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Lung biopsy in interstitial lung disease: balancing the risk of surgery and diagnostic uncertainty

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Diagnostic guidelines now need to be amended to better correspond to the pragmatic management of ILD <http://ow.ly/97M8304aylG>

Challenges to diagnosing interstitial lung disease

The efficacy and approval of two antifibrotic drugs [1, 2], the increased mortality of idiopathic pulmonary fibrosis (IPF) from corticosteroids and anticoagulants [3, 4], and the availability of data from multiple drug trials have tremendously increased the need for an accurate diagnosis of interstitial lung disease (ILD). As stated in international guidelines [5], in the appropriate clinical setting with all possible causes of ILD ruled out, the presence of a definite usual interstitial pneumonia (UIP) pattern on chest computed tomography (CT) is sufficient for the diagnosis of IPF. In the absence of a UIP pattern on CT, establishing a secure diagnosis of IPF requires a surgical lung biopsy [5]. This approach, therefore, relies heavily on the CT appearance of ILD that is stratified into three categories, namely UIP, possible UIP and inconsistent with UIP. In theory, a lung biopsy should be contemplated in patients with a pattern of possible UIP or inconsistent with UIP. All possibly relevant information available is then synthesised during the multidisciplinary discussion among clinicians, radiologists and pathologists, all being experts in the field of ILD, a process that increases the accuracy of the diagnosis [6] and impacts management [7]. The multidisciplinary discussion also allows the diagnosis to be made with higher confidence than by clinicians or radiologists alone (although reproducibility between different teams needs to be optimised for diagnoses other than IPF [8]), and has become the gold standard for the diagnosis of ILD.

One challenge with this diagnostic approach is that many patients with a CT pattern of possible UIP or inconsistent with UIP do not undergo a surgical lung biopsy. There are multiple reasons for that [9], including the legitimate perception by some physicians and patients that the risk of performing a lung biopsy may be excessive. Often, the biopsy is deemed impracticable due to age, disease severity or comorbidities [10]. Although every clinician and thoracic surgeon routinely needs to evaluate the benefit/risk balance of a lung biopsy in patients with ILD, and the benefit of a secure and tentatively early diagnosis is now well established, the literature to evaluate the risk associated with a surgical lung biopsy is surprisingly scarce.

Evaluating the risk of a surgical lung biopsy

In this issue of the *European Respiratory Journal*, HUTCHINSON *et al.* [11] aimed to assess the risk of a surgical lung biopsy. Using hospital statistics from a national secondary care dataset in the UK from 1997 to 2008, they estimated in-hospital mortality following surgical lung biopsy to be 1.7%, 30-day mortality to

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be 2.4% and 90-day mortality to be 3.9%. Furthermore, they identified male sex, increasing age and increasing comorbidities as risk factors for mortality following open surgery. Unlike in previous studies, HUTCHINSON *et al.* [11] were able to assess mortality at several stages, including re-admissions and late mortality. The results are generally comparable to those obtained by the same group using data from a large secondary care dataset from the USA, identifying 1.7% in-hospital mortality following elective surgical lung biopsy for ILD [12].

This study based on epidemiologic data adds to previous accumulating evidence from case series [13–18] indicating that the risk of surgical lung biopsy is clinically significant, even if it is lower than that in older series with probably less careful selection of cases [19, 20]. As emphasised by the authors [11], mortality after a surgical lung biopsy can be compared, for example, to that of lobectomy for lung cancer (2.3%) [21], a therapeutic, not diagnostic, procedure. Clinicians and patients should be aware of, and understand, the risk involved, which needs to be balanced with the benefit of making or securing a diagnosis of ILD.

Limitations to this study include the absence of information about the CT pattern or lung function that obviously can have a major impact on the risk of thoracic surgery [15, 17]. The authors used hospital diagnostic codes (International Classification of Diseases) and procedure codes rather than medical files, which might lead to some errors, for example, when assessing whether a biopsy was elective (scheduled) or nonelective (emergency), when evaluating the risk associated with a specific diagnosis, or when assessing the presence of comorbidities that might have been underestimated. Only 27% of them were older than 65 years, which suggests that the risk estimate in subjects older than 74 years may lack accuracy. The exact cause and mode of death could not be evaluated. Medications, such as corticosteroids, immunosuppression, anticoagulants and oxygen requirement, were not analysed. It is likely that acute exacerbations represented an important cause of re-admission and death, but this could not be ascertained due to the methodology. Practice has changed since the 1997–2008 period of the study and it is likely that the mortality with video-assisted thoracoscopic surgery is lower than with open surgery. Collectively, these limitations indicate that numbers provided by the study by HUTCHINSON *et al.* [11] cannot be directly extrapolated to our next patient in the clinic; however, the results contribute to guidance on whether the benefit of an accurate diagnosis may outweigh the potential harm of a lung biopsy.

Despite the crude mortality, surgical lung biopsy can still be considered a relatively safe procedure, if not performed in patients and situations at risk. Elderly patients with comorbidities, those with functionally severe disease or immunocompromised status, or with hypoxaemic respiratory failure or acute exacerbation of IPF [22], should not have a surgical lung biopsy. The risk is low, however, in patients younger than 65 years with no significant comorbidity, who have chronic progressive disease and mild-to-moderate impairment in lung function. Nonelective lung biopsy should be considered especially carefully, as in-hospital mortality was 4.6%, compared to 1.0% for elective surgery [11]. Although not specifically evaluated in the study by HUTCHINSON *et al.* [11], patients with suspected acute exacerbation of IPF, acute symptoms or accelerated subacute disease seem to be at higher risk of mortality, and should generally not be referred for lung biopsy (in other words, the more urgent the procedure, the higher the mortality risk). Overall, a more cautious approach and a possibly lower mortality rate can be expected now that risk factors have been identified. In the future, it is conceivable that cryobiopsy may be associated with a lower risk of mortality than video-assisted thoracoscopic surgery [23], although published studies show a variable incidence of complications.

Diagnosing ILD without lung biopsy

Further information provided by the study by HUTCHINSON *et al.* [11] is the relatively low number of surgical lung biopsies performed, with only 2820 patients with a diagnosis of ILD undergoing this procedure in National Health Service hospitals in the UK over a 12-year period. This translated to an estimate of 0.47 biopsies per 100 000 population and only 13 annual biopsies per thoracic surgical centre in England (in 2008). As a comparison, the crude estimated incidence of IPF in the UK was 4.6 per 100 000 population [24]. The authors estimated that only 5% of clinically suspected IPF were biopsied. The incidence of IPF has been more recently estimated to 18.7 per 100 000 in Canada [25]. The incidence of ILD in general can be considered several-fold higher than that of IPF; it is estimated to be 32 per 100 000 in men and 26 per 100 000 in women [26]. Overall, the data suggest that only a small minority of patients who are theoretically eligible for a lung biopsy actually undergo the procedure, contrasting with data from clinical trials and from IPF registries [27].

How, then, shall the clinician proceed with the diagnostic process in subjects with idiopathic ILD and a non-UIP pattern on CT, who do not undergo a lung biopsy? The very fact that a provisional diagnosis of IPF (or of connective tissue disease-related ILD) was identified as a risk factor for increased mortality following surgical lung biopsy [12] challenges the current, somewhat inflexible guidelines for the diagnosis of IPF. Hence, the combination of a CT pattern of possible UIP and absence of a lung biopsy is a relatively

common situation in patients with suspected IPF [27]. This leaves us with theoretically “unclassifiable” idiopathic ILD, which in fact often corresponds to a condition left “unclassified” by the current definition of IPF [9]. Recent data show that the progression of disease is the same in patients diagnosed with IPF, with or without honeycombing on CT [28]. There is also recent recognition that patients with a chest CT inconsistent with UIP may have pathological UIP [29, 30], another situation not yet considered in guidelines. In the correct clinical setting, a histological pattern of UIP is not excluded by CT appearances more suggestive of alternative diagnosis including nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis or sarcoidosis [30]. Although one may consider that, in the appropriate clinical setting, all patients with pathological UIP and a discordant CT (inconsistent with UIP) actually have IPF [31], a previous study has demonstrated that patients with a histopathological pattern showing UIP and a CT interpreted as indeterminate or suggesting nonspecific interstitial pneumonia had a better prognosis than those with histological UIP and a CT pattern of UIP [32]. In this context, should all cases of idiopathic, pathological UIP be called IPF whatever the imaging pattern? This is a nosology question that currently finds no clear answer in the literature, and only evolution of disease with or without therapy can provide some clues.

Managing diagnostic uncertainty

As is frequently the case in medicine, clinicians who manage patients with ILD have to deal with some diagnostic uncertainty and yet have to take medical decisions to best advise the patients about how to manage their disease. There are a number of things that can help us in this difficult situation. Multidisciplinary decisions increase the accuracy of the diagnosis and allow, at least in theory, the diagnosis to be based on the consensus of experts rather than on the opinion of individual physicians. In the field of ILD, diagnosis is a dynamic process, and that is the reason why cases with a non-definite diagnosis at the time of multidisciplinary discussion may need to be reconsidered in light of evolution, and in the meantime, receive a diagnosis with a terminology that acknowledges diagnostic uncertainty, such as “IPF, working diagnosis” (*i.e.* a flexible approach to IPF diagnosis) [10]. Indeed, disease behaviour (*e.g.* integrating the course of disease and outcome with treatment) considerably improves the approach to disease characterisation [7, 33], although this has not yet been formally evaluated. Clinical data (age of the patient) [34], progress in characterisation of CT patterns [35], alternative methods to obtain biopsy material such as a cryobiopsy [23, 36], possibly biomarkers and genetics [37, 38], and bronchoalveolar lavage, can also contribute to improved diagnosis of ILD. Diagnostic guidelines, which have made IPF clinical trials possible, now need to be amended to better correspond to the pragmatic management of ILD in the “real world”.

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