CHEST

Transbronchial Cryobiopsy for the Diagnosis of Interstitial Lung Diseases

CHEST Guideline and Expert Panel Report

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PODCAST

BACKGROUND: Transbronchial cryobiopsy (TBC) is increasingly recognized as a potential alternative to surgical lung biopsy (SLB) for the diagnosis of interstitial lung disease (ILD). The goal of this analysis was to examine the literature on TBC as it relates to diagnostic utility and safety to provide evidence-based and expert guidance to clinicians.

METHODS: Approved panelists developed key questions regarding the diagnostic utility and safety of TBC for the evaluation of ILD using the PICO (Population, Intervention, Comparator, Outcome) format. MEDLINE (via PubMed) and the Cochrane Library were systematically searched for relevant literature, which was supplemented by manual searches. References were screened for inclusion, and vetted evaluation tools were used to assess the quality of included studies, to extract data, and to grade the level of evidence supporting each recommendation or statement. Graded recommendations and ungraded consensus-based statements were drafted and voted on using a modified Delphi technique to achieve consensus.

RESULTS: The systematic review and critical analysis of the literature based on four PICO questions resulted in six statements: two evidence-based graded recommendations and four ungraded consensus-based statements.

CONCLUSIONS: Evidence of the utility and safety of TBC for the diagnosis of ILD is limited but suggests TBC is safer than SLB, and its contribution to the diagnosis obtained via multidisciplinary discussion is comparable to that of SLB, although the histological diagnostic yield appears higher with SLB (approximately 80% for TBC vs 95% for SLB). Additional research is needed to enhance knowledge regarding utility and safety of TBC, its role in the diagnostic algorithm of ILD, and the impact of technical aspects of the procedure on diagnostic yield and safety.

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KEY WORDS: evidence-based medicine; guidelines; interstitial lung disease; transbronchial cryobiopsy

ABBREVIATIONS: CHEST = American College of Chest Physicians; COI = conflict of interest; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MDD = multidisciplinary discussion; PICO = Population, Intervention, Comparator, Outcome; SLB = surgical lung biopsy; TBC = transbronchial cryobiopsy; UIP = usual interstitial pneumonia

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Summary of Recommendations

1. In patients with suspected interstitial lung disease (ILD), we suggest that transbronchial cryobiopsy (TBC) can be used to provide histopathologic findings for multidisciplinary discussion diagnosis (Weak Recommendation, Very Low-Quality Evidence).

Remarks: The choice between TBC and surgical lung biopsy (SLB) should be based on local availability and expertise, benefit-risk assessments, and patient preference following informed consent. In some instances, a nondiagnostic TBC may be followed by SLB or repeat TBC. In other cases, an SLB may be preferred. To date, the published data on safety and diagnostic yield for TBC have largely been confined to a relatively small, but increasing, number of specialized centers with established experience, which limits their external validity.

2. In patients with suspected ILD undergoing TBC, we suggest biopsy of at least two different sites (either different segments in the same lobe or different lobes) (Weak Recommendation, Low-Quality Evidence).

Remarks: TBC of two sites is associated with a substantially higher risk of pneumothorax compared with TBC of one site (24.6% vs 15.2%). The risk of increased pneumothorax must be weighed against the benefit of improved diagnostic yield, particularly in patients with advanced structural damage in the lung parenchyma.

3. In patients with suspected ILD undergoing TBC, we suggest biopsy with the tip of the cryoprobe located 1 cm from the pleura (Ungraded Consensus-Based Statement).

Remarks: This recommendation is based on histological considerations and safety. In cases of suspected IPF, the histological pattern is typically predominant in the subpleural areas. The distance from the pleura for biopsies was chosen to balance histological yield with the risks of pneumothorax and bleeding.

4. In patients with suspected ILD undergoing TBC, we suggest the use of fluoroscopy (Ungraded Consensus-Based Statement).

Remarks: Distance from the cryoprobe tip to the pleura can be inferred from the resistance felt when it reaches the pleura and from the distance measured on fluoroscopy when the beam is perpendicular to the axis of the cryoprobe. The routine use of fluoroscopy is suggested, and sampling of segments which allow for a more perpendicular beam path should be favored.

5. In patients with suspected ILD undergoing TBC, we suggest that TBC be performed with a bronchial blocker either through an endotracheal tube or rigid bronchoscope (Ungraded Consensus-Based Statement).

Remarks: In the case of endobronchial bleeding, prophylactic placement of a bronchial blocker allows for immediate tamponade without further positioning maneuver. While we acknowledge that TBC via rigid bronchoscopy without prophylactic balloon placement may be considered when performed at expert centers, the systematic use of a bronchial blocker is suggested.

6. In patients with suspected ILD undergoing TBC, we suggest the use of a small cryoprobe (1.9 mm) rather than a larger cryoprobe (2.4 mm) (Ungraded Consensus-Based Statement).

Remarks: The smaller diameter cryoprobe is easier to maneuver in the airway and facilitates tactile feedback of when the cryoprobe reaches the pleura, which may reduce the risk of bleeding and pneumothorax.

Background

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal lung diseases characterized by varying histopathologic patterns of inflammation and fibrosis.[1] These distinct histopathologic patterns are associated with a variety of clinical contexts with specific clinical implications regarding course of disease, management strategies, and prognosis.[2] The most commonly encountered pattern,

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usual interstitial pneumonia (UIP), is the defining histological finding in idiopathic pulmonary fibrosis (IPF), but is also seen in other clinical contexts, including in some patients with connective tissue disease-associated ILD or chronic hypersensitivity pneumonitis, with distinct prognostic implications. An UIP pattern, whether in IPF, hypersensitivity pneumonitis, or rheumatoid lung disease, is often associated with a poor outcome.[3-5]

Interstitial lung diseases present with diffuse parenchymal opacities on thoracic imaging. High-resolution CT scanning in patients with interstitial pneumonias demonstrates various patterns of parenchymal abnormalities, including characteristic combinations of ground-glass opacities, reticular opacities, and sometimes honeycombing. Prior studies correlating radiologic and histopathologic features have provided data that allow recognition of some histopathologic patterns based on imaging features (types of opacities and distribution) depicted on high-resolution CT scanning. For example, basal and subpleural predominant distribution of reticular opacities with traction bronchiectasis and honeycombing without other features to suggest an alternative diagnosis, allows a confident diagnosis of UIP without histopathologic confirmation.[6,7]

In many ILD patients, the etiology of disease is uncertain, and a specific diagnosis cannot be made from typical imaging features, resulting in diagnostic and management uncertainty. For such patients, the current gold standard for establishing the underlying histopathologic pattern is a surgical lung biopsy (SLB). However, there is significant mortality and morbidity associated with SLB, particularly for patients who may have UIP, are older than 65 years, have significant lung impairment, or are experiencing an acute exacerbation of ILD.[8,9] The largest retrospective study published to date, comprising data from 2000 to 2011 in the United States, reported an inpatient mortality rate after SLB for ILD of 1.7% for elective procedures and 16% for nonelective procedures.[8] The same study estimated that approximately 12,000 such SLBs were performed annually during the study period.

As a general rule, conventional transbronchial forceps biopsies have not been considered sufficient in this context except for specific case scenarios.[10] While histopathologic features of UIP may be identified on transbronchial forceps biopsy specimens in hindsight and appear specific, the sensitivity of conventional forceps biopsies for UIP seems relatively low, around 30%.[11,12] Conversely, transbronchial forceps biopsies are very useful in some situations, which should not generally lead to consideration of surgical lung biopsy, such as in granulomatous diseases and cryptogenic organizing pneumonia, for instance.[13] In some selected cases, however, SLB is still considered.[6,7] In recent years, transbronchial cryobiopsy (TBC) has been explored as an alternative to SLB. The proposed advantage of TBC is that it might provide clinically useful histopathologic findings (as biopsies are larger than standard bronchoscopic forceps biopsies and without crush artifact which often hinders pattern recognition) while being less invasive with lower risks of morbidity and mortality compared with SLB. To be an alternative to SLB, ideally TBC should provide a comparable diagnostic yield.

As TBC is increasingly adopted as a potential alternative to SLB for the diagnosis of ILD, concerns have been raised over the safety and utility of the procedure.[14-17] While expert recommendations[18] have been proposed before, methodologically robust guidance is needed to provide and update on current knowledge of the utility and safety of the procedure, its potential role in the diagnostic algorithm of ILD, and technical aspects of the procedure demonstrated to affect the diagnostic yield and safety of the procedure. The expert panel acknowledges that the following recommendations are largely based on weak evidence, should not be regarded as binding, and that individual clinicians should feel free to approach this issue in the context of the particular circumstances of their patient.

Methods

Expert Panel Composition

The co-chairs of the panel (F. M. and L. B. Y.) were reviewed for potential conflicts of interest (COIs) and approved by CHEST's Professional Standards Committee. Additional panelists were nominated by the co-chairs based on their expertise relative to potential guideline questions. The panel consisted of the guideline co-chairs, nine panelists (S. K. D., T. V. C., A. U. W., J. H. R., M. L., V. P., J. H., F. H., and O. B. R.), a methodologist (L. B. F.), and an additional panelist (M. M. W.) serving as a liaison to CHEST's Guidelines Oversight Committee. Inclusion of a patient representative was initially considered but due to the relative paucity of data available, the expected low-quality evidence, and tentative nature of recommendations, the chair and co-chair did not feel that it was necessary at this time.

Conflicts of Interest

All panel nominees were reviewed for potential COIs by the Professional Standards Committee. Nominees who were found to

have no substantial COIs were approved, whereas nominees with potential intellectual and financial COIs that were manageable were "approved with management." Panelists approved with management were prohibited from voting on recommendations in which they had substantial COIs. A grid used to track COIs was created for each key clinical question and used during voting to ensure management terms were observed (e-Table 1).

Key Question Development and Systematic Literature Searches

The expert panel drafted a total of four key clinical questions using the Population, Intervention, Comparator, Outcome (PICO) format (Table 1). With the help of the methodologist, the panel reviewed the PICO questions to identify and finalize search terms, inclusion and exclusion criteria, and databases to be searched.

The methodologist performed a systematic search of the literature for all PICO questions in November 2017 using MEDLINE (via PubMed) and the Cochrane Library. A combination of the National Library of Medicine's medical subject headings and other key words specific to the PICO elements of the key questions were used to identify studies. MEDLINE (via PubMed) search strategies are available (e-Appendix 1). Reference lists of retrieved studies were also reviewed, and additional studies were manually added to the search results. Searches were limited to English language results but were not limited by study design or publication date; however, the inclusion criteria limited study designs to systematic reviews, randomized controlled trials, and prospective and retrospective cohort studies. Case reports and case series were excluded. Study selection is detailed in e-Figures 1a and 1b (PRISMA diagrams).

Study Selection and Data Extraction

Results from the completed literature searches were reviewed for relevance over two rounds of study selection. Panelists screened the identified studies using predefined inclusion and exclusion criteria based on the PICO components of the key questions. During the first round, panelists reviewed the titles and abstracts of identified studies. References deemed potentially relevant then underwent a second round of full-text screening, during which a final inclusion decision was made. For both rounds of screening, inclusion decisions were made independently and in parallel by two panelists and then compared. Disagreements were resolved through discussion by the original pair of panelists to reach consensus.

Structured data tables were used to extract relevant data from all studies included after the second round of screening. Working in pairs, one panelist independently performed data extraction, and the other panelist independently reviewed the extracted data. Discrepancies were resolved through discussion by the original pair of panelists. Completed evidence tables for each PICO question are available (e-Table 2).

Risk of Bias Assessment

The methodologist assessed the risk of bias in all included studies using the following assessment tools, as appropriate, based on study design: Cochrane Risk of Bias tool for randomized controlled trials, the Cochrane Bias Methods Group Tool to Assess Risk of Bias in Cohort Studies, and the Documentation and Appraisal Review Tool for systematic reviews.[19-21]

Meta-analysis

After completion of the quality assessment and data extraction, the computer program OpenMeta[analyst][22] was used to run meta-analyses when data were homogenous and poolable. A random-effects model and the method of DerSimonian and Laird were used to pool the individual estimates. Risk ratios were used to report the results for dichotomous outcomes and mean difference for continuous outcomes with accompanying 95% CIs. Statistical heterogeneity was assessed using the Higgins I^2 value and the χ^2 test. A Higgins' I^2 value $\geq$ 50% and P values $<$ .05 were considered to represent significant heterogeneity.

Assessing the Overall Quality of the Body of Evidence

The overall certainty (quality) of the evidence was assessed for each outcome of interest using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[23] Evidence profiles were created using the GRADEPro Guideline Development Tool, which categorized the overall quality of the evidence for each outcome as either high, moderate, low, or very low. Each quality rating represents the confidence in the estimated effects for an outcome (Table 2).

Recommendation Drafting

The panel drafted recommendations based on the evidence that addressed the key clinical questions. Recommendations were graded using the CHEST grading system based on the GRADE approach (Table 3).[24] In instances in which there was insufficient evidence, but guidance was still warranted, a weak suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade.[25]

Consensus Development

All drafted recommendations and suggestions were presented to the panel in an anonymous online voting survey to achieve consensus via a modified Delphi technique. Panelists were requested to indicate their level of agreement with each statement using a five-point Likert scale derived from the GRADE grid.[26] Additionally, panelists had the option to provide open-ended feedback on each statement. Conflict of interest grids were included with the voting survey, and panelists with COIs related to individual recommendations were not permitted to vote on those statements in accordance with their management terms. Per CHEST policy, each statement required a 75% voting participation rate and at least 80% consensus for approval. Any recommendation or suggestion that did not meet these criteria was revised by the panel based on the feedback provided, and a new voting survey that incorporated suggested changes was disseminated and completed.

Peer Review Process

Reviewers from the Guidelines Oversight Committee, the CHEST Board of Regents, and the *CHEST* journal reviewed the methods used and content of the manuscript for consistency, accuracy, and completeness. The manuscript was revised according to feedback from the reviewers.

Results

Diagnostic Yield

1. In patients with suspected interstitial lung disease (ILD), we suggest that transbronchial cryobiopsy (TBC) can be used to provide histopathologic findings for multidisciplinary discussion diagnosis (Weak Recommendation, Very Low-Quality Evidence).

Remarks: The choice between TBC and surgical lung biopsy (SLB) should be based on local availability and expertise, benefit-risk assessments, and patient

preference following informed consent. In some instances, a nondiagnostic TBC may be followed by SLB or repeat TBC. In other cases, an SLB may be preferred. To date, the published data on safety and diagnostic yield for TBC have largely been confined to a relatively small, but increasing, number of specialized centers with established experience, which limits their external validity.

Four observational studies comparing the diagnostic yield of TBC and SLB met inclusion criteria, including two prospective studies[17,27] and two retrospective studies.[28,29] A small prospective cohort study (n = 21) compared the histological diagnostic yield of TBCs and SLBs performed sequentially in the same patients.[17] TBC was diagnostic in 17/21 (81%) cases and SLB was diagnostic in 21/21 (100%) of cases. Poor concordance between TBC and SLB was reported (kappa = 0.22). The concordance of TBC and SLB with multidisciplinary discussion (MDD) diagnoses was fair (kappa = 0.31 [95% CI, 0.06-0.56]) and moderate (kappa = 0.51 [95% CI, 0.27-0.75]), respectively. These analyses included four TBCs which were nondiagnostic, and the study has been criticized for other limitations.[30] Another prospective multicenter cohort study (n = 65) also compared histological diagnostic yields of TBCs and SLBs performed sequentially in the same patients.[27] Histopathologic agreement was 70.8% with good concordance (kappa = 0.7) and for TBCs with high or definite diagnostic confidence at MDD (39/65, 60% of cases), the concordance with SLB was 94.9%. In this study, high confidence or definite final MDD diagnoses were reached in 39 (60%) of 65 TBCs compared with 48 (74%) of 65 SLBs (P = .090).

Two retrospective studies from the same institution and including overlapping patient populations also analyzed diagnostic yield but assessed different diagnostic outcomes.[28,29] In the first study, assessing diagnostic confidence in the MDD diagnosis of IPF, 117 patients were evaluated; 58 underwent TBC and 59 underwent SLB.[29] Histopathologic diagnoses were achieved in 91% (53/58) of the TBC cohort and in 98% (58/59) of the SLB cohort with a higher confidence of diagnosis of UIP in the SLB cohort (52% [21/40] vs 85% [35/41]; P = .0015). Significant increases in diagnostic confidence upon MDD were reported after adding histological information from either TBC (29 to 63%; P = .0003) or SLB (30 to 65%; P = .0016) (e-Table 3a).

The second study, with a much larger cohort, assessed the comparative histopathologic diagnostic yield and safety of TBC and SLB among 447 patients with ILD.[28] In this analysis, TBC was diagnostic in 246/297 (82.8%) compared with SLB, which was diagnostic in 148/150 (98.7%). This represents a significantly different histopathologic diagnostic rate in favor of SLB (P = .013).

Two meta-analyses compared the diagnostic yields of TBC and SLB.[31,32] Sharp et al[31] found a histological diagnostic yield of 84.4% (95% CI, 76-91%) for TBC compared with a 91.1% yield for SLB (95% CI, 87-93%). Iftikhar et al[32] report yields for TBC and SLB of 83.7% (95% CI, 77-89%) and 92.7% (95% CI, 88-96%), respectively. The lesser yield of TBC in this analysis is hypothesized to be related to sampling error, rather than to a lesser reliability of the biopsy histological interpretation.

Four additional observational studies (n = 19-55 patients) retrieved by our search parameters evaluated the yield of TBC in achieving a diagnosis.[33-36] Together, with the Ravaglia et al[28] and Romagnoli et al[17] studies considered above, these six studies included 457 patients (range, 19-297) undergoing TBC for ILD. These studies reported a diagnostic yield between 72% and 87% with a median of 79% (e-Table 3b). Based on our analysis of these studies, the weighted pooled estimate of diagnostic yield was 82.5% (95% CI, 79-86%; I^2 = 0%) (e-Fig 2). Diagnostic yield outcome data from these studies were assessed to be low-quality evidence.

Four additional observational studies that were not retrieved by our search criteria due to lack of SLB comparator or were excluded due to inclusion of patient populations that overlap with those of studies included in our analysis include an additional 651 patients (n = 40-402) undergoing TBC for ILD.[37-40] Histopathologic diagnostic yields in these studies range from 73.4% to 87.8%. Similarly, additional systematic reviews of the histopathologic diagnostic yield of TBCs have also been published recently, albeit with considerable overlap of study populations with those of the studies included in this analysis.[28,41,42] These reviews report pooled diagnostic yields for TBC between 81% and 85.9%.

Evidence of the comparative diagnostic yield and safety of TBC and SLB provided by the observational studies included in this analysis is of low to very low quality. These data suggest the histopathologic diagnostic yield of TBC is in the range of 80% or greater, consistently below that of SLB as quoted in the studies above (91.1%-98.7%) and from a meta-analysis which showed a yield from SLB approaching 95% (e-Table 3c).[43]

TABLE 1] PICO Questions

Study Characteristic	Inclusion Criteria	Exclusion Criteria
KQ 1: Comparative Diagnostic Yield of Transbronchial Cryobiopsy and Surgical Lung Biopsy		
Population	Patients with suspected interstitial pneumonia for which a surgical lung biopsy is needed	Individuals not eligible for surgical lung biopsy
Interventions	Transbronchial cryobiopsy	None
Comparators	Surgical lung biopsy	None
Outcomes	Diagnostic yield of the procedure, histological diagnosis, multidisciplinary discussion diagnosis	None
Study design	Systematic review, RCT, prospective and retrospective cohort studies	Case series/reports
KQ 2: Comparative Safety of Transbronchial Cryobiopsy and Surgical Lung Biopsy		
Population	Patients with suspected interstitial pneumonia for which a surgical lung biopsy is needed	Individuals not eligible for surgical lung biopsy
Interventions	Transbronchial cryobiopsy	None
Comparators	Surgical lung biopsy	None
Outcomes	Pneumothorax, bleeding, hospitalization, exacerbation, mortality	None
Study design	Systematic review, RCT, prospective and retrospective cohort studies	Case series/reports
KQ 3: Comparative Diagnostic Yield of Transbronchial Cryobiopsy Procedural Characteristics		
Population	Patients with suspected interstitial pneumonia undergoing transbronchial lung cryobiopsy	None
Interventions	Transbronchial cryobiopsy: a) of one lobe; b) of one segment; c) with a 1.9 mm probe; d) with a freeze time of $\leq$ 5 seconds; e) of a distance $\leq$ 1 cm from the pleura; f) using an endobronchial blocker; g) using fluoroscopy	None
Comparators	Transbronchial cryobiopsy: a) of more than one lobe; b) of more than one segment; c) with a 2.4 mm probe; d) with a freeze time $>$ 5 seconds; e) of a distance $>$1 cm from the pleura; f) without using an endobronchial blocker; g) without using fluoroscopy	None
Outcomes	Diagnostic yield of the procedure, histological diagnosis, multidisciplinary discussion diagnosis	None
Study design	Systematic review, RCT, prospective and retrospective cohort studies	Case series/reports
KQ 4: Comparative Safety of Transbronchial Cryobiopsy Procedural Characteristics		
Population	Patients with suspected interstitial pneumonia undergoing transbronchial lung cryobiopsy	None
Interventions	Transbronchial cryobiopsy: a) of one lobe; b) of one segment; c) with a 1.9 mm probe; d) with a freeze time of $\leq$ 5 seconds; e) of a distance $\leq$ 1 cm from the pleura; f) using an endobronchial blocker; g) using fluoroscopy	None
Comparators	Transbronchial cryobiopsy: a) of more than one lobe; b) of more than one segment; c) with a 2.4 mm probe; d) with a freeze time $>$ 5 seconds; e) of a distance $>$1 cm from the pleura; f) without using an endobronchial blocker; g) without using fluoroscopy	None
Outcomes	Pneumothorax, bleeding, hospitalization, exacerbation, mortality	None
Study design	Systematic review, RCT, prospective and retrospective cohort studies	Case series/reports

KQ = Key Question; PICO = Population, Intervention, Comparator, Outcome; RCT = randomized controlled trial.

TABLE 2] Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Wording of definitions from Balshem et al.[23]

Since the diagnosis of ILD is not based solely on histology but following MDD, the diagnostic yield of MDD in the above studies was also considered. In those studies that assessed the MDD diagnostic yield of TBC, it was found in all to be either similar to[33,35] or greater than[29,39,40] the histological diagnostic yield alone. Additionally, Tomassetti et al[29] reported that diagnostic confidence upon MDD with the addition of histological information from TBC was similar to that of SLB (63% vs 65%, respectively) for IPF. In one meta-analysis, the pooled estimate of MDD diagnostic yield for TBC was below the pooled estimate of histopathologic diagnostic yield of an isolated observation (79% [95% CI, 65-93%] vs 83% [95% CI, 73-94%], respectively).[42]

Safety

Two observational studies comparing the safety (mortality and morbidity) of TBC and SLB met inclusion criteria, one retrospective study[28] and one prospective study.[17] Ravaglia et al[28] retrospectively compared the safety of TBC (n = 297) and SLB (n = 150) procedures performed at a single medical center (e-Table 4a). The mortality rate due to adverse events after the biopsy procedure was lower in the TBC cohort than in the SLB cohort (1/297 [0.3%] vs 4/150 [2.7%]; $P = .045$), with a relative risk of 0.13 (95% CI, 0.01-1.12). Severe bleeding (defined as causing hemodynamic or respiratory instability, requiring tamponade or other surgical interventions, transfusions, or admission to the ICU) was the same in both biopsy cohorts (0/297 [0 %] vs 0/150 [0%]). The rate of acute exacerbation of the underlying ILD was lower in the TBC cohort than in the SLB cohort (1/297 [0.3%] vs 5/150 [3.3%]) with a relative risk of 0.101 (95% CI, 0.012-0.857). The mean time of hospitalization was lower in the TBC cohort than in the SLB cohort (2.6 days vs 6.1 days; $P < .0001$). Safety outcome data from this study were assessed to be very low-quality evidence.

In addition to these comparative studies, the systematic literature searches identified five observational studies that reported on the safety of TBC.[33,35,44-46] Four of these observational studies (n = 32-74) evaluated the mortality rate following TBC.[33,35,45] Together with the comparative Ravaglia et al[28] study, these five studies included 532 patients undergoing TBC and report mortality rates between 0% and 4.1% with a median of 0.3% (e-Table 4b). The weighted pooled estimate of mortality between 30 and 90 days after TBC was 0.5% (95% CI, 0.1%-1.1%; $I^2 = 0\%$) (e-Fig 3a). Evidence of mortality rate from these studies was assessed to be very low quality.

Seven observational studies including 628 patients (n = 21-297) evaluated the rate of pneumothorax following TBC.[17,28,33,35,44-46] The pneumothorax rate ranged from 1.4% to 20.2% with a median of 9.5% (e-Table 4b). The weighted pooled estimate of pneumothorax rate following cryobiopsy was 9.8% (95% CI, 3.4-16.3%; $I^2 = 89.9\%$) (e-Fig 3b). Evidence of rate of pneumothorax from these studies was assessed to be very low quality.

Six observational studies including 607 patients (n = 32-297) evaluated the rate of severe bleeding (defined as causing hemodynamic or respiratory instability, requiring tamponade or other surgical interventions, transfusions, or admission to the ICU) following TBC.[28,33,35,44-46] The rate of severe bleeding ranged from 0% to 6.3% with a median of 1.1% (e-Table 4b). The weighted pooled estimate of severe bleeding following TBC was 0.3% (95% CI, 0.1-0.7%; $I^2 = 0\%$) (e-Fig 3c). Five observational studies including 310 patients (n = 32-75) evaluated the rate of moderate bleeding (defined as bleeding controlled by endobronchial blocker or cold saline) following TBC.[33,35,44-46] The rate of moderate bleeding ranged from 1.8% to 47%. The weighted pooled estimate of rate of moderate bleeding was 8.7% (95% CI, 2.2-15.2%; $I^2 = 86.7\%$) (e-Fig 3d).

TABLE 3] CHEST Grading System

Grade of Recommendation	Benefit Vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are very confident that the true effect lies close to that of the estimate of the effect	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Strong recommendation, very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, high-quality evidence	Benefits closely balanced with risks and burden	We are very confident that the true effect lies close to that of the estimate of the effect	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect
Weak (conditional) recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak (conditional) recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, very-low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Ungraded Consensus-based Suggestions			
Ungraded Consensus-Based Statement	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Evidence of bleeding rates from these studies was assessed to be very low quality. Furthermore, quantitative and qualitative estimates of bleeding complications are limited by the use of various severity scales across publications and inherent rater subjectivity.

While the evidence from these observational studies is of low to very low quality, the available data suggest an appreciably lower rate of mortality and acute exacerbation in favor of TBC compared WITH SLB.

Sampling Site

2. In patients with suspected ILD undergoing TBC, we suggest biopsy of at least two different sites (either different segments in the same lobe or different lobes) (Weak Recommendation, Low-Quality Evidence).

Remarks: TBC of two sites is associated with a substantially higher risk of pneumothorax compared with TBC of one site (24.6% vs 15.2%). The risk of increased pneumothorax must be weighed against the benefit of improved diagnostic yield, particularly in patients with advanced structural damage in the lung parenchyma.

The issue of histological heterogeneity in ILD was addressed by prior research on SLB. Several studies have demonstrated that interlobar histological variability was frequent in subjects with UIP when SLBs were performed in different lobes or on analysis of explant specimens from patients with UIP.[47,48] Usual interstitial pneumonia and nonspecific interstitial pneumonia were detected in different lobes of the same lung in up to 26% of cases. It is accordingly reasonable to infer from the surgical literature that TBCs obtained from different sites may mitigate the problem of sampling error. The need to biopsy different locations in the lung may be more relevant for TBC, as TBC samples are smaller than SLB samples.

Two observational studies compared the diagnostic yields of TBCs sampling one site and TBCs sampling multiple sites and met inclusion criteria.[40,49] Both studies suggest that TBCs obtained from at least two different sites (different segments of the same lobe or two lobes of the same lung) increase the diagnostic yield significantly. In a prospective study, Ravaglia et al[49] enrolled 46 patients with suspected diffuse parenchymal lung disease. All patients underwent TBC using a 2.4 mm probe and a freezing time of 5 seconds. Patients were randomly assigned to group A (four samples obtained from the same segment) or group B (two samples obtained from one segment and two samples obtained from a different segment of the same lobe). Analysis of the samples was performed sequentially, and pathologists reformulated their histopathologic diagnosis with the addition of each sample. The mean diagnostic yield of the procedure combining the two groups and considering only the first sample was 69%. When a second biopsy was performed in the same segment, the mean diagnostic yield improved to 78%, but this was not statistically significant ($P = .340$). Only when the two samples were obtained from two different segments did the diagnostic yield increase significantly to 96% ($P = .004$) (e-Table 5a). There were more pneumothoraces in group B vs A (6/23 vs 1/22), but this difference was not statistically significant ($P = .096$) (e-Table 5b).

These results were confirmed by a retrospective analysis of a large cohort of 699 patients who underwent TBC.[40] Both histological (92.5% vs 84.8%; $P = .001$) and MDD (92.9% vs 88.4%; $P = .43$) diagnostic yields were significantly better when samples were obtained from two sites (n = 267, different segments of the same lobe [n = 166; 62%] or different lobes [n = 101; 38%]) compared with sampling of one site, respectively (e-Table 5c). Both 2.4 mm and 1.9 mm probes were used, with no significant differences in terms of histological (88% vs 84.9%, respectively; $P = .49$) or MDD (90.6% vs 98.4%, respectively; $P = .201$) diagnostic yield (e-Table 5d). The freezing time of the 2.4 mm probe was 5 seconds, and the freezing time of the 1.9 mm probe was 7 to 8 seconds. The risk of pneumothorax was increased when samples were taken from different sites (one site: 15.2%; two sites: 24.6%; $P = .002$) (e-Table 5e).

While these prospective and retrospective studies comparing diagnostic yield provide low-quality evidence, the available data suggest that TBC sampling from two sites (two segments or two lobes) compared with one site results in a higher diagnostic yield, although at the expense of more pneumothoraces.

Distance From Pleura

3. In patients with suspected ILD undergoing TBC, we suggest biopsy with the tip of the cryoprobe located 1 cm from the pleura (Ungraded Consensus-Based Statement).

Remarks: This recommendation is based on histological considerations and safety. In cases of suspected IPF, the histological pattern is typically predominant in the subpleural areas. The distance from the pleura for

biopsies was chosen to balance histological yield with the risks of pneumothorax and bleeding.

The literature search did not return any studies that addressed the impact of differential distances of the cryoprobe from the pleura during TBC on diagnostic yield or safety. A suggested distance of the cryoprobe tip to the pleura of 1 cm is based on both histological and safety considerations. Diagnosis of IPF requires sampling at the level of the secondary lobule of the lung, which is typically located in close proximity to the pleura. Samples obtained 1 cm away from the pleural lining allow for adequate histological specimens while mitigating the risk of pneumothorax associated with more distal biopsies. Conversely, biopsies obtained too proximally expose patients to potential bleeding complications due to laceration of larger bronchial arterial vessels or pulmonary veins.[18]

Fluoroscopy Use

4. In patients with suspected ILD undergoing TBC, we suggest the use of fluoroscopy (Ungraded Consensus-Based Statement).

Remarks: Distance from the cryoprobe tip to the pleura can be inferred from the resistance felt when it reaches the pleura and from the distance measured on fluoroscopy when the beam is perpendicular to the axis of the cryoprobe. The routine use of fluoroscopy is suggested, and sampling of segments which allow for a more perpendicular beam path should be favored.

Adequate positioning of the cryoprobe may influence the rate and severity of complications.[18] Biopsies too close to the pleura may increase the rate of pneumothorax, while biopsies obtained too proximally may disrupt larger blood vessels resulting in severe bleeding. Fluoroscopy may allow for better control of the position of the cryoprobe in the subpleural area, and could mitigate these risks.

One observational study that addressed the influence of the use of fluoroscopy during TBC on the rate of pneumothorax met inclusion criteria. Dhooria et al[50] compared rates of pneumothorax in patients who underwent TBCs performed without fluoroscopy vs those of patients who underwent TBCs with fluoroscopy in an attempt to position the cryoprobe tip between 1.5 and 2 cm from the parietal pleura. Pneumothorax occurred in nine of 43 patients (20.9%) who underwent TBC without the use of fluoroscopy. Significantly fewer pneumothoraces occurred (5/85 [5.9%]; $P = .01$) in patients who underwent TBC with the use of fluoroscopy (e-Table 6a). The influence of fluoroscopy on bleeding severity was not reported.

Bronchial Blocker Use

5. In patients with suspected ILD undergoing TBC, we suggest that TBC be performed with a bronchial blocker either through an endotracheal tube or rigid bronchoscope (Ungraded Consensus-Based Statement).

Remarks: In the case of endobronchial bleeding, prophylactic placement of a bronchial blocker allows for immediate tamponade without further positioning maneuver. While we acknowledge that TBC via rigid bronchoscopy without prophylactic balloon placement may be considered when performed at expert centers, the systematic use of a bronchial blocker is suggested.

Bleeding after TBC is common, and severe bleeding may occur.[38,42,51-53] The risk of severe bleeding is increased during TBC as each sample needs to be removed en-bloc with the bronchoscope (as the larger biopsy size precludes retrieval through the working channel of the bronchoscope), with the bronchoscope reinserted in the patient airway only after the sampled tissue has been released from the cryoprobe tip after thawing. This process results in the inability to keep the bronchoscope wedged after biopsy, a technique used to contain endobronchial bleeding after conventional forceps biopsies, and significant blind time during which substantial endobronchial bleeding may go unnoticed.

One observational study addressing the influence of prophylactic bronchial blocker balloon use during TBC on the incidence of bleeding met inclusion criteria.[50] Moderate to severe bleeding, defined as bleeding requiring cold saline, postoperative mechanical ventilation, transfusion, or escalation of care, occurred in five of 14 patients (35.7%) who underwent TBC without prophylactic balloon placement. The incidence of such bleeding was significantly lower in patients who underwent TBC with prophylactic balloon placement (2/114 [1.8%]; $P < .001$) (e-Table 6b).

This evidence suggests prophylactic balloon placement may mitigate the risk of bleeding during TBC and increase the safety of the procedure. Preferably, the balloon is placed in the segment feeding the target area and pushed down beside the bronchoscope within the rigid bronchoscope or through an extra channel attached to the flexible tube.[54,55] Rigid bronchoscopy is preferred by some for its ability to control endobronchial bleeding, but when used with jet ventilation could theoretically increase the risk of

iatrogenic pneumothorax. The balloon is inflated immediately after the cryoprobe and bronchoscope are retrieved en-bloc from the airway. The amount of inflation needed, and the integrity of the bronchial blocker, should be established before the biopsy is obtained.

Cryoprobe Size

6. In patients with suspected ILD undergoing TBC, we suggest the use of a small cryoprobe (1.9 mm) rather than a larger cryoprobe (2.4 mm) (Ungraded Consensus-Based Statement).

Remarks: The smaller diameter cryoprobe is easier to maneuver in the airway and facilitates tactile feedback of when the cryoprobe reaches the pleura, which may reduce the risk of bleeding and pneumothorax.

Two cryoprobes are available to obtain samples during TBC, a small 1.9 mm probe and a large 2.4 mm probe. The size of the cryoprobe may affect the safety of the biopsy procedure.

One observational study comparing the safety of TBC procedures by cryoprobe size used met inclusion criteria. In this recent retrospective study including 699 patients, Ravaglia et al[40] report that the pneumothorax rate was significantly lower when using the smaller (1.9 mm) cryoprobe than when using the larger cryoprobe (2.4 mm) (2.7% vs 21.2%; $P < .0001$). The limited data do not suggest a difference in bleeding, defined as requiring endoscopic aspiration or procedures, surgical intervention, transfusion, or admission to the ICU, between the small and large cryoprobes (11% vs 12.8%; $P = .646$) (e-Table 6c).

Further Research

The data on TBC in the diagnosis of ILD remain limited and accordingly recommendations are necessarily provisional and contingent upon future research findings. Specifically, the results of several studies evaluating the concordance between TBC and SLB in the same patient are expected in the near future and may further clarify the histological yield of TBCs. There is a prospective trial in the United States (NCT01972685) directly comparing SLB to cryobiopsy for ILD which has completed enrollment and is expected to be published within the year.[56] As mentioned above, however, the decision to proceed with TBC over SLB should consider not only diagnostic yield but also the respective risk profiles of both interventions. Future research should compare the respective contributions of TBCs and SLBs to the confidence in diagnosis and interobserver agreement, and the effect of biopsies on management strategies and patient outcomes. Research should also focus on improving the technical aspects of the procedure, to ensure patient safety and adequate specimen acquisition: the use of a smaller probe that can be retrieved through the working channel of the bronchoscope, the optimal number and location of TBCs, and the education and competency standards to perform the procedure, among other technical considerations, should form the basis of future research projects.

Conclusions

Data on the utility and safety of TBC for the diagnoses of ILD remain limited. Conversely, a substantial body of evidence suggests that SLB, with an estimated 12,000 procedures performed annually for ILD in the United States alone, is associated with significant morbidity and mortality.[8] While the use of SLB is increasingly questioned in the ILD community, recent guidelines on IPF continue to recommend SLB as a possible option in patients with possible UIP/IPF when the diagnosis cannot be established on radiologic grounds alone.[6,7] TBC appears to be safer than SLB, and its contribution to the diagnosis following MDD is essentially equivalent to that of SLB when local expertise (clinicians, radiologists, and pathologists) is available. Our comprehensive and systematic review of the literature suggests that TBC may be considered as an alternative to SLB, provided certain precautions are exercised, such as prophylactic use of a bronchial blocker and fluoroscopy. These recommendations should be viewed as provisional, and contingent upon confirmation of these preliminary data and the availability of clinical pathologist experts in ILD.

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