



Transbronchial cryobiopsy for diffuse parenchymal lung diseases: evidence that demands a (favorable) verdict

Matthew Aboudara¹, Fabien Maldonado²

¹St. Luke's Health System, Division of Pulmonary and Critical Care, University of Missouri-Kansas City, Kansas City, MO, USA; ²Vanderbilt University Medical Center, Division of Allergy, Pulmonary and Critical Care, Nashville, TN, USA

Correspondence to: Fabien Maldonado, MD. 1301 Medical Center Drive, B-817 The Vanderbilt Clinic, Nashville, TN 37232-5735, USA.

Email: fabien.maldonado@vumc.org.

Comment on: Troy LK, Grainge C, Corte TJ, *et al.* Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020;8:171-81.

Submitted Mar 30, 2020. Accepted for publication Apr 30, 2020.

doi: [10.21037/atm-20-2995](https://doi.org/10.21037/atm-20-2995)

View this article at: <http://dx.doi.org/10.21037/atm-20-2995>

For almost two decades now, the standard approach to the diagnosis of diffuse parenchymal lung disease (DPLD) has been the multidisciplinary discussion (MDD) (1). In their seminal work, Flaherty and colleagues demonstrated that the diagnosis of DLPD cannot be made in isolation but requires the expert input of thoracic radiologists, pulmonary pathologists, and pulmonologists. Importantly, they highlighted that diagnostic confidence increases as additional information is sequentially provided to the clinical scenario [such as high resolution computed tomography (HRCT) interpretations, clinical data and surgical lung biopsy (SLB) interpretations], with nearly half of cases being ultimately influenced by the final histopathology (2). They also showed while that the diagnosis of idiopathic pulmonary fibrosis (IPF) can be made without SLB in selected cases, histopathology remained the most important contributor to the final diagnosis. This also held true for non-IPF idiopathic interstitial pneumonias, preserving SLB as a crucial piece of contributory information to the final MDD diagnosis. Subsequently, in the pivotal pirfenidone and nintedanib trials, SLB was performed in 16–30% of subjects (3,4). This parallels the literature which suggests that in patients with HRCT features indeterminate for usual interstitial pneumonia (UIP), up to 30% may have histopathological UIP/IPF (5). Indeed, current guidelines recommend SLB in patients for whom the HRCT shows probable, indeterminate, or alternative diagnosis of IPF (6,7).

While it is clear that histopathology plays a crucial role

in the diagnostic process, enthusiasm has waned, however, in recent years as data have emerged revealing that SLB in DPLD patients carries a much higher risk than previously recognized. An landmark Mayo Clinic study, albeit widely criticized, reported a 17% 30-day mortality from SLB in patients ultimately diagnosed with usual interstitial pneumonia, the histology correlate of IPF (8). This was confirmed in a recent large study, demonstrating a 1.7% in-hospital mortality rate after elective surgeries, with an alarming 16% death rate for non-elective cases (9). This methodologically sound study suggested that close to 10,000 people had died after SLB during the ten-year study period. In addition, SLB does not always provide an entirely reliable biopsy specimen and is prone to sampling error even with the advantage of larger biopsy specimens. In a large series of 389 explanted lungs in which pre-transplant SLB data were available, SLB had misclassified 12% (27/217) of cases when compared to the explanted lung (10). This should not discount histopathology as an important diagnostic element, but rather underscores the critical role that a MDD plays in incorporating all necessary radiographic, clinical, and pathology data points when developing a final consensus diagnosis.

Because of the (I) obvious need for biopsy tissue in a sizable proportion of patients and (II) the inherent risks of SLB, transbronchial cryobiopsy (TBCB) was introduced as a potentially safer and as efficacious biopsy method. TBCB is a procedure performed via either flexible or rigid bronchoscopy under general anesthesia in which a flexible

cryoprobe is advanced to pre-planned diseased locations within the lung based upon the HRCT. The cryoprobe is then frozen for 3–5 seconds (sometimes longer depending on the time taken to generate a 5 mm ice ball at the tip of the cryoprobe) and adjacent tissue is extracted *en-bloc* with the cryoprobe. This method has allowed for consistently larger and more intact samples without crush artifact than traditional transbronchial biopsy forceps (11). The overall diagnostic yield is approximately 73% with clinically significant bleeding occurring in 15% and pneumothorax in 10% (12). While these complications have been a source of concern within the interventional pulmonology and interstitial lung disease (ILD) communities, evidence-based recommendations have been published to help standardize the procedure and mitigate risk (13,14). These key measures include (I) the use of a prophylactic balloon blocker that is inflated immediately after the biopsy is taken (II) use of fluoroscopy to guide biopsies and (III) use of an endotracheal tube or rigid bronchoscopy under general anesthesia. Proper training and mentorship in the technique and careful patient selection are critical for optimal performance and safety of the procedure.

Notwithstanding this complication rate, doubts over the diagnostic utility have persisted, compared to the large biopsy samples from SLB (average specimen volume of 12 cm³) with historical diagnostic rates of 90% (15). Histopathology should, however, be considered as one of many contributing factors to the MDD process. The question, then, should not be whether samples obtained by cryobiopsy are histologically equivalent to SLB (using SLB as the reference standard), but rather whether their contribution to the MDD consensus diagnosis approaches that of SLB.

To address this question, data have until recently been mainly limited to retrospective series and methodologically uncertain studies. Lentz and colleagues, in a retrospective study analyzing the impact of cryobiopsy on final consensus MDD diagnosis, showed a confident histopathological diagnosis in 44%, but which increased to 68% in the context of a MDD, again stressing the important input from a panel of experts (16). Attempting to compare diagnostic yield between SLB and TBCB, Ravaglia and colleagues retrospectively reviewed 447 cases at their institution (150 VATS-SLB and 297 TBCB). They reported a diagnosis in 82.8% of patients with TBCB and 98.7% after VATS-SLB ($P=0.013$) (17), however the diagnosis was based entirely on histopathology and not consensus MDD.

A retrospective, but methodologically robust study

by Tomasetti and colleagues evaluated the impact of contributory data from TBCB and SLB specimens to the MDD process. Patients had HRCT atypical for UIP and two blinded pathologists and radiologists reviewed the data. Following the process described by Flaherty et al, data were added in a step-wise fashion and the confidence in consensus diagnosis at each step was assessed (clinical-radiographic data, followed by bronchoalveolar lavage information, then biopsy data, and finishing with a MDD for consensus diagnosis). Interestingly, a similar degree of final MDD consensus diagnosis was demonstrated with either TBCB or SLB (29% to 63% and 30% to 65%, respectively) (18).

A small prospective study of 21 patients recently raised doubts, however, as it reported poor diagnostic concordance between TBCB and SLB histology specimens obtained in the same patients. This study involved patients who underwent TBCB in 2 separate lobes followed by immediate video assisted thoracoscopy surgery (VATS)-SLB of the same lobes during the same anesthesia event (19). A single pathologist blinded to the sampling method and to any clinical or radiological data reviewed all samples. Histopathologic agreement between TBCB and SLB specimens occurred in only 38% of cases (8/21), with κ -concordance of 0.22. When compared to local MDD diagnoses, TBCB had a 48% agreement with final MDD consensus diagnosis compared to SLB specimens exhibiting a 62% agreement. The authors note that SLB altered the diagnosis and management plans in 52% (11/21) of patients and suggested that VATS-SLB should remain the standard of care (19). These conclusions were however criticized as over-reaching as the study had significant methodological flaws, a small sample size and did not use MDD as a comparative gold standard (20). While this study was provocative in its conclusions, it ultimately failed in providing an answer to the central question surrounding the utility of TBCB comparative to SLB in the diagnosis of ILD.

In an effort to address this issue in a sufficiently powered and methodological sound manner, Troy *et al.* conducted the Diagnostic Accuracy of Transbronchial Lung Cryobiopsy for Interstitial Lung Disease Diagnosis (COLDICE) study across nine Australian centers (21). All candidates were screened through a centralized MDD to determine biopsy candidacy that included review of physician-verified history of exposures, connective tissue disease symptoms, disease severity indices, serologies, and HRCT images. Once biopsy was determined necessary, the patient underwent a TBCB in a standardized manner that is consistent with

current guideline recommendations. Severity of bleeding was recorded, and immediate post-procedure pneumothorax was assessed with either ultrasound or fluoroscopy. During that same anesthesia event, two SLB were done in the same lobes as the TBCB by a thoracic surgeon via VATS with a double lumen endotracheal tube. Complications were assessed at 6 weeks, 3 months and 6 months.

The pathologic review was rigorous and blinded. The two sets of biopsies (TBCB and SLB) were deidentified and then randomly assigned to three pathologists who performed an individual interpretation and then a consensus agreement for a specific histologic diagnosis. The members of the MDD team were then presented data in a stepwise fashion (as previously described) with histopathology presented last. The members then recorded their confidence of diagnosis as low (51–60%), high (70–89%), or definite (90–100%).

The two primary endpoints were histologic agreement between TBCB and SLB and agreement on final consensus MDD diagnosis for matched specimens. Several secondary end points were also collected, such as interobserver agreement between the three pathologists, proportions of TBCB and SLB cases that lead to a change in diagnostic confidence, and procedural features predictive of diagnostic agreement.

The authors enrolled 65 subjects, all of whom underwent both a TBCB and SLB, yielding a total of 130 combined specimens that were analyzed by pathologists. These 130 specimens were then discussed in random order at MDD, with TBCB and SLB specimens for the same subjects presented at separate times. The patients had a mean forced vital capacity of 84% and DLCO 63% with a mean 6-minute walk test of 458 meters. None were on supplemental oxygen.

During the procedure, the median number of TBCB samples was five with a mean tissue sample size of 7.1 mm. By comparison, the SLB sizes were on average 46.5 mm in long axis.

The consensus histopathologic agreement for a specific diagnosis was 69%, κ 0.47 (0.30–0.64), indicative of a moderate agreement. The most common histologic diagnosis was usual interstitial pneumonia (UIP) followed by hypersensitivity pneumonitis (HSP).

For the MDD final diagnoses, raw agreement between TBCB and SLB was 76%, κ of 0.62 (0.47–0.78), suggesting a good agreement. A high or definite MDD diagnosis was reached in 60% (39/65) of TBCB and 74% (48/65) of SLB ($P=0.090$). A high confidence or definite TBCB

diagnosis was concordant with SLB in 95% of cases (37/39), indicating little additional contribution from SLB in this scenario.

Twenty-six TBCB specimens were categorized as unclassifiable or low confidence by MDD diagnosis. Of these, 23% (6/23) were reclassified into high or definite by SLB. Interestingly, in the remaining 77% (20/26), SLB offered no additional diagnostic confidence to the MDD.

Probably of most importance is the consistent observation that histopathology was a major contributing factor in final consensus MDD diagnosis. The addition of biopsy data to clinical-radiographic information impacted the diagnosis in 74% (48/65) TBCB specimens and 77% (50/65) SLB specimens, mainly by offering a specific histopathologic diagnosis.

Because of the design of the study, complications were difficult to attribute to any one particular procedure. However, mild-moderate bleeding complications from TBCB were seen in 22% (14/65). Two patients had an acute exacerbation of IPF and one of these patients died at 50 days post-surgery, providing a 90-day mortality of 2%.

The results from COLDICE provide much more needed data to clarify the utility of TBCB in the diagnosis of DPLD within the context of current guideline recommendations. Biopsy with a HRCT definite for UIP is not indicated, but tissue still remains a vital component of the diagnostic algorithm in many cases and TBCB appears reasonably positioned as the initial diagnostic modality. COLDICE was helpful in that it demonstrated good agreement between both histopathologic and MDD consensus diagnosis and confirmed that a definite TBCB diagnosis can be trusted. Interestingly, a biopsy (whether TBCB or SLB) was not helpful in 12% of cases, highlighting the diagnostic complexity of DPLD and the need for a panel of experts to care for these patients. Several caveats need to be considered, however, when incorporating TBCB into an ILD program. First, the procedure does carry risk and should only be performed by individuals with proper training in the technique and able to deal with significant airway hemorrhage and tension pneumothorax if these complications were to occur. The bronchoscopists in COLDICE were experienced and the ability to obtain adequate tissue with specific diagnostic features with minimal complications would not be generalizable without this type of bronchoscopy team in place. Second, replication of the diagnostic yield outside of an MDD composed of expert pulmonology pathologists, thoracic radiologists

and pulmonary ILD experts is not known and experience within the community may be different than what is seen in advanced lung disease academic medical centers. The patient selection was conservative, with no patients requiring supplemental oxygen and all with fairly minor lung function impairments. The 2% 90-day mortality is a reminder that even within this patient population, a biopsy is not without risk.

In summary, TBCB appears to be an efficacious and reasonable first line option in patients who are selected for biopsy by a multi-disciplinary team of ILD experts. With the addition of recently published guidelines, the procedural standardization and resultant safety should improve to mitigate risk while increasing diagnostic yield. Patient selection still remains important and further work is needed to determine if TBCB can be safely performed in patients with a higher risk than standard SLB patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-2995>). FM reports receiving unrestricted educational grant from ERBE. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Aboudara M, Maldonado F. Transbronchial cryobiopsy for diffuse parenchymal lung diseases: evidence that demands a (favorable) verdict. *Ann Transl Med* 2020;8(20):1324. doi: 10.21037/atm-20-2995