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ROLE OF SURGICAL LUNG BIOPSY IN THE DIAGNOSIS OF FIBROTIC INTERSTITIAL LUNG DISEASES

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A surgical lung biopsy (SLB) is an important diagnostic procedure in the evaluation of patients with fibrotic interstitial lung disease (fILD). It is generally considered for patients who (1) lack a confident clinical- radiographic diagnosis after appropriate non-invasive evaluation, (2) are not at excessively increased risk for post-operative complications, and (3) are expected to benefit from a change in treatment based on biopsy results.

Indications, Contraindications, and Decision-Making

SLB has an overall diagnostic yield of approximately 90% for ILD when considered in the context of multidisciplinary discussion (MDD). However, it is not required to achieve a confident diagnosis in a large proportion of cases of fILD, and it is therefore critical that patients undergo a thorough non-invasive evaluation before consideration of SLB. A thorough evaluation of fILD generally includes a detailed history and physical examination, appropriately performed high- resolution computed tomography (HRCT) of the chest, and serologic evaluation for autoimmune disease (and in some cases, hypersensitivity pneumonitis). Using the information obtained from thorough non-invasive evaluation, the following questions can help guide the decision whether to proceed to SLB.

(1) What is the leading (or provisional) diagnosis and level of confidence in this diagnosis?

- If a confident clinical diagnosis can be made based on non-invasive evaluation, then SLB is not indicated.
- For patients with suspected idiopathic pulmonary fibrosis (IPF):
- 2018 ATS/ERS/JRS/ALAT guidelines recommend that patients with an HRCT definite usual interstitial pneumonia (UIP) pattern NOT undergo SLB because a confident diagnosis can be made on clinical grounds alone (>90% confidence).
- For patients with suspected IPF with probable, indeterminate, and alternative diagnosis patterns on HRCT (i.e., <90% confidence), SLB is

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generally recommended but should be considered on a case-by-case basis. Additional factors to consider during the clinical decision making in these patients are the training/experience of the radiologist, confidence in the HRCT interpretation, and individual patient characteristics. For example, patients who are older (e.g. > 60 years), do not have clinically meaningful secondary risk factors for ILD, and have a probable UIP pattern on HRCT read by an experienced thoracic radiologist with high confidence, are often considered to have sufficiently high pre- test probability of IPF to preclude the need for SLB for a confident diagnosis.2,3

- IPF guidelines also recommend, when feasible, that diagnosis of IPF and the decision to perform SLB be considered in the context of MDD due to evidence suggesting improvements in diagnostic confidence provided by MDD when experienced pulmonologists, rheumatologists, thoracic radiologists and pulmonary pathologists confer.
- Although consensus guidelines are not currently available for other fILDs, a similar approach taken for suspected IPF may be applied to other forms of fILD. For example, for patients with suspected chronic hypersensitivity pneumonitis (CHP), the identification of an exposure likely to cause CHP and a combination of HRCT features typical of CHP, may provide sufficient confidence in the diagnosis of CHP without SLB.4-6However, it is appreciated that there is significant practice variation as to which combinations of exposure history, ancillary testing for antigen sensitization (e.g. antigen-specific antibodies), HRCT features, and need for demonstration of bronchoalveolar lavage lymphocytosis are sufficient to provide a confident diagnosis of CHP. Therefore, consideration of this information in individual cases in MDD may be helpful in assigning diagnostic confidence and determining the need for SLB.
- For cases of suspected connective tissue disease-associated ILD (CTD-ILD), it is generally agreed that SLB is NOT indicated for patients with a confirmed systemic CTD diagnosis, if the radiographic pattern is consistent with the underlying disease and its pulmonary manifestations, since verification of the histopathologic pattern on SLB has not been demonstrated to alter treatment decisions. Many patients will be treated with immunosuppressive medications targeting the underlying CTD. Biopsy may be considered in a small number of these patients when the radiologic appearance or the clinical course is atypical.
- For patients with suspected autoimmune etiology of their ILD who do not meet criteria for a systemic CTD, the role of SLB is controversial and must be considered on a case-by-case basis. A framework for evaluating these patients has been proposed based on criteria that include clinical, serologic, and morphologic (HRCT and/or SLB) “domains” under the nomenclature of interstitial pneumonia with autoimmune features (IPAF).7 However, it should be recognized that IPAF criteria are currently considered a research classification tool, likely encompass a heterogenous group of patients on a spectrum between idiopathic and autoimmune etiologies, and have not been proven to predict treatment responses. In the spirit of these criteria, high confidence of an autoimmune etiology may be provided in some cases by a combination of clinical, serologic, and HRCT features without need for SLB. In other cases, especially when

HRCT features are not strongly suggestive of a pattern more typical of autoimmune disease, SLB may be helpful in determining the likelihood of an autoimmune etiology when considered in the context of clinical, serologic, and HRCT features. SLB alone is not sufficient to establish a diagnosis of autoimmune ILD.

- For patients with suspected drug-induced ILD, pneumoconiosis, or smoking- related ILD, compatible exposure history and HRCT patterns may be sufficient to make a confident diagnosis in many cases.
- For any patient with fILD who lacks a confident diagnosis, and especially for those whom a leading (provisional) diagnosis cannot be made, the following two questions may help guide the decision to recommend SLB.

(2) If a confident diagnosis cannot be made, then based on the provisional and alternative diagnoses, how likely are SLB results to alter treatment decisions?

In current practice, fILDs are generally treated with one of three basic strategies:

(1) anti-fibrotic medications currently approved for IPF, (2) immunosuppressive therapy, or (3) expectant management. In cases where SLB results are reasonably likely to shift diagnostic confidence sufficiently to select one of these three strategies (e.g. IPF vs. CHP, IPF vs. CTD-ILD, IPF vs. other idiopathic interstitial pneumonia), then SLB should be considered. In contrast, SLB may not be appropriate for cases where the treatment strategy is unlikely to be altered based on SLB results. Examples include cases where the same immune suppressing medication would be selected as the treatment choice regardless of SLB results (e.g. CHP vs CTD-ILD) or where treatment is unlikely to alter life course (e.g. end-stage disease/appropriate for hospice, need for urgent lung transplantation, or presence of another life-threating co-morbidity).

(3) If SLB is likely to alter treatment decisions, then is the patient at acceptable risk for complications of SLB?

Risk of short-term death from SLB has been estimated at 1.7% for elective procedures and 16% for non-elective procedures.1 However, risk of death varies depending on the type of procedure performed (open lung surgery has a higher risk of death than video-assisted thoracoscopic surgery (VATS)), center-level factors (surgical expertise, anesthesia expertise, and SLB volume), and patient- level factors (see below). There is also the risk of obtaining a non-diagnostic biopsy of about 10%, which can result from either inadequate sampling or non-diagnostic histopathology. Other potential complications of SLB include acute exacerbations of the underlying ILD (6.1%, highest risk in IPF), severe bleeding (0.2%), persistent air-leak (5.9%), respiratory infection (6.5%), neuropathic or chest wall pain (4.5%), and delayed wound healing (3.3%).1
While there are no absolute contraindications to SLB, the decision to perform SLB requires careful consideration of its benefits and risks on a case-by-case basis. As with any surgical procedure, determining the risks of SLB includes consideration of several patient-level factors that may confer higher than average or unacceptable risk of SLB. The following is a list of patient-level factors that should be considered when determining risks of SLB.

- Increased age (e.g. age > 74)
- Co-morbidities: multiple (e.g. Charlson score >=2) or severe/unstable (e.g. cardiac, hepatic, renal, dementia, cancer)
- Pulmonary hypertension
- FVC < 50-55%
- DLCO < 35-40%
- Hypoxemic respiratory failure (i.e. need for supplemental oxygen)
- Non-elective, hospitalized, or rapidly progressive disease
- Corticosteroid therapy (e.g. prednisone dose > =20 mg daily)
- Frailty or poor functional status
- Composite risk categorization based on age, sex, and co-morbidities8

Clinical Decision-Making and Patient Engagement

Consideration of each of the above questions in MDD or referral to a specialty center for MDD, may aid the clinician in the decision whether or not to recommend SLB to an individual patient. Once the clinician has made the decision to recommend SLB, it is important to recognize that decision thresholds are relatively arbitrary and value-based, and individual patients may value benefits and risks differently from clinicians. Therefore, patients should be engaged in an informed decision- making discussion about expected benefits of SLB (Questions 1-2) and potential risks of SLB (Question 3), weighed against the alternative decision of initiating empiric therapy or expectant management based on the provisional or leading diagnosis.

Practical Guidance to Minimize Risk and Maximize Yield from SLB

Once the decision has been made to proceed to SLB, it is important to implement strategies to reduce the risk of post-operative complications from SLB and maximize its diagnostic yield. Communication among involved practitioners, including the pulmonologist, thoracic surgeon (ideally experienced and interested in SLB for ILD), radiologist, anesthesiologist, and pathologist is vital, and institutional protocols implementing these strategies should be considered.

Minimizing Risk

SLB can typically be obtained minimally invasively via video-assisted thoracoscopic surgery (VATS) approaches. Overall, the data indicate that VATS has lower morbidity and mortality than open lung biopsy via thoracotomy (OLB), with a lower rate of pleural effusions, pneumothorax, persistent air leak, and hemothorax. VATS also typically has shorter operative times, and reduced analgesic use, pleural drainage duration, and hospital stay.9-11 In both OLB and VATS, anesthesia management should be modified to attempt to reduce the risk of ventilator-associated lung injury (which is thought to be a cause of acute exacerbations), including:

- minimizing FiO2
- Using low tidal volumes and peak airway pressures
- minimizing peri-operative fluids.

Other peri-operative considerations include the selective use of stress- dose corticosteroids for those on chronic corticosteroid therapy and use of non- narcotic adjunctive pain strategies post-operatively to improve respiratory mechanics and mobilization such as non-steroidal anti- inflammatory drugs, acetaminophen, gabapentin, and local nerve blocks. Institutional volume of SLBs has also been associated with lower post- operative mortality.12

Maximizing Yield

Sampling: Multiple biopsies are needed to assess disease distribution and ensure sufficient sampling of a heterogeneous disease. A minimum of 2 biopsies from 2 different lobes should be obtained, with avoidance of the most severely affected areas. The reason for this is that histologic patterns can be discordant between different lobes and different areas within the same lobe. Examples include coexisting UIP and fibrotic NSIP pattern from different lobes, UIP pattern and emphysema in different lobes, and focal acute lung injury superimposed on otherwise fibrosing lung disease. Sample site selection should be correlated with preoperative HRCT scan to identify areas of high yield for abnormalities and also to avoid areas that only show fibrosis and honeycomb changes (i.e. end-stage fibrosis).1,13,14 The minimum biopsy size has not been well-studied in the literature, but adequate wedge biopsies are typically at least 3 x 2 x 1 cm.

Laterality should be decided based on HRCT disease distribution. If the disease is present equally amongst the right and left lung, there is insufficient data to recommend biopsy of one side versus the other. In these cases,

some practitioners may prefer to biopsy the right lung in order to sample 3 different lung lobes. Intraprocedural palpation and manipulation of tissue should be minimized to avoid hemorrhage and atelectasis.

Pathologic Assessment: An intraoperative frozen section evaluation of the specimen may be performed, if available, to evaluate adequacy of tissue sampling at the time of biopsy. If no abnormal tissue is present or only end-stage fibrotic lung is identified, additional biopsy sampling may be recommended.

Intraoperative frozen section may also be helpful if pulmonary hemorrhage is of concern clinically. For permanent section evaluation, SLB tissues must be adequately inflated to prevent atelectasis that may hinder pathologic assessment. This can be achieved either by carefully injecting the tissue with formalin (using a small bore needle and syringe) or floating the specimen in formalin with repeated gentle shaking of the container for a minimum of an hour. The entirety of the SLB specimens should be submitted for microscopic assessment. Hematoxylin and eosin staining (H&E) is the most important stain for microscopy evaluation.

Occasionally, trichrome stain may be evaluated to further assess the fibrotic component. Special stains for microorganisms (GMS, PAS, AFB or equivalent) are only required if there is clinical or histologic concern for infection. Elastic stain may be evaluated to assess vascular changes, and iron stain may be used if there is concern for asbestos-related lung disease. Interpretation of SLB should be performed by a pathologist with interest and experience in fILD. If a pathologist has insufficient experience or interest, an expert thoracic pathologist opinion may be helpful.

Correlation with HRCT scan and clinical information are also important for pathologists to consider when interpreting SLB.

Alternative Invasive Diagnostic Procedures for fILD

Alternative invasive diagnostic procedures to SLB include bronchoalveolar lavage fluid analysis, transbronchial forceps biopsies, and transbronchial cryobiopsies. Detailed discussion of alternative diagnostic procedures and their performance for the diagnosis of fILD is beyond the scope of this statement; however, they generally provide less diagnostic information for the diagnosis of fILD compared to SLB and carry their own specific procedural risks. Emerging tests, such as genomic classifiers, may improve the diagnostic utility of these procedures in the near future.

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