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REVIEW

Cryobiopsy in Interstitial Lung Disease: Is It Prime Time?

Stephanie F. Hampton[1] · Matthew Schimmel[1] · Abesh Niroula[1]

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Abstract

Purpose of Review Transbronchial cryobiopsy (TBCB) may be used as an alternative to surgical lung biopsy (SLB) for the histopathologic evaluation of interstitial lung disease (ILD) at experienced centers. The purpose of this review is to discuss recent guidelines and evidence for the use of TBCB in the diagnosis of ILD including technique, review of efficacy, safety, and future perspectives.

Recent Findings TBCB delivers reasonable diagnostic efficacy and offers meaningful contributions to multidisciplinary discussion (MDD) by increasing diagnostic confidence, providing prognostic information, and influencing management. TBCB has a favorable safety profile compared to SLB when performed at centers of expertise; however, a steep learning curve is well documented.

Summary TBCB is an acceptable alternative to SLB in the evaluation of ILD when performed with appropriate expertise. Further research on diagnostic efficacy, safety in high-risk populations, use of imaging guidance techniques, and necessary procedural training is required.

Keywords Transbronchial lung cryobiopsy · Cryobiopsy · Interstitial lung disease · Diffuse parenchymal lung disease · Idiopathic pulmonary fibrosis · Surgical lung biopsy

Introduction

Interstitial lung disease (ILD) comprises a group of disorders characterized by lung parenchymal inflammation and/or fibrosis, many with overlapping features that differ widely in prognosis and management [1]. Achieving an accurate and confident diagnosis of ILD poses a significant challenge, and, for this reason, multidisciplinary discussion (MDD) has become the gold standard of diagnosis [1–4]. While many diagnoses are made with clinical and radiologic information alone, histopathologic data may be required to inform treatment decisions, particularly in undefined fibrotic lung disease [5, 6].

✉ Abesh Niroula
abesh.niroula@emory.edu

Stephanie F. Hampton
stephanie.faye.hampton@emory.edu

Matthew Schimmel
matthew.evan.schimmel@emory.edu

[1] Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Emory University School of Medicine, Atlanta, GA, USA

Surgical lung biopsy (SLB) is the reference standard for tissue acquisition, as it delivers large peripheral samples with preservation of lung architecture and high diagnostic yield of approximately 90% [5, 7, 8]. However, SLB is associated with significant morbidity and mortality and may only be suitable for select patients [9–11]. Less-invasive procedures such as transbronchial forceps biopsy (TBB) may be adequate for centrilobular and perilymphatic diseases, but specimens are prone to crush artifacts and often insufficient for evaluation of idiopathic interstitial pneumonia [5, 12–14].

Transbronchial cryobiopsy (TBCB) is a bronchoscopic technique capable of providing larger samples (Figs. 1 and 2) with less crush artifacts than TBB and has shown promise as a less-invasive alternative to SLB [15–17]. However, concerns regarding efficacy, safety, and lack of procedural standardization have prevented its widespread adoption [5]. Although the 2018 multi-society idiopathic pulmonary fibrosis (IPF) clinical practice guidelines made no recommendation for the incorporation of TBCB in ILD diagnostic algorithms, recent studies have led to the release of new and updated guidelines with conditional recommendations for the use of TBCB as an alternative to SLB at experienced centers [5, 6, 18••, 19]. This review aims to discuss recent

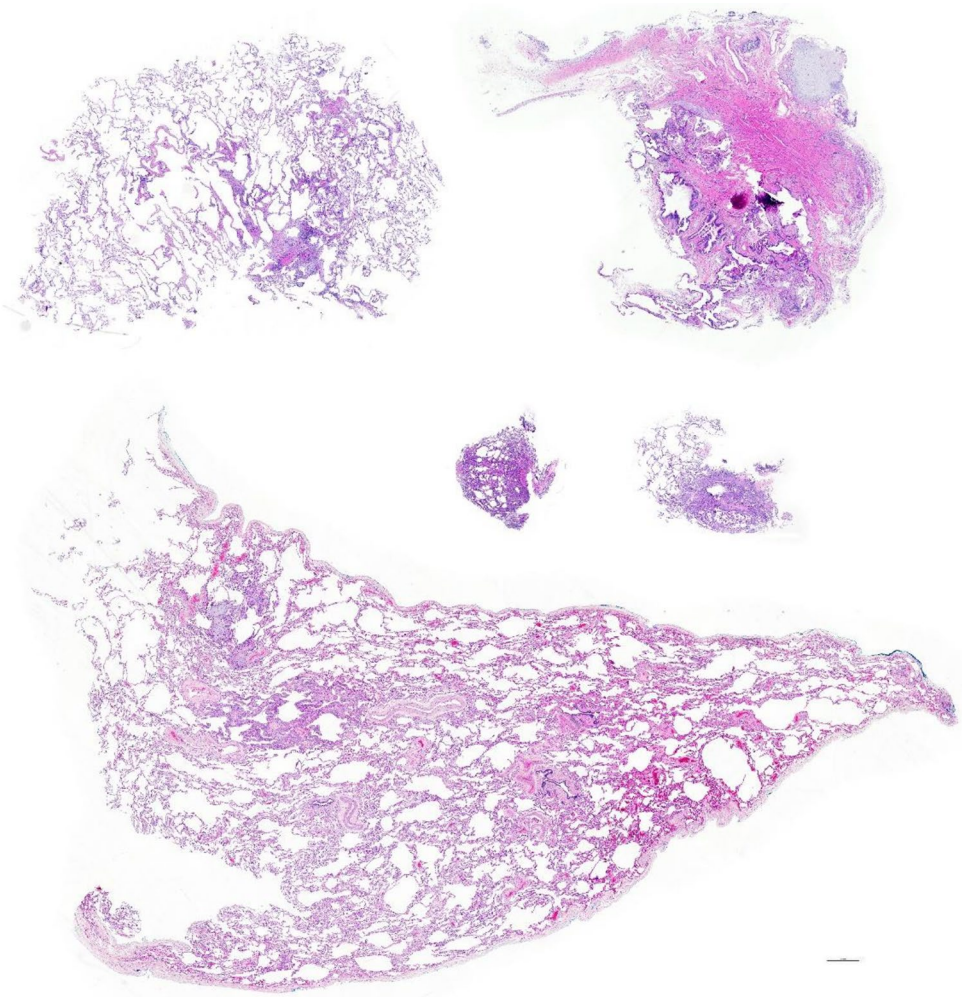

Fig. 1 Pathological Slide representation of Different lung biopsy Samples. **A**: Top two slides from Bronchoscopic cryobiopsy sample. **B**: Middle two slides from Bronchoscopic Transbronchial forceps biopsy sample. **C**: Bottom slide prepared from wedge biopsy sample

guidelines and evidence for the use of TBCB in the diagnosis of ILD including technique, review of efficacy, safety, and future perspectives.

What Is Transbronchial Cryobiopsy?

Initially described in 2009 as a novel technique for peripheral lung tissue sampling, TBCB involves advancement of a cryoprobe through the working channel of a flexible bronchoscope and subsequent freezing of the surrounding tissue using either carbon dioxide or nitrous oxide gas [15, 20, 21]. The liquefied gas is released under pressure through a small orifice at the tip of the cryoprobe and undergoes rapid expansion, causing a dramatic temperature drop and freezing of the surrounding tissue (Joule–Thomson effect). The tissue adheres to the cryoprobe tip, which is then abruptly pulled away during the rapid freezing phase and thawed in saline (freeze–thaw cycle) [15]. There are different version of cryounits and probes now available in the market (Fig. 2A).

Since its introduction, variability in procedural technique and reporting of complications has made assessment of efficacy and safety of TBCB challenging. To improve procedural standardization, several expert guidelines have been released, which recommend that the procedure be performed with a 1.9-mm cryoprobe rather than 2.4-mm probe under fluoroscopy through either an endotracheal tube or rigid bronchoscope with a prophylactic endobronchial blocker, and with 3 to 5 samples taken from at least 2 different segments or lobes 1 cm (cm) away from the pleura [19, 22–24]. Figure 3 depicts sites of different types of lung biopsy in correlation with some common interstitial lung disease HRCT (high resolution chest tomography) findings.

Efficacy of Transbronchial Cryobiopsy

Several measures have been used to evaluate the efficacy of TBCB in ILD: diagnostic yield, diagnostic agreement to SLB, and TBCB specimen contribution to MDD.

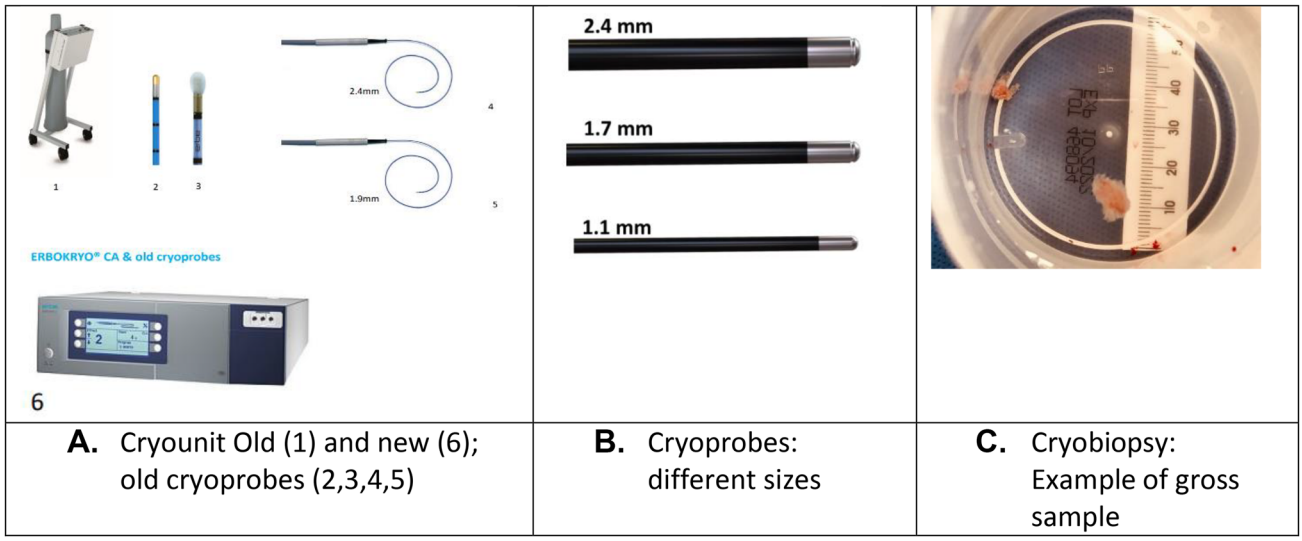

Fig. 2 Cryounits(**A**) , probe sizes (**B**) and gross sample (**C**)

Diagnostic Yield

Assessment of TBCB diagnostic yield is challenging, as histopathology is not diagnostic of ILD but requires interpretation within the context of MDD [1–4]. Diagnostic yield is expressed in the literature as either histopathologic yield or yield of final MDD diagnosis and varies significantly across studies. While smaller studies cite diagnostic yields as low as 47% [13, 25], most recent systematic reviews and meta-analyses report diagnostic yields of approximately 80%, with study sizes ranging between 12 and 699 patients [8, 26•, 27].

Multiple factors contribute to diagnostic yield variability across studies. A study by Almeida et al. best describes the association of inexperience and diagnostic yield, which is influenced by both the proceduralist and pathologic interpretation of TBCB specimens [28]. This retrospective study included the first 100 TBCBs performed at a single institution and found that histopathologic yield increased after 50 procedures from 74 to 90% ($p = 0.04$) [28]. A systematic review by Rodrigues et al. supports these findings, reporting MDD diagnostic yield of 81% at experienced centers (defined as having performed ≥ 70 procedures) compared to overall pooled diagnostic yield of 77% for all studies [8].

The number of samples and sites also impacts diagnostic yield, although the optimal number of biopsies remains unknown [19, 26•]. Ravaglia et al. performed the largest retrospective study that included 699 patients and found that diagnostic yield increased from 66 to 93% ($p < 0.0001$) when 2 or more biopsies were taken from 2 or more segments or lobes; however, diagnostic yield did not increase further when greater than 2 samples were obtained [29]. Meta-analysis by Kheir et al. reported increased diagnostic yield from 77 to 85% when three or more samples were collected, although the authors did not perform a subgroup analysis distinguishing between 2 and 3 samples or number of sites [26•]. These findings may have clinical implications for patients deemed high risk of complications, as fewer samples may be collected in these patients and, thus, may be of less utility [29]. Interestingly, in a recent study by Zayed et al. [27], higher diagnostic yield had no correlation with bronchoscopic approach, either flexible or rigid

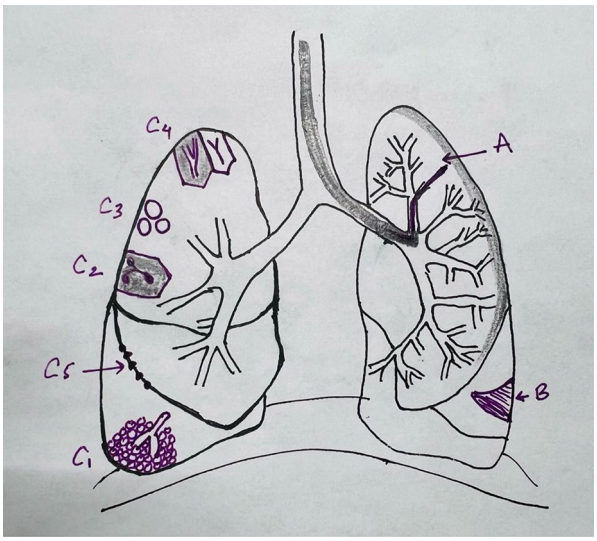

Fig. 3 Graphical representation of Right and Left lung: Left lung showing location of different types lung biopsy. Right lung with description of common ILD findings in HRCT. A: Site for bronchoscopic biopsy with forceps or cryobiopsy. B: Site for wedge biopsy. C: HRCT findings in ILD. C1: Honeycombing. C2: Ground glass opacity with centrilobular pattern. C3: Cysts. C4: Consolidation with traction bronchiectasis. C5: Perifissural nodules and thickening

bronchoscope, cryoprobe size of 1.9 mm or 2.4 mm, sample tissue size, and number of segments or lobes biopsied.

Finally, variability in diagnostic yield across studies may also be impacted by underlying disease pathology. Early concerns arose regarding the ability of TBCB to accurately identify a UIP pattern, as the diagnostic criteria for UIP are derived from SLB specimens and require the demonstration of subpleural and paraseptal fibrosis, findings frequently absent from the more centrilobular-based TBCB specimens. Identification of a UIP pattern has prognostic significance, as patients with this pattern experience more progressive disease and lower survival rates [30–34], and the inability of TBCB to accurately identify this pattern would represent a significant limitation compared to SLB. Such a limitation, however, has not been borne out in studies to date [5, 34–36•]. A post-hoc analysis of COLDICE by Cooper et al. demonstrated that, although only a minority of histopathologic UIP criteria were met in TBCB specimens, when a probable UIP pattern was applied to TBCB specimens, these features strongly predicted a UIP pattern in the paired SLB specimen [37•]. These findings are reflected in the updated 2022 multi-society IPF guidelines, which state that UIP or probable UIP pattern on TBCB in the context of MDD is comparable to those diagnosed via SLB [6].

Diagnostic Agreement Between TBCB and SLB

Although TBCB is proposed as an alternative to SLB, to date, no randomized trials have been performed comparing TBCB to SLB. However, four prospective studies have directly compared TBCB to SLB by performing the procedures sequentially in the same patient and evaluating diagnostic agreement [36•, 38, 39•, 40] (Table 1).

Romagnoli et al. was the first study to directly compare TBCB to SLB [38]. This prospective two-center study included 21 patients who underwent TBCB followed by SLB. Specimens were reviewed by one blinded pathologist and reported as a single, most likely histopathologic diagnosis; this was then compared to the MDD consensus diagnosis informed by both TBCB and SLB results. While histopathologic agreement between TBCB and SLB was only 38% (kappa coefficient [k] 0.22, 95% CI 0.18–0.62), this study has been met with significant methodological criticism for not comparing individual contributions of TBCB and SLB to MDD, exclusion of a differential diagnosis, and its statistical analysis [38, 41, 42].

Troy et al. published the COLDICE study in 2020, which was a larger prospective multicenter study of 65 patients that followed the results of Romagnoli and colleagues [39•]. In this study, 3 blinded pathologists reviewed both specimens, and two separate MDDs were held per patient, each informed by either TBCB or SLB results. Histopathologic and MDD diagnostic agreement was 70.8% (*k* 0.7, 95% CI 0.55–0.86) and 76.9% (*k* 0.62, 95% CI 0.47–0.78), respectively, and diagnostic agreement increased to 95% when a high-confidence TBCB MDD diagnosis was made. When TBCB MDD diagnoses were reported as unclassifiable or low confidence, however, only 23% were reclassified into high confidence by SLB results. This suggests SLB is of limited utility when a high-confidence MDD diagnosis informed by TBCB histopathology is made and may only be beneficial in a minority of non-informative TBCB results.

The CHILL Study, by Wahidi et al., demonstrated similar findings to the COLDICE study [39•, 40]. This small, multicenter study performed sequential TBB, TBCB, and SLB in 16 patients, which were reviewed in a single, unblinded MDD, and reported low agreement of TBB to TBCB and SLB diagnoses, and moderate histopathologic and MDD agreement between TBCB and SLB of 62.5% (*k* 0.46, 95% CI 0.23–0.68) and 68.8% (*k* 0.6, 95% CI 0.39–0.81), respectively [40].

Most recently, Fortin et al. published the CAN-ICE study, a multicenter prospective study including 20 patients who underwent TBCB and SLB [36•]. Histologic samples were reviewed by three blinded pathologists, and separate MDDs informed by either TBCB or SLB specimens were held by 3 independently blinded ILD teams—i.e., three different centers. Within-center MDD diagnostic agreement was 61.7% (*k* 0.46, 95% CI 0.29–0.63), whereas between-center agreement was significantly reduced for TBCB and

Table 1 Summary of the 4 major studies comparing TBCB and SLB in a prospective manner, using sequential procedural interventions

	N	Pathology	*Pathologic agreement	**MDD agreement	Disease prevalence	
					IPF	fHP
Romagnoli	21	1, blinded	38% (*k* 0.22)	—	**43%**	**5%**
COLDICE	65	3, blinded	70.8% (*k* 0.70)	76.9% (*k* 0.62)	**53.8%**	**27.8%**
CHILL	16	1, blinded	62.5% (*k* 0.46)	68.7% (*k* 0.60)	**19%*** **	**50%**
CAN-ICE	20	3, blinded	56.7% (*k* 0.38)	61.7% (*k* 0.46)	**25%**	**51.7**

*Raw agreement between histopathologic diagnosis attributed to TBCB and SLB specimens by pathologists.**Raw agreement between TBCB and SLB specimens for the final MDD diagnosis. ***Final MDD diagnosis of UIP via SLB

higher for SLB (k 0.29, 95% CI 0.09–0.49 and k 0.71, 95% CI 0.52–0.89, respectively). In high-confidence TBCB diagnoses, agreement only increased to 72.4%, substantially less than the COLDICE findings. Notably, agreement was higher in patients with SLB-MDD diagnosis of IPF compared to fibrotic hypersensitivity pneumonitis (fHP), 81.2% vs. 51.6% $p = 0.047$, respectively. The authors highlight that this finding is consistent with prior studies [36•, 38, 39•, 40] and may explain the reduced diagnostic performance, as the prevalence of SLB-MDD IPF was 53.8% in the COLDICE study compared to 25% in the CAN-ICE study. These findings suggest that the accuracy of TBCB may be dependent upon the underlying disease, particularly when differentiating IPF and fHP, which have overlapping pathologic features.

Contribution to MDD

As MDD is the gold standard for diagnosis in ILD, most experts favor contribution to MDD as the best measure of procedural efficacy. The contribution of TBCB specimens in MDD has been evaluated in terms of MDD diagnostic confidence and management.

Hetzel et al. was the first prospective multicenter study to evaluate the impact of TBCB in MDD diagnostic confidence [43]. TBCB reportedly increased the frequency of definite or confident diagnoses made, as compared to clinicoradiologic data alone, from 11.7 to 54%. Similarly, Troy et al. found that TBCB increased diagnostic confidence, as TBCB changed diagnoses from low to high confidence or provided an unanticipated diagnosis in 74% of TBCB samples, compared to 77% of SLB samples [39•]. This is clinically relevant as SLB is not recommended in high-confidence MDD diagnoses, demonstrating that TBCB may negate the need for SLB in cases with diagnostic uncertainty [5, 44].

Histopathologic data is often used to distinguish IPF from non-IPF in cases of diagnostic uncertainty. Such a distinction is important to guide management, as antifibrotic therapy has been shown to slow the rate of decline in patients with IPF and remains the mainstay of therapy, while non-IPF cases are frequently treated with immunosuppressive regimens [45]. In recent years, however, indications for antifibrotics in non-IPF ILD have increased, calling into question the utility of biopsy data in MDD management [46–48]. In a retrospective study by Tomassetti et al., histopathologic data, either by TBCB or SLB, changed treatment strategy in 34% of cases, with trends to prescribe antifibrotics and immunosuppressants more and recommend steroids and a "wait-and-see" approach less [49•]. This study also found that biopsy data led to diagnostic reclassification in 20% of cases, increased confidence in 33% of cases, and changes in therapeutic strategy in 33% of these cases, with worse survival in those patients reclassified as IPF. While this study supports the value of histopathology in the multidisciplinary management of ILD, it is limited by its single-center nature with antifibrotic prescribing practices that may not be reflective of real-world practice, as well as its lack of power to detect a difference between TBCB and SLB outcomes.

Safety of Transbronchial Cryobiopsy

TBCB is less invasive than SLB, with lower mortality and rates of severe complications [6–11, 18••, 26•, 27, 50]. Procedural mortality from TBCB is low, with systematic reviews and meta-analyses citing rates of 0.3–0.9% [7, 8, 26•, 27, 51–53], whereas two studies, the largest including 32,000 patients who underwent SLB, cite SLB mortality rates of 1.7–1.9% in elective cases and 16–20.2% in nonelective cases [9, 11].

Pneumothorax and bleeding are the most common complications of TBCB, with severe bleeding and acute exacerbation of ILD being rare [7, 8, 13, 25, 26•, 27, 29, 39•, 43, 50–54•, 55–61]. Rates of pneumothorax vary among studies, with some reporting an incidence as high as 39% [59, 60], while systematic reviews and meta-analyses cite rates from 5.6–10% [7, 8, 26•, 27, 51–53]. Higher rates of pneumothorax have been reported in those with more progressive fibrosis and associated with use of larger cryoprobes, number of samples, and close distance to the pleura [22, 29, 51, 62]. While overall bleeding rates are estimated at 30% [26•], most bleeding is reported as mild to moderate and readily controlled with the recommended use of a prophylactic endobronchial blocker [7, 8, 13, 26•, 27, 29, 39•, 43, 52, 54•, 55–61]. In comparison, complication rates of SLB are estimated at 10–14% and include persistent air leak, thoracic pain, infection, extended hospital stays, and acute exacerbation of ILD [8–11, 63–68].

Evidence evaluating the safety of TBCB in high-risk patients is limited, as advanced lung impairment and pulmonary hypertension are often considered relative contraindications [22]. A prospective study by Bondue et al. compared patients at high risk of complications (defined as either body mass index > 35, age > 75, forced vital capacity < 50% or diffusing capacity of carbon monoxide < 30%, pulmonary artery systolic pressure > 45, or clinically significant cardiac disease) to low-risk patients and found no significant difference in complication rates, although this study was limited by small sample size [54•]. Matta et al. performed a retrospective study in 17 critically ill patients who underwent TBCB, mostly performed at bedside without fluoroscopy, with reported pneumothorax rates of 35%, no episodes of severe bleeding, and no mortality directly attributable to TBCB [59].

While early studies report high complication rates that were largely due to lack of procedural standardization prompting development of clinical practice guidelines [19, 22–24], higher complication rates are also associated with less-experienced centers and operators. Study by DiBardino et al., describes high complication rates with the introduction of TBCB at a new institution [69]. This was a retrospective, single-center case series that included the first 25 consecutive TBCB cases performed by interventional pulmonologists and reported high complication rates, including a high incidence of pneumothorax and severe bleeding, which led to discontinuation of the cryobiopsy program at the institution [69]. A larger retrospective study of the first 100 TBCB cases was later published by Almeida et al., which reported pneumothorax rates of 24% in the first 50 procedures that decreased to 12% in the subsequent 50, although this was not statistically significant [28]. In this study, they reported that procedural proficiency occurred at the 70th procedure, indicating a learning curve associated with the introduction of TBCB to a new center.

Guidelines for Transbronchial Cryobiopsy in Interstitial Lung Disease

Currently, the European Respiratory Society (ERS), American College of Chest Physicians (CHEST), and the multisociety IPF Clinical Practice Guidelines suggest that TBCB is an acceptable alternative to SLB in patients with undefined ILD, requiring histopathologic evaluation. These recommendations are limited to experienced centers with standardized protocols, where procedural risk can be mitigated as much as possible [6, 18••, 19].

The ERS clinical practice guidelines aim to define the role of TBCB in ILD, although uncertainty on how to incorporate TBCB into clinical practice remains [18••]. First, evidence is largely based on uncontrolled case series with variability in diagnostic accuracy, with more experienced centers reporting better success with TBCB than less-specialized centers, limiting generalizability [18••, 25, 28, 29]. Second, no randomized clinical control trials have directly compared TBCB to SLB, making current available data prone to selection bias. Third, the guidelines lack clarity on which patients should be selected for TBCB. The ERS guidelines suggest TBCB can be performed in patients deemed unsuitable surgical candidates, although other guidelines recommend using similar criteria used for SLB [6, 22]. There is a paucity of data in high-risk populations [6, 22]. Finally, the guidelines emphasize that the use of TBCB should be limited to centers with experience in performing and interpreting TBCB, however, do not define "experienced center" or the necessary training required.

Future Perspectives

Reduced diagnostic yield and high complication rates of pneumothorax and bleeding are the main limitations of TBCB. Appropriate biopsy site selection is vital to maximize efficacy and minimize risk, as samples obtained < 1 cm from the pleura are at greater risk of pneumothorax, more centrally obtained samples are at greater risk of severe bleeding, and more densely fibrotic tissues are more likely to be noninformative [22, 29]. Adding imaging guidance techniques may improve diagnostic accuracy and complication rates.

Radial endobronchial ultrasound (REBUS) and electromagnetic navigational bronchoscopy (EMNB) are two commonly used technologies for imaging guidance, particularly for the management of peripheral parenchymal lesions. The data regarding the use of these techniques to aid TBCB is limited. REBUS-guided TBCB uses a radial ultrasound, passed through the working channel of a bronchoscope, to obtain a circumferential view of surrounding structures (i.e., vasculature and pleura) to assist in biopsy site selection. While a randomized trial by Pannu et al. comparing REBUS-guided TBCB to conventional fluoroscopy-guided TBCB demonstrated technical feasibility, REBUS was not found to reduce bleeding complications, although this study was limited by small sample size [70]. EMNB utilizes virtual airway reconstruction and electromagnetic navigation to guide the bronchoscopist to the desired location [71]. One study demonstrated that using EMNB for imaging guidance in TBCB is technically feasible, although data regarding safety and efficacy is lacking [71]. Similarly, robotic bronchoscopy (RB) may also be used as an imaging guidance technique for TBCB in the future [72].

Confocal laser endomicroscopy (CLE) and endobronchial optical coherence tomography (EB-OCT) are novel imaging techniques that generate high-resolution images of tissues with resolutions of 3.5 microns and 10–15 microns, respectively [73]. CLE, available as a probe that can be used through the working channel of a bronchoscope, provides real-time images by emitting laser light to visualize elastin fibers. Early studies have demonstrated that CLE is technically feasible, able to differentiate areas of normal lung from fibrotic lung, identify the visceral pleura, and potentially even differentiate between different ILD patterns [74, 75]. EB-OCT uses near-infrared light to visualize tissues to generate two- and three-dimensional images [73]. Although no studies have investigated the use of EB-OCT as an imaging guidance technique for TBCB, Nandy et al. demonstrated that EB-OCT alone may be able to distinguish UIP from non-UIP patterns, citing sensitivity and specificity of 100% for histopathologic UIP and clinical diagnosis of IPF with high agreement to SLB specimens [76]. While there is

currently no established role for EB-OCT in clinical practice, it may be a suitable adjunct to TBCB in the future as a guide for biopsy site selection.

Genomic classifiers (GC), a technique that detects a molecular signature for UIP pattern using machine learning and whole-transcriptome RNA sequencing from genomic data, have also garnered interest as a method to improve diagnostic accuracy with less-invasive techniques. Despite estimated sensitivity of 68% and specificity of 92% in identifying UIP pattern in patients with undiagnosed ILD undergoing TBB, the role of GC with TBCB remains undefined [6].

Conclusions

In summary, TBCB offers acceptable diagnostic efficacy and a favorable safety profile compared to surgical lung biopsy when performed with appropriate expertise. Future studies focused on comparing TBCB to SLB, the safety of TBCB in high-risk patients, and the use of advanced imaging to guide the site of biopsy are needed for further guidance. In addition, the implementation and development of educational programs including procedural training are required to improve its safety profile.

Acknowledgements Image courtesy: Image 1. Pathology slides: Frank Schneider MD. Image 2C. Cyobiopsy gross sample picture: Keriann VanNostrand MD. Image 3. ERBE cryoprobes and unit.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest No conflicts of interest or disclosures.

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- •• Of major importance

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