

## Surgical lung biopsy for interstitial lung disease: when considered necessary, should these be done in larger and experienced centres only?

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Ascertaining an accurate diagnosis for people confronted with new onset interstitial lung disease (ILD) is central to informing discussions around prognosis and treatment choices. In people with idiopathic pulmonary fibrosis (IPF), treatment with both Pirfenidone and Nintedanib has been shown to reduce the rate of disease progression (1, 2), whereas historical use of immunosuppression was shown in the landmark PANTHER study to be harmful (3). In other conditions such as hypersensitivity pneumonitis or sarcoidosis, an accurate diagnosis helps to inform prognosis, allow removal from harmful exposure, and justify consideration of treatment with corticosteroids and/or immune modulating agents if required (4, 5).

With the advent of high resolution computed tomography (HRCT) scans of the chest and recognized patterns and distribution of images, an accurate diagnosis can be ascertained in the appropriate clinical setting. For example, in IPF, a definite usual interstitial pneumonia (UIP) pattern on high resolution computed tomography (HRCT) in the appropriate clinical context (aged over 60, bibasal crackles, no alternative exposure history attributable to the manifested ILD or serological markers for connective tissues disease) is sufficient to consider treatment according to latest guidelines (6-8). However, in the absence of connective tissue diseases and/or exposures of environmental factors known to induce hypersensitivity pneumonitis, and when the HRCT imaging features reveal patterns that are indeterminate for UIP or otherwise, histopathology features, usually by means of a surgical lung biopsy, may be required to make an accurate diagnosis.

This would suggest that surgical lung biopsy (SLB) features frequently in the diagnostic work-up for ILD, but this is not necessarily the case (9). Rates of histological confirmation for IPF vary significantly in epidemiological studies (10-12) and clinical trials (1, 2, 13). Besides the risks associated with SLB, concerns about inter-observer variation in interpretation of the histopathology (14), varying

pathology in different areas of the lung (15) and the possibility of no clear diagnosis (or unclassifiable disease) despite SLB are some reasons for the reluctance of some clinicians and patients to opt for surgery. The emerging evidence that SLB carries a risk of mortality has further tipped the scales against subjecting patients to SLB for some clinicians. Numerous studies, mainly case series, have reported risks of SLB in ILD: early single-centre series touted alarming risks but often included patients who would not be biopsied today with significant pre-morbid risk factors (16), while more recent reviews, albeit heterogenous in their study composition, report 30-day mortality of around 2% (17, 18). A 2% chance of dying from a diagnostic test however suggests it is crucial we learn more about how to ensure surgical biopsy for ILD is as safe as possible.

The study from Fisher *et al* published in this journal contributes to this debate (19). The authors use a large administrative clinical dataset from Ontario, Canada, with over 3000 surgical lung biopsies for ILD over a 13 year period (until 2014). Their primary objective was to consider whether centres that performed higher numbers of surgical lung biopsies had better mortality rates than lower volume centres. There is good reason for this hypothesis: similar data exists for multiple types of surgery (20, 21) and sub-specialist surgery such as lung transplantation is usually performed in fewer centres to maintain expertise. Centres with greater procedural experience of surgical lung biopsy might offer more specialist assessment and patient selection, increased surgical skill, or more experienced post-operative care, and confirming this might have implications for where patients choose to undergo surgery.

What do the data show? Firstly, Fisher *et al* report a 30-day mortality of around 2% for elective procedures. This is comparable to data from the USA and UK (22, 23), and suggests we now have an international consensus around the mortality risk for all-comers undergoing planned surgical biopsy for ILD. The mortality from non-elective procedures however was far higher at 20%, again similar to other data (22). This reinforces the need for a debate as to whether there is any place for unplanned biopsies in these high risk populations. Re-admission within 30 days (possibly suggestive of post-operative complications) occurred in around 10% of patients in this study. Surgical lung biopsy clearly has a risk profile that needs careful communication with patients.

Secondly, the headline figures suggest a lower post-operative mortality in higher volume centres, as hypothesised. The authors elegantly state that for every additional 50 biopsies performed in a year, the risk of dying within 30 days reduces by 16%. However, when stratifying by elective or non-elective procedures, this effect appears to be driven primarily by urgent and emergency cases, with most variability due to patient characteristics rather than hospital differences. The suggestion of a trend persisted for elective biopsies but was no longer statistically significant.

Finally, the authors noted a surprising increase in post-operative mortality in later years, and they speculate that this may be due to more aggressive biopsy strategies to confirm IPF as a result of recent developments in the field, for example licensing of anti-fibrotics and the risks of immunosuppression. This is slightly concerning and warrants further study in alternative data sources, ideally with more clinical data on underlying risk factors and precise diagnoses to compare fitness of patients being referred for biopsy and whether this has changed over time.

There are several strengths to this work. The authors have used a comprehensive and clinically-rich data source covering a population of 13 million people, with appropriate exclusions to ensure no patients with cancer slipped into the mix. They have applied sophisticated modelling to consider the impact of centre volume, with sensible stratification by elective and non-elective patients on the basis of previous work. They were able to assess risk factors identified previously, for example gender and age, as well as the impact of long term oxygen therapy, which perhaps unsurprisingly was significantly associated with mortality in elective patients. These results show consistency with studies derived from other datasets in the UK and USA. A major limitation to the study was the lack of adequate power when stratifying by elective vs non-elective procedures, which may explain why the association loses significance for elective cases.

Should clinicians then seek out larger centres when contemplating surgical lung biopsy? The data presented suggest this is primarily an issue for non-elective cases, but the mortality rates are so high for these patients that a major question is whether we should contemplate doing these procedures at all. One explanation for the lower mortality in higher volume centres is that there is more clinical experience and that the clinical care is better in these centres, but it is also possible that the busier centres may know better when to say 'no' to a high-risk biopsy, whereas smaller centres may 'have a go', less aware of the presence of higher risk features. For elective cases, while the theory is intuitive, the data currently available do not support a major difference between high and low volume centres, and the key factor affecting mortality is likely to be optimal patient selection, with a focus on identified risk factors including age, gender and co-morbidity. A pre-existing oxygen requirement would suggest even an elective biopsy is overly risky. The suggestion of a trend towards lower mortality for elective patients in higher volume centres justifies further research in this area however, and a larger study of mortality-volume associations for elective cases – ideally with additional clinical details – would be desirable. Given that the mortality of surgical lung biopsy is comparable to lobectomy for lung cancer (24) – a curative procedure – the prospect of concentrating expertise and therefore reducing mortality may be a means to lower procedural risk to a more acceptable level to patients. Nevertheless, the risks associated with non-elective SLB in

the patient with more advanced disease (as indicated by the need for supplemental oxygen at rest) is so substantial that both the confronted clinician and patient should carefully weigh the risk-benefit ratio before subjecting the patient to SLB even in higher volume centres.

Clinicians should also consider whether there are alternatives to surgical lung biopsy in people with undiagnosed ILD. Experts differ in their recommendations on the use of SLB in certain situations, for example, the recent ATS / ERS / JRS / ALAT guidelines make a conditional recommendation *for* surgical lung biopsy when HRCT shows 'probable UIP' (6), whereas a recent Fleischer statement opts *against* biopsy in this cohort (7). A growing number of centres are building experience with transbronchial cryobiopsy (25): this appears to offer good quality samples, a diagnosis in 80% of cases, and complication rates that are improving with greater understanding of optimal procedural techniques, for example haemorrhage control (26-28), however, the lack of clear standardisation means that latest guidelines currently make no recommendation for the procedure in indeterminate cases – suggesting that experienced centres work towards a standardised approach before widespread adoption (6). Work using machine learning and RNA sequencing to identify UIP on conventional transbronchial lung biopsy samples has also shown promise (29-31), and a recent validation of this approach on a prospective cohort may allow a diagnosis without the need to proceed to conventional SLB (32). Biomarkers to distinguish sub-types of ILD have been enthusiastically pursued but have not progressed beyond the research sphere so far (6, 33-35). A pragmatic approach to diagnosis would be to loosen criteria for anti-fibrotics (or undertake trials to support this approach), and accept trials of treatment for probable and indeterminate disease on imaging. It is likely that variation exists between multi-disciplinary teams on their approach to biopsy, and consensus views on challenging cases would be helpful.

In summary, the study by Fisher et al identifies an important clinical question with potential significant implications for ILD care. The theory that higher volume centres may yield lower mortality after surgical lung biopsy is attractive, although for elective cases – which should form the vast majority of those biopsied – the data are suggestive rather than conclusive. We need further studies, using either administrative data or potentially prospective registries, to explore this issue further. Such data, building on the current work, could make surgical biopsy a safer and more attractive proposition to people with new onset ILD. At the same time, we need continued research into less invasive methods of diagnosis, such as transbronchial cryobiopsy and molecular classification using machine learning in conventional transbronchial lung biopsy. Ascertainment of an accurate diagnosis with minimum procedure associated risks is vital to ensure our patients get the subsequent high level of evidence-based care they deserve.

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