



The future of surgical lung biopsy: moving from the operating room to the bronchoscopy suite

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Abstract: Assessment of patients with suspected interstitial lung disease includes a complete work-up consisting of history and physical examination, laboratory studies, lung function testing, high-resolution CT scan, bronchoscopy with bronchoalveolar lavage, and cardiology workup. Presently, definitive diagnosis of interstitial lung disease is even more important because of newly available therapeutics. The high risk/benefit ratio perceived in the literature for surgical lung biopsy motivates research for new biopsy techniques that ideally would have the same or better diagnostic yield as surgical lung biopsy with less morbidity, mortality and cost. If endoscopic transbronchial lung cryobiopsy can be shown to be associated with a low morbidity rate and high accuracy, we may be able to obtain a definitive histological diagnosis in a great majority of interstitial lung disease cases and forego complex, inefficient and inaccurate methods of disease diagnosis. Several groups have published prospective and retrospective series on endoscopic transbronchial lung cryobiopsy for interstitial lung disease with promising results and diagnostic yields up to 83% (range, 74–91%). The main complications associated with endoscopic transbronchial lung cryobiopsy are pneumothoraces and bleeding. The optimal techniques and specific settings for endoscopic transbronchial lung cryobiopsy is currently being investigated. In this paper, we present a review of the literature for endoscopic transbronchial lung cryobiopsy and future perspectives.

Keywords: Interstitial lung disease (ILD); cryobiopsy, endoscopic procedures

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Introduction

Endoscopic transbronchial lung cryobiopsy (TBLC) is becoming an important diagnostic tool in the diagnostic algorithm of interstitial lung disease (ILD). The exact methodology for carrying out the endoscopic procedure, the standardization of the technique as well as the comparison to the gold standard, surgical lung biopsy (SLB), in ILD is currently under investigation. In this paper, we present a review of the literature for TBLC and future perspectives.

ILD

ILD is challenging to diagnose, due to the fact that many subtypes of ILD have overlapping clinical and radiological features. ILD is defined as lung disease characterized by varying patterns of inflammation and fibrosis that affect the alveolar structures, interstitium, small blood vessels and small airways. ILD represents a heterogeneous group of more than 200 different rare pulmonary disorders. The reported prevalence is between 17.3 and 80.9 per 100,000,

Table 1 Investigations for interstitial lung disease (5-9)

Investigations	Specific tests
History	Symptoms, date of onset, comorbidities, smoking history, environmental or occupational exposures, family history
Examination	Signs of pulmonary hypertension or right heart failure, signs of connective tissue diseases (e.g., Raynaud's phenomenon), inflammatory arthritis
Serology	FBC, ANCA, ANA, ENA, RF, anti-CCP, ds-DNA, ACE, NT-pro-BNP, myositis antibodies
Lung function tests	Spirometry, DLCO
HRCT scan	Reticular opacities in basal and peripheral distribution of lung, traction bronchiectasis, honeycombing in subpleural location of lung, ground glass opacities
Lung tissue specimens	Bronchoalveolar lavage (BAL) Endoscopic transbronchial forceps biopsy (TBB) Endoscopic transbronchial lung cryobiopsy (TBLC) CT-guided transthoracic lung biopsy (CT-TLB) Video-assisted thoracoscopic surgery (VATS) biopsy Thoracotomy biopsy

ILD, interstitial lung disease; FBC, full blood count; ANCA, anti-neutrophil cytoplasmic antibody; ANA, antinuclear antibodies; ENA, extractable nuclear antigen; RF, rheumatoid factor; CCP, cyclic citrullinated; ds-DNA, double-stranded DNA; ACE, angiotensin-converting enzyme; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; DLCO, diffusion lung capacity for carbon monoxide.

and incidence between 3.6 and 31.5 per 100,000/year (1-4). The different histologic patterns have been associated with diverse clinical scenarios, with a wide variety of possible diagnoses and substantial implications on treatment options and prognosis (5,6).

Presently, the diagnostic gold standard for ILD is both a multidisciplinary discussion (MDD) with the real-time integration of clinical, radiological and pathological data by experts in ILD. Biopsy is considered a last step, however, often a necessary one, in the complex diagnostic algorithm of ILD. When performed as a diagnostic tool, a lung biopsy with histologic analysis can impact the management of ILD for the treatment and the prognosis in more than three quarters of cases (2,3).

Investigations for ILD

The identification of the specific types of ILD does not rely on a single test. It conversely relies on several clinical parameters and the clinical judgment of experts. Assessment of patients with suspected ILD includes a complete work-up consisting of history and physical examination, laboratory studies, lung function testing, high-resolution CT scan, bronchoscopy with bronchoalveolar lavage

(BAL), and cardiology workup (5-8) (*Table 1*). Data from studies correlating radiological and histological features has allowed to identify and characterize, in combination with clinical judgment, a significant proportion of patients with ILD. For instance, a typical usual interstitial pneumonia pattern on a high-resolution CT scan, in a compatible clinical context, is sufficient to establish the diagnosis of idiopathic pulmonary fibrosis (IPF) (7,8), with a specificity of 94–100% (10-12) and a sensitivity of 48–73% (10-12). However, only about 50% of patients with IPF present with this radiologic pattern, and many cases present with clinical contexts that cannot exclude alternative diagnoses (13). In these specific cases, a histological evaluation is indicated to reach a definitive diagnosis. In ILD other than IPF, radiological intra-observer agreement is often poor, consequently diagnosis is difficult even with MDD (14). Nowadays, definitive diagnosis of ILD is even more important because of the newly available therapeutics, i.e., pirfenidone or nintedanib, that change the prognosis of the disease in appropriately diagnosed patients (13).

Parenchymal lung tissue sampled to investigate ILD can be obtained through various strategies including BAL, endoscopic transbronchial forceps biopsy (TBB), CT-guided transthoracic lung biopsy (CT-TLB), SLB and more

recently, TBLC.

TBB is not recommended as a standard test in the diagnostic algorithm of ILD based on current guidelines (7,15,16). The specimens obtained are often too small (1–3 mm) and contain artifacts, which limit the histological evaluation of specimens. In a recent trial from Pajares *et al.*, histological diagnosis was obtained in only 34.1% of patients who had a TBB (17). The diagnostic yield of this technique was of 29.1% (17). Other published results reveal similar diagnostic yields with TBB (18,19). The low diagnostic yield can be explained by the involvement of terminal and respiratory bronchioles in ILD that are not easily accessed with forceps. TBB therefore misrepresents the overall disease process in ILD.

CT-TLB for ILD is described by Padrao *et al.* in a retrospective study from Portugal of 169 patients (20). A definitive or probable diagnosis was made in 66.3% of cases (20). The most frequent diagnosis was organizing pneumonia in 36.2% of cases (20). The diagnostic yields associated with CT-TLB are based mainly on retrospective series. The diagnostic yields range from 20% to 66% (20). The major complications were pneumothorax (17.8%), mild hemoptysis (7.7%) and hemothorax (1.2%). Mortality occurred in 0.59% of cases (20).

SLB is the current gold standard technique to obtain lung tissue specimens in suspected ILD (15,16). The diagnostic yield is 95% (42% to 100%) in a recently published meta-analysis (15,16). Moreover, in 40% to 90% of SLB, the result of the histological analysis changes the treatment strategy. It is very relevant for disease patterns where larger tissue samples are required, such as IPF where there is geographical heterogeneity of disease (9). However, SLB is currently only used in 4% to 5% of suspected ILD because of the associated significant complications (21). The reported rate of major postoperative complications is between 12.9% and 19.1% (22,23). Major complications include prolonged air leak, pneumonia, acute exacerbation of underlying interstitial pneumonia, readmission and prolonged postoperative mechanical ventilation. The postoperative mortality for SLB in patients with ILD is between 1.8% and 3.6% for elective cases and increases to 16% in non-elective cases (16,22-26). We must remember that patients selected for SLB often have very poor lung function and have uncertain diagnosis after other investigations. These patients often have restrictive fibrotic lung parenchyma. These patients undergo general anesthesia with mechanical ventilation, one lung ventilation (OLV) in video-assisted thoracoscopic

surgery (VATS). Chest tubes inserted during surgery can stay in place for several days and cause pain and splinting. A typical admission to the hospital for a minimum of 2 to 3 days for straightforward elective cases is required. Low risk patients including those younger than 65 years, with no significant comorbidity and preserved lung function are not initially considered for SLB (21,27). The high risk/benefit ratio perceived in the literature for SLB motivates research for new biopsy techniques that ideally would have the same or better diagnostic yield as SLB with less morbidity, mortality and cost. As mentioned, less invasive methods used to diagnose ILD are of insufficient sensitivity (7,15). If TBLC can be shown to be associated with a low morbidity rate and high accuracy, we may be able to obtain a definitive histological diagnosis in a great majority of ILD cases and forego complex, inefficient and inaccurate methods of disease diagnosis.

History of cryobiopsy

TBLC is a relatively new endoscopic technique used to obtain lung parenchyma specimens. It is a minimally invasive technique performed with a flexible or rigid bronchoscope under deep sedation or general anesthesia. Its use in ILD was first described by Babiak *et al.* in 2009 (28). A flexible cryoprobe was introduced into selected bronchi under fluoroscopic guidance in 41 patients and compared with TBB. The biopsy procedures were evaluated on specimen size, specimen quality and complications. Specimens from TBLC were of greater size and quality compared to TBB (mean specimen area 15.11 mm² for TBCL *vs.* 5.82 mm² for TBB). Two pneumothoraces were observed. According to Babiak, TBCL also contributed to definitive diagnosis in a substantial number of cases (28).

Cryoprobes exist since 1960. These probes are used as therapeutic tools for airway tumor debulking through multiple freeze-thaw cycles that cause cell death and necrosis. This technology is also used for cryoadhesion to remove tissue e.g., granulation or tumor from the airway. As the tissue rapidly freezes, it adheres to the probe and is avulsed. It is extracted with a quick pullback movement. The same principle applies to TBLC.

Cryobiopsy principles

The principle behind cryobiopsy using a cryoprobe is the Joule-Thomson effect. Compressed gas, most commonly carbon dioxide or nitrous oxide, is released at high flow



Figure 1 Endoscopic transbronchial lung biopsies.

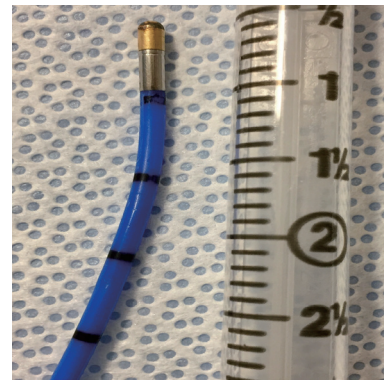


Figure 2 Flexible cryoprobe.

Table 2 Contraindications to endoscopic transbronchial lung cryobiopsy (based on expert opinion) (31,32)

Resting hypoxemia

Severe lung restriction on lung functions testing, i.e., FVC <50% or oxygen diffusion issues, i.e., DLCO <35% of predicted

High bleeding risk, i.e., bleeding diathesis, anticoagulant therapy in therapeutic dosage or thrombocytopenia (platelets <50×10⁹/L)

Adverse reaction to general anesthesia

Pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg)

Cervical instability (e.g., rheumatoid arthritis)

FVC, forced volume vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

at the tip of the probe. The rapid gas expansion cools the tip of the probe to -79°C when using carbon dioxide or -89°C when using nitrous oxide, freezing the surrounding tissue (28,29). As the tissue rapidly freezes, it adheres to the probe and is avulsed. It is extracted with a quick pullback movement (*Figure 1*).

Cryobiopsy is an endoscopic intervention and can be performed as an outpatient procedure. Presently, various techniques of TBLC for ILD have been described (28-30). Flexible cryoprobes of either 1.9 or 2.4 mm in diameter are used (*Figure 2*). Fluoroscopic guidance can also be used to determine the distance of the probe from the pleura and to confirm the location of the probe. In the literature, the freezing time is heterogeneous (5 to 8 seconds). Factors that can influence the freezing time are use of carbon dioxide or nitrous oxide, size of the probe, tissue properties and bronchus location i.e., lobar, segmental or subsegmental.

Based on expert opinion, contraindications to TBLC are based on bleeding risk and severity of hypoxemia (*Table 2*). Contraindications include resting hypoxemia, severe lung restriction on lung functions testing [i.e., forced vital capacity (FVC) <50%] or oxygen diffusion issues [i.e.,

diffusing capacity of the lung for carbon monoxide (DLCO) <35% of predicted], high bleeding risk [i.e., bleeding diathesis, anticoagulant therapy in therapeutic dosage or thrombocytopenia (platelets <50×10⁹/L)], adverse reaction to general anesthesia, pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg) and cervical instability as in rheumatoid arthritis (31,32). None of these recommended contraindications are based on evidence.

To prevent hemorrhagic complications, a Fogarty catheter or endobronchial balloon occlusion catheter can be used. The balloon catheter is used as a hemostatic bronchial balloon. The balloon is prophylactically placed near and proximal to the site of cryobiopsy in case of bleeding. The balloon can be prophylactically inflated immediately following each cryobiopsy attempt.

Review of published lung cryobiopsy studies (main study characteristics and outcomes)

As an emerging diagnostic technique for ILD, TBLC is a promising alternative to SLB as described in a recent meta-analysis published by Sethi *et al.* that included 31 studies

and 1,443 patients (33). The enthusiasm for TBLC has led to an increase in lung biopsy in patients with ILD without specific diagnosis. The enthusiasm has led to two recent expert opinion papers published on the subject in 2018 and 2019 (31,32). *Tables 3-5* present a summary of studies on endoscopic TBLC. Case series, meta-analysis and animal studies are analyzed.

Several groups have published prospective and retrospective series on TBLC for ILD with promising results and diagnostic yields up to 83% (range, 74-91%) (24,25,30,39-41). However, because this is an emerging technique, there is no standard way to perform TBLC, and the technical aspects for performing TBLC are heterogeneous among published series (23-25,30,41,52,57,58).

The main complications associated with TBLC are pneumothoraces and bleeding. The meta-analysis published by Sethi *et al.* reports an overall complication rate of 23.1%, with a pooled incidence of pneumothorax of 9.4% and a significant bleeding rate of 14.2% (33). These results are similar to the results described previously by other authors (24,51,52,57). Pneumothoraces are the consequence of a biopsy obtained too close to the visceral pleura, causing a disruption in its continuity. Significant bleeding is alleged to be caused by a biopsy taken in more proximal areas of the lung, where blood vessels are larger and the tract to the main airway is shorter (38). The size of the sample might also play a role in the development of these complications. Some authors have hypothesized that with longer freezing times, larger samples are obtained, with the downside being the increased risk of severe bleeding (53). There is very limited data on the influence of different technical components for performing TBLC, and definition of the optimal settings to obtain the best quality samples with the lowest incidence of complications are in need of scientific investigation.

Ravaglia *et al.* recently published an observational, retrospective cohort study on 699 patients with the use of TBLC in ILD (30). A definitive diagnosis was obtained with histologic analysis in 87.8% of cases (30). With the integration of MDD, diagnosis was obtained in 90.1% of cases (30). The diagnostic yield was significantly influenced by the number of samples taken (1 *vs.* 2 or more) ($P < 0.005$) and the different locations of samples taken for fibrotic lung diseases ($P < 0.001$). The complication rate was 19.2% for pneumothorax, 7.6% for moderate hemorrhage and 0.7% for severe hemorrhage (30). Factors that significantly influenced the risk of pneumothorax were the different

locations of samples taken, location of samples in lower lobes, the use of 2.4 mm probe and a high radiologic fibrotic score (30). Radiologic fibrotic score evaluates the distribution of reticular abnormalities, the presence of traction bronchiectasis and honeycombing. Mortality occurred in 0.4% (3 patients) of cases within 30 days of TBLC. Risk of bleeding was increased in samples taken in lower lobes ($P = 0.027$). For this study, Ravaglia presented strategies, in order to optimize the TBLC technique (*Table 6*) (30).

Advantages and disadvantages of TBLC

There are multiple advantages to TBLC that make it an interesting diagnostic technique for ILD (*Table 7*). This explains the increase in its popularity in some centers.

Studies on standardization of endoscopic TBLC technique and comparison with SLB

There exists a need for a standardized technique for performing TBLC to optimize quality of specimens and prevent complications. Studies evaluating technical aspects of TBLC and comparing TBLC to SBL are presently taking place.

Molina and Liberman presented the first phase of their study on technical aspects of TBLC at the Second Conference of the American Association for Bronchoscopy and Interventional Pulmonology in 2019. The study defines the optimal settings for TBLC using an *ex-vivo* porcine model by assessing the influence of different technical parameters on specimen quality and size. The technical parameters analyzed were probe size, freezing time and distance from the probe to pleura. One-hundred and thirty-two biopsies were taken in an *ex-vivo* porcine lung model after 181 attempts from 5 sets of lungs. They systematically evaluated different parameters using 1.9- and 2.4-mm probes, 3, 5, 8, 10, 15 and 20 seconds of freezing time and distances from pleura to the tip of the probe of 5, 10 and 20 mm. On Multivariate regression analysis including all samples and settings, there was a strong association between freezing time and sample weight and area. The main outcome was that freezing time is the main determinant of sample size for cryobiopsy in an *ex-vivo* porcine lung model, while probe size and distance from the tip of the probe to pleura had no significant influence. The second phase, presently underway, consists of analyzing in a canine model, the quality of specimens obtained by TBLC and the associated complications based on different protocols

Table 3 Summary of studies on endoscopic transbronchial lung cryobiopsy

Author	Year	#Pts	Design	Gas	Probe (mm)	Fluoroscopy	# of Bx per pt/total	Freeze time (s)	Distance to pleura (mm)	Bx size	Outcomes	Complications
Ravaglia (30)	2019	699	Retrospective	N/A	1.9 and 2.4	Yes	3.3	5-8	10	30.35 mm ²	Dx yield 87.8%; Dx yield MDD 90.1%	Ptx 19.2%; severe bleeding 0.7%; mortality 0.4%
Ravaglia (24)	2016	297	Retrospective (vs. SLB)	N/A	2.4	Yes	N/A	5	10	N/A	Dx yield TBLC 82.8% (vs. SLB 98.7%); Mortality 0.3% (vs. 2.7% SLB); Ptx: 20.2%	
Pajares (17)	2014	77	Randomized (vs. TBB)	N/A	2.4	Yes	TBLC 3.7 (vs. TBB 3.5)	3-4	N/A	14.7 mm ² (vs. 3.3 mm ²)	Histopathologic Dx 74.4% (vs. 34.1% TBB); Dx yield 51.3% (vs. 29.1% TBB)	Bleeding 56.4% vs. 34.2% (NS)
Babiak (28)	2009	41	Retrospective (vs. TBB)	N ₂ O	2.4	Yes	2	4	10	15.11 mm ² (vs. 5.82 mm ²)	Definitive Dx in 39/41 pts	Ptx 4.87%
Lentz (29)	2017	104	Retrospective	CO ₂	1.9	Yes	2.2	4-5	15-20	6.9 mm	Management change 70%; confident histopathologic Dx 44%	Severe bleeding 4%; Ptx 3%; admission 6%; respiratory failure 2%
Ussavarungsi (34)	2017	74	Retrospective	N/A	1.9	Yes	3	3-5	N/A	9.2 mm	Dx yield 51%	Ptx 1.4%; bleeding 22%; abscess 1.4%
Sriprasart (35)	2017	74	Retrospective	N/A	1.9 and 2.4	Yes	3	5-8	10	63 mm ²	Dx yield 87%	Ptx 6.8%; severe bleeding 2.2 %; death 4%
Cascante (36)	2016	55	Prospective	N ₂ O	2.4	Yes	2.8	3-4	10-15	20.7 mm ²	Definitive Dx 69%; probable Dx 20.8%; unclassified 12.7%	Ptx 14.5%; bleeding 10.9%
Fruchter (37)	2014	75	Retrospective	N ₂ O	2.4	Yes	3	4	10-20	9 mm ²	Definite Dx 70%; probable Dx 28%	Ptx 2.6%; bleeding 4%
Lentz (38)	2018	104	Retrospective	CO ₂	1.9	Yes	2.2	4-5	15-20	6.9 mm	Definitive Dx 68.3%; Dx yield MDD 92.3%	Ptx 3%; bleeding 4%
Almeida (39)	2017	100	Retrospective	N ₂ O	2.4	Yes	3	5-6	10-20	5.4 mm/ 19.5 mm ²	Dx yield 82%	Ptx 18%; bleeding 3%
Casoni (40)	2014	69	Prospective	CO ₂	2.4	Yes	3	5-6	10	43.11 mm ²	Dx yield 76%; specimen area correlates with Dx yield	Ptx 28%; death 1.4%

Table 3 (continued)

Table 3 (continued)

Author	Year	#Pts	Design	Gas	Probe (mm)	Fluoroscopy	# of Bx per pt/total	Freeze time (s)	Distance to pleura (mm)	Bx size	Outcomes	Complications
Dhooria (41)	2017	128	Retrospective	N ₂ O	1.9	Variable	3	3-6	15-20	5 mm	Dx yield 78.1%	Less Ptx with fluoro: 5.9% vs. 20.9%; less bleeding occlusive balloon: 1.8% vs. 35.7%
Bango-Álvarez (42)	2017	106	Prospective	N/A	1.9	No	3	5	N/A	5.1 mm/ 15.7 mm ²	Definitive Dx 86%	Ptx 4.7%; moderate bleeding 16%
Linhas (43)	2017	90	Prospective	N/A	2.4	Yes	4	5	10	4 mm	N/A	Ptx 24%; bleeding 14.4%
Ravaglia (44)	2017	46	Randomized	CO ₂	2.4	Yes	4	5	N/A	29-30 mm ²	Better Dx yield when sample from 2 different segments from same lobe	Ptx 16%
Kronborg-White (45)	2017	38	Prospective	CO ₂	1.9 and 2.4	Yes	4	5-7	10	6.4 mm	Contribute to Dx in 74%	Ptx 26%; chest tube 21%; moderate bleeding 15%
Echevarria-Uraga (46)	2016	100	Retrospective	N ₂ O	2.4	Yes	N/A	4	10-20	N/A	98% of samples had Dx value	Ptx 3%; bleeding 13%
Gershman (47)	2015	300	Retrospective (vs. TBB)	N ₂ O	2.4	Yes	N/A	4	N/A	N/A	TBLC as safe as TBB	Ptx 5% (vs. 3%) NS; bleeding 5% (vs. 4%) NS; admission 3% (vs. 1%) NS
Griff (48)	2014	52	Retrospective	CO ₂	1.9	Yes	1 or 2	3-5	10-20	6.9 mm	Correlation with clinical Dx in 79%	No major complication
Fruchter (49)	2013	15	Retrospective immunocompromised	N ₂ O	2.4	Yes	2	4	N/A	9 mm ²	Change in management in 80%	Bleeding 6.7%
Griff (50)	2011	15	Prospective	N/A	N/A	Yes	1	5	10-20	17.1 mm ²	Larger specimens compared to forceps Bx, contains alveolar tissue more often	No major complication

Pts, patients; Bx, biopsy; N/A, not available; Dx, diagnostic; MDD, multidisciplinary discussion; Ptx, pneumothorax; TBLC, endoscopic transbronchial lung cryobiopsy; SLB, surgical lung biopsy; TBB, transbronchial lung biopsy; NS, not statistically significant.

Table 4 Meta-analysis of endoscopic transbronchial lung cryobiopsy

Author	Year	# Pts in total	Bx size	Outcomes	Complications
Ravaglia (24)	2016	781	N/A	Dx yield 81%	Ptx pooled probability 0.06; moderate bleeding pooled probability 0.12
Iftikhar (25)	2017	642 (TBLC) + 1,549 (SLB)	N/A	Dx yield: 83.7% (vs. 92.7% SLB); sensitivity: 87% (vs. 91% SLB); specificity: 57% (vs. 58% SLB)	Ptx 9.5%; moderate/severe bleeding 4.9%
Sethi (33)	2019	1,443	23.4 mm ²	Dx yield 72.9%	Ptx 9.4%; bleeding 14.2%
Dhooira (51)	2016	805	20.4 mm ²	Dx yield (definitive Dx) 76.9% and (definitive + probable) 85.9%; less artifact with TBLC	Ptx 6.8%; severe bleeding 0.3%; death 0.1%
Johansson (52)	2016	731	N/A	Dx yield 74–98%, 83% pooled; Dx yield MDD 51–98%, 79% pooled	Ptx 12%; moderate/severe bleeding 39%

Pts, patients; Bx, biopsy; N/A, not available; Dx, diagnostic; Ptx, pneumothorax; TBLC, endoscopic transbronchial lung cryobiopsy; SLB, surgical lung biopsy.

Table 5 Summary of animal studies of endoscopic transbronchial lung cryobiopsy

Author	Year	# Animals	Design	Gas	Probe (mm)	Fluoroscopy	# of Bx per pt/total	Freeze time (s)	Distance to pleura (mm)	Bx size	Outcomes
Ing (53)	2016	2 sheep	Animal <i>in vivo</i> (freeze time vs. size)	N/A	1.9	Yes	49 total	1–6	10	Mean ranged from 4.7 to 15.3 mm ²	Correlation between freezing time and Bx size. Optimal is 3 s (associated with minimal complications) 1 case of severe hemorrhage (6 s freezing time) Ptx 3
Franke (54)	2016	2 pigs	Animal <i>ex-vivo</i> cryo (vs. TBB)	CO ₂	1.1	N/A	42 total	2–6	10	8.08 mm ² (vs. 2.61 mm ²)	Less artifact and more alveolar tissue with cryo Specimen weight increase with activation time
Franke (55)	2010	3 pigs	Animal <i>in vivo</i> vs. TBB	CO ₂	1.9 and 2.4	N/A	70 total	1–3	N/A	Depending on probe size and freeze time	Diameter of cryobiopsies was at least 30% larger than that of forceps biopsies
Franke (56)	2009	Lung (porcine, liver (bovine and porcine), gastric mucosa (porcine))	Animal <i>in vitro</i>	CO ₂	1.0, 1.2, 1.9, 2.4	N/A	10 per setting	1–6	N/A	Depending on probe size and freeze time	Diameter increase with freeze time, probe size, and pressure on tissue

Bx, biopsy; Pt, patient; N/A, not available; Dx, diagnostic; Ptx, pneumothorax; TBB, transbronchial biopsy.

Table 6 Strategies to optimize endoscopic transbronchial lung cryobiopsy technique suggested by Ravaglia (20,30,31)

Categories	Strategies
Number of specimens	Obtain 2 samples from 2 different sites in order to enhance the diagnostic yield (e.g., from different lobes in case of interlobar radiographic heterogeneity) as well as taking samples from different segments in the same lobe to increase the diagnostic yield
Probe size	Utilize the 1.9 mm probe (2.4 mm probe may be associated with a significantly increasing the diagnostic yield)
Location of specimens	Sampling from lower lobes may be associated with a higher rate of complication (both bleeding and pneumothorax) than in upper lobes
Lung function reserve	The risk of pneumothorax also increases in cases of impaired lung function (FVC <50% and DLCO <35%) and sampling 2 sites
Use of a hemostatic bronchial balloon	It is preferable to intubate the patients (either with rigid tracheoscope or flexible tube), always using bronchial blockers or catheters

FVC, forced vital capacity; DLCO, diffusion lung capacity for carbon monoxide.

Table 7 Advantages and disadvantages of endoscopic transbronchial lung cryobiopsy

Advantages
Minimally invasive technique
Possibility to perform as outpatient procedure
Reproducible
Larger parenchyma size specimens than TBB
High quality specimens, similar to SLB
Diagnostic yield similar to SLB (under investigation)
Fewer complications than SLB
Less expensive than SLB
Ability to perform under deep sedation as opposed to general anesthesia
Disadvantages
Non standardized technique
Very heterogeneous technical components among series
Major complications include pneumothorax and bleeding
No standardized protocol
Concerns that a lung tissue specimen is many-fold smaller in magnitude than SLB may be more vulnerable to sampling error and incorrect histopathological interpretation

SLB, surgical lung biopsy; TBB, transbronchial lung biopsy.

(probe size, freezing time and distance to pleura) to devise a standardized technique for TBLC.

The study COLDICE is presently recruiting patients in Australia to evaluate the agreement between TBLC and

SLB sampled concurrently from the same patients, for both histopathological and MDD diagnoses (9). The accuracy of TBLC will be assessed by agreement with VATS at both histopathological analysis and MDD diagnosis (9).

Conclusions

In conclusion, TBLC is an emerging technique with an interesting diagnostic yield of 83% for ILD. The yield may be improved with better techniques without compromising safety. Technique is probably not the only factor that influences the diagnostic yield for TBLC. Obtaining the biopsy in the most affected segment of the lung and the number of biopsies taken are also important factors. Future perspectives may be to evaluate performing TBLC under navigational bronchoscopy, radial endobronchial ultrasound or under direct guidance using real-time computed tomography.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/ccts.2019.11.03>). ML serves as an unpaid editorial board member of *Current Challenges in Thoracic Surgery* from Mar 2019 to Mar 2021. JM reports personal fees from Hoffman-La Roche, personal fees from

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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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