsy where fibrotic areas are wrapped around emphysematous spaces. The authors also reported effects on pulmonary function and pulmonary resistance. Interestingly, all 3 patients in this group presented pulmonary hypertension and a non-specific pattern was found at PFT.

Lee et al. [18] demonstrated that following SLB for diffuse pulmonary disease, 84.2% patients had a change in their medical therapy. In addition, 63.3% of patients were then reported to have had a clinical improvement (measured by imaging and clinical examination).

Despite 69.9% of patients of our series receiving a DPD, only 45.6% had a change in their medical therapy following biopsy. This outcome should be carefully considered in the context of a mortality rate of 4.9%. However, a change in treatment is not necessarily synonymous with a clinical improvement. Furthermore, a change in treatment may not necessarily be directed by a definitive biopsy result: in the series by Qureshi et al. [19], 59.5% of those with a specific diagnosis had a change in therapy compared with 55.2% of those who received no diagnosis ($P = 0.664$).

In conclusion, SLB provides a DPD in the majority of patients; however, it is not without its limitations. It can lead to significant morbidity and mortality, particularly in patients with severe restrictive respiratory impairment and pulmonary hypertension, and has associated financial costs. We, therefore, propose that patients should be carefully selected for SLB following discussions at a multidisciplinary team meeting in order to make optimal use of this resource. We recommend that a surgeon with experience in cardio-respiratory pathophysiology be an active part of this team. Proceeding to SLB is recommended only if histological diagnosis is crucial in directing therapeutic treatment.

Conflict of interest: none declared.

REFERENCES


