



Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases

Micaela Romagnoli, Thomas Colby, Jean-Philippe Berthet, Anne Sophie Gamez, Jean-Pierre Mallet, Isabelle Serre, Alessandra Cancellieri, Alberto Cavazza, Laurence Solovei, Andrea Dell'Amore, et al.

► To cite this version:

Micaela Romagnoli, Thomas Colby, Jean-Philippe Berthet, Anne Sophie Gamez, Jean-Pierre Mallet, et al.. Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases. *American Journal of Respiratory and Critical Care Medicine*, 2019, 199 (10), pp.1249-1256. 10.1164/rccm.201810-1947OC . hal-02067403

HAL Id: hal-02067403

<https://hal.science/hal-02067403>

Submitted on 19 Jun 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases

Micaela Romagnoli^{1,2}, Thomas V. Colby³, Jean-Philippe Berthet⁴, Anne Sophie Gamez¹, Jean-Pierre Mallet¹, Isabelle Serre⁵, Alessandra Cancellieri⁶, Alberto Cavazza⁷, Laurence Solovei⁴, Andrea Dell'Amore⁸, Giampiero Dolci⁸, Aldo Guerrieri⁹, Paul Reynaud¹, Sébastien Bommart^{10,11}, Maurizio Zompatori¹², Giorgia Dalpiaz¹³, Stefano Nava⁹, Rocco Trisolini², Carey M. Suehs¹, Isabelle Vachier¹, Nicolas Molinari¹⁴, and Arnaud Bourdin^{1,11}

¹Department of Respiratory Diseases, ⁴Department of Thoracic Surgery, ⁵Department of Pathology, ¹⁰Department of Radiology, ¹¹PhyMedExp, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale, and ¹⁴L'Institut Montpelliérain Alexander Grothendieck, CNRS, Centre Hospitalier Universitaire de Montpellier, University of Montpellier, Montpellier, France; ²Department of Interventional Pulmonology, ⁸Department of Thoracic Surgery, ⁹Department of Pulmonology, and ¹²Department of Radiology, S'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; ³Emeritus, Department of Laboratory Medicine Pathology, Mayo Clinic, Scottsdale, Arizona; ⁶Department of Pathology, Maggiore and S'Orsola-Malpighi Hospital, Bologna, Italy; ⁷Department of Pathology, Azienda USL-IRCCS, Reggio Emilia, Italy; and ¹³Department of Radiology, Bellaria Hospital, Bologna, Italy

Abstract

Rationale: The diagnostic concordance between transbronchial lung cryobiopsy (TBLC)—versus surgical lung biopsy (SLB) as the current gold standard—in interstitial lung disease (ILD) cases requiring histology remains controversial.

Objectives: To assess diagnostic concordance between TBLC and SLB sequentially performed in the same patients, the diagnostic yield of both techniques, and subsequent changes in multidisciplinary assessment (MDA) decisions.

Methods: A two-center prospective study included patients with ILD with a nondefinite usual interstitial pneumonia pattern (on high-resolution computed tomography scan) confirmed at a first MDA. Patients underwent TBLC immediately followed by video-assisted thoracoscopy for SLB at the same anatomical locations. After open reading of both sample types by local pathologists and final diagnosis at a second MDA (MDA2), anonymized TBLC and SLB slides were blindly assessed by an external expert pathologist (T.V.C.). Kappa-concordance coefficients and percentage agreement were computed

for: TBLC versus SLB, MDA2 versus TBLC, MDA2 versus SLB, and blinded pathology versus routine pathology.

Measurements and Main Results: Twenty-one patients were included. The median TBLC biopsy size (longest axis) was 7 mm (interquartile range, 5–8 mm). SLB biopsy sizes averaged 46.1 ± 13.8 mm. Concordance coefficients and percentage agreement were: TBLC versus SLB: $\kappa = 0.22$ (95% confidence interval [CI], 0.01–0.44), percentage agreement = 38% (95% CI, 18–62%); MDA2 versus TBLC: $\kappa = 0.31$ (95% CI, 0.06–0.56), percentage agreement = 48% (95% CI, 26–70%); MDA2 versus SLB: $\kappa = 0.51$ (95% CI, 0.27–0.75), percentage agreement = 62% (95% CI, 38–82%); two pneumothoraces (9.5%) were recorded during TBLC. TBLC would have led to a different treatment if SLB was not performed in 11 of 21 (52%) of cases.

Conclusions: Pathological results from TBLC and SLB were poorly concordant in the assessment of ILD. SLBs were more frequently concordant with the final diagnosis retained at MDA.

Keywords: idiopathic pulmonary fibrosis; lung histology; bronchoscopy; multidisciplinary approach; deep sedation

Supported by Boehringer Ingelheim Italy unrestricted grant 1199-308, an award from the French association Le Nouveau Souffle, the French Fondation du Souffle et Fonds de dotation Recherche en Santé Respiratoire, and the University Hospitals of Montpellier (reference: 9607). Neither the funders nor the study sponsor had a role in study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the report for publication.

Author Contributions: M.R., I.S., I.V., N.M., and A.B. designed the study. M.R., I.V., and A.B. coordinated the study. M.R., J.-P.B., A.S.G., A.G., and A.B. included patients. M.R., J.-P.M., and A.B. performed transbronchial lung cryobiopsies. J.-P.B., L.S., A.D.'A., and G. Dolci performed surgical lung biopsies. S.B., M.Z., and G. Dalpiaz interpreted computed tomography scans. J.-P.M., A.G., S.B., M.Z., G. Dalpiaz, S.N., and R.T. participated in multidisciplinary assessments. I.S., A. Cancellieri, and A. Cavazza performed nonblinded tissue pathology. T.V.C. performed blinded tissue pathology. A.S.G., P.R., and I.V. participated in data collection. C.M.S. and N.M. performed statistical analyses. M.R., C.M.S., and A.B. wrote the first draft of the manuscript. All authors critically revised the manuscript for intellectually important content. All authors gave final approval for the publication of the work, and all accepted responsibility for the integrity of the work.

Correspondence and requests for reprints should be addressed to Micaela Romagnoli, M.D., Ph.D., Pulmonology Unit, Santa Maria di Cà Foncello Hospital, Piazzale dell'Ospedale 1, 31100 Treviso, Italy. E-mail: miki.romagnoli@gmail.com.

Scientific Knowledge on the

Subject: Although surgical lung biopsy still represents the gold standard for lung histology in those interstitial lung disease cases where histology is requested at multidisciplinary assessment, several publications suggest the alternative option of transbronchial lung cryobiopsy as a less-dangerous, quasiequivalent substitute for surgical lung biopsy. However, the concordance between the two techniques when performed sequentially in the same patients has never been demonstrated.

What This Study Adds to the

Field: We demonstrate poor concordance between the two procedures, which has the potential to affect therapeutic decisions. Surgical lung biopsy was more often concordant with the final diagnosis retained at multidisciplinary assessment and remains the biopsy technique of choice when histology is required for the differential diagnosis of diffuse interstitial lung diseases.

The differential diagnosis of diffuse interstitial lung diseases (ILDs) includes a range of diseases corresponding to varying treatment choices and to large differences in disease prognoses. Disagreement in the final diagnosis can impact medical decisions, and final consensus on ILD diagnoses are currently ideally achieved as the result of multidisciplinary assessment (MDA) (1). Lung histology can provide crucial information for the diagnostic process, especially when the combined results from clinical, laboratory, high-resolution computed tomography (HRCT), and, optionally, BAL remain inconclusive. Recent data from large randomized trials suggest that histological information is required in at least 30% to 40% of cases (2–4).

Surgical lung biopsy (SLB) is considered the current gold standard for obtaining adequate lung biopsy specimens, resulting in a histologic diagnosis in more than 90% of cases (5). However, because of its relative complexity, cost, and risk of mortality (particularly in older subjects and in patients with significant comorbidities or severe

respiratory impairment), less than 50% of all potential cases are eligible, and biopsy rates have notably declined since the early 2000s (6). Given the risks involved, the decision for an SLB should be made individually, taking into account the risk/benefit ratio for a given patient, the potential impact on treatment options, and patient preferences.

Unfortunately, endoscopic transbronchial lung (TBL) biopsy using conventional forceps, although less invasive, is much less likely to be helpful for ILD diagnosis. Because of the relatively small size of forceps specimens (whose largest dimensions are on the order of 1–3 mm) and the potential limitation of crush artifacts (7), successful diagnosis is reported in only 20% to 30% of cases (8, 9). Consequently, empiric management and subsequently poorer outcomes have probably characterized many patients presenting with an ILD requiring an SLB in principle but ineligible (for a variety of reasons) for this procedure.

TBL biopsy with a cryoprobe, or cryobiopsy, is a relatively new technique that provides larger (7–10 mm maximum diameter) and better-preserved lung samples than “classic” forceps-TBL biopsies. More than two dozen case series and several small randomized trials have been published, with a reported diagnostic yield of 70% to 80% and an improved safety profile compared with SLB (10).

Although TBL cryobiopsy (TBLC) has been presented as a valid, potentially “less-invasive” tool for histologic ILD diagnosis, recent guidelines do not recommend for or against performing TBLC or SLB because of a lack of related evidence, including intrapopulation comparisons between the two (11). In this same line of thought, one of the main reported concerns is the absence of studies directly comparing TBLC to the gold standard procedure, the surgical lung biopsy (10, 11), to finally validate this procedure in the ILD diagnostic workup. The main aim of this study was therefore to compare the concordance between sequential TBLC and SLB for the histologic diagnosis and MDA diagnosis and management of ILDs in patients without a definite usual interstitial pneumonia (UIP) pattern on chest HRCT scan.

Methods

Study Design and Population

A prospective two-center study was conducted in the Department of Respiratory

Diseases, Montpellier University Hospitals, and in the Interventional Pulmonology Unit, University S’Orsola Hospital, Bologna, Italy. Between January 2016 and March 2018, adult patients presenting with clinical and radiologic features of ILDs, according to current international consensus criteria (9), were first consecutively evaluated at an MDA meeting (MDA1). If histology was indicated at MDA1, informed consent was obtained, and patients were prospectively included to undergo both TBLC and SLB under video-assisted thoracoscopy (VATS) in the same session. Further eligibility criteria included an FVC greater than 50% of the predicted normal value, a DL_{CO} greater than 35% of the predicted normal value, and a pulmonary systolic arterial pressure estimated by echocardiography of less than 40 mm Hg. Exclusion criteria included coagulopathy (platelet count < 70,000 × 10⁹/L; prothrombin time international normalized ratio > 1.5), FEV₁ less than 1 L absolute value, diffuse bullous disease at HRCT scan, hemodynamic instability, and severe hypoxemia (PaO₂ ≤ 55 mm Hg in room air).

Clinical assessment preceding the two procedures included data for age, sex, smoking, environmental exposures, past medical history, current medications, physical examination, laboratory results, pulmonary function values, and cardiologic assessment. Biopsies were performed under surgical conditions (*see* the online supplement for complete procedure details), with patients undergoing a rigid bronchoscopy, with TBLC performed in two different lobes (upper and lower) under deep sedation, followed by a VATS procedure for surgical lung biopsies in the same lobes under general anesthesia. After obtaining the histological results (performed unblinded, as in routine practice, but with both TBLC and SLB samples available) from the local pathology services at the respective sites (I.S. in Montpellier, A. Cancellieri in Bologna, and A. Cavazza in Reggio Emilia), a second MDA (using both TBLC and SLB results) was conducted (MDA2) for the final diagnosis and treatment decisions.

After MDA2, samples from TBLCs and SLBs were anonymized and read by an expert pathologist (T.V.C.) who was blinded to the preceding clinical course of events, the pairing of TBLC and SLB samples, and the pathological and MDA diagnoses at the respective sites. All slide interpretations

were performed according to identical reference criteria. Diagnoses were based on what was considered the most likely or most favored diagnosis solely on the basis of histopathology, and a differential diagnosis was not included.

The study was registered at clinicaltrials.gov (NCT02763540) and approved by the local independent ethics committee in France (Comité pour la Protection des Personnes Sud Méditerranée I; reference number: 15 98) and by the Ethical Committee of the S'Orsola-Malpighi Hospital in Bologna, Italy (Comitato Etico Indipendente dell'Azienda Ospedaliero-Universitaria di Bologna, Policlinico S'Orsola-Malpighi, reference number 70/2016/O/Sper).

Analyses

Statistics were performed in the R programming environment (12). Centrality was described as numbers followed by percentages for qualitative variables, means with their SD for quantitative variables deemed normal after a Shapiro-Wilks test, and medians with their interquartile ranges for other variables. Kappa-concordance coefficients and percentage agreement (both with their 95% confidence intervals [CIs]) were computed for TBLC versus SLB, MDA2 versus TBLC, MDA2 versus SLB, as well as between blinded and routine pathology reports. Quantitative variables were compared between biopsy procedures using paired *t* tests or paired Mann-Whitney tests, as appropriate.

Results

Description of the Population

Between January 2016 and March 2018, 62 patients with ILDs were prospectively screened at the two participating centers in France and Italy. Forty-one patients were excluded, as shown in Figure 1. A total of 21 patients for whom the MDA1 indicated that further lung histology was required were included in the study. Of note, of the 41 screened patients with ILD with an indication for histology during MDA1, 12 did not consent; in the remaining 29, the most common exclusionary criterion was an autoimmune process discovered in the meantime.

Individual patient characteristics are given in Table 1. Dyspnea was the referring symptom in 18 of 21 patients, whereas 3

were marginally dyspneic on exertion. Ten patients had weak titers of untypeable antinuclear/antineutrophil cytoplasmic antibodies or rheumatoid factor. Chronic cough (*n* = 14) and crackles (*n* = 15) were the most frequently reported “other” symptoms/signs. Gastroesophageal reflux was reported in 5 of 21 patients, with the final MDA2 diagnosis being idiopathic pulmonary fibrosis (IPF) in four of the latter patients and idiopathic nonspecific interstitial pneumonia (NSIP) in one (cases 2, 9, 10, 16, and 18, respectively). The descriptions of the corresponding HRCT patterns are also given in Table E1 in the online supplement. Biopsy samples were taken in two different lobes for both techniques. Side and lobe/segment selection was guided by chest HRCT scan findings.

The quality of TBLC tissue samples was judged good to excellent for most, as shown in Table E2. A total of 97 cryobiopsies (4.6/patient; median size [longest axis], 7 mm; interquartile range, 5–8 mm) and 42 surgical lung biopsies (mean ± SD for size: 46.1 ± 13.8 mm) were performed (Table E2). Cryobiopsies were performed in two different lobes, aiming for different segments within lobes, in all patients except two, where the TBLC procedure was performed in only one lobe (cases 1 and 18). One of the latter cases was due to moderate bleeding fully controlled via Fogarty balloon (case 1), and the other case was due to a tortuous bronchial anatomy of the upper right lobe, which did not enable TBLC performance under safe conditions (case 18).

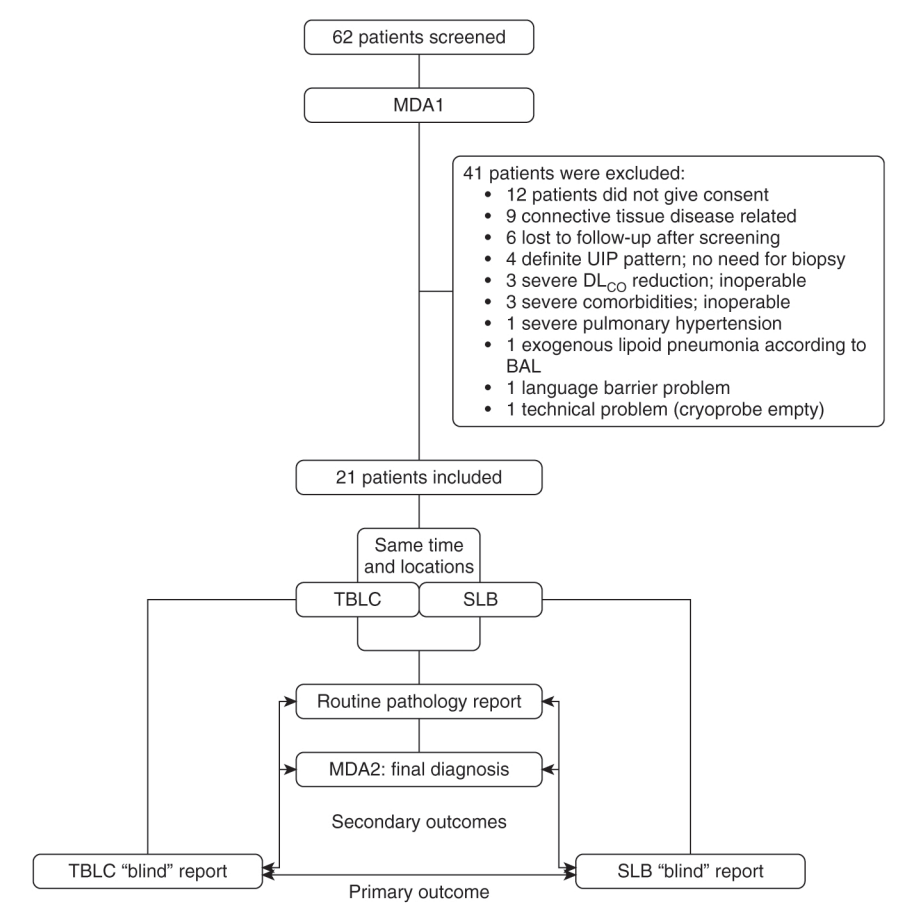


Figure 1. The study flowchart. Among 62 screened patients, 41 were excluded and 21 finally included in the study. After an initial multidisciplinary assessment meeting (MDA1), transbronchial lung cryobiopsies (TBLCs) and surgical lung biopsies (SLBs) were performed on all study participants and their results included in a routine pathology report. A second multidisciplinary assessment meeting (MDA2) was held to determine a final diagnosis. The primary outcome consisted in determining concordance between blinded TBLC and SLB results as well as between each type of biopsy and the MDA2 final diagnosis. UIP = usual interstitial pneumonia.

Table 1. Population Characteristics

	Population (N = 21)
Age, yr	65 (60–69)
Sex, male	10 (47.62)
FVC% predicted	80.05 ± 18.36
DL _{CO} % predicted	52.15 ± 15.87
Smoking status	
Never	7 (33.33)
Former	12 (57.14)
Current	2 (9.52)
Years smoking (former and current smokers only)	28.65 ± 12.38
Pack-years (former and current smokers only)	31.85 ± 21.26
Environmental factors	
Welder	1 (4.76)
Asbestos	2 (9.52)
Extrapulmonary signs	
Xerostomy	1 (4.76)
Raynaud phenomenon	1 (4.76)
Mycosis fungoides	1 (4.76)
HIV positivity	1 (4.76)
Relapsing pneumothorax	1 (4.76)
Other	
GERD	5 (23.81)
Cannabis consumer	1 (4.76)
Pneumothorax	1 (4.76)
Sibling received a lung transplant	2 (9.52)
Consanguinity, thalassemia	1 (4.76)

Definition of abbreviation: GERD = gastroesophageal reflux disease.
Descriptive statistics are presented as numbers (with percentages) for qualitative variables, mean ± SD for normally distributed (according to a Shapiro-Wilk test) variables, and median (interquartile range) for other variables.

The median total number of samples per procedure was five (interquartile range, 4–5; range, 2–6) for TBLC, and in all cases two for SLB (no variation for the surgical procedure).

Outcomes

The blinded assessment of histologic samples by the external expert pathologist (T.V.C.) indicated that TBLC and SLB histologic diagnoses were fully concordant for only 8 of 21 cases (with a percentage agreement of 38% [95% CI, 18–62%]), with a corresponding kappa-concordance coefficient of 0.22 (95% CI, 0.01–0.44) (Tables 2 and 3). For the remaining 13 cases, TBLC was not diagnostic for 4 of 21 cases (19%), despite good sample quality on average, whereas SLB was diagnostic in all cases. For the other nine cases (42.8%), TBLC and SLB showed several differences in elementary lesions and different final patterns (Table 2, including cases 1, 2, 6, 7, 10, 14, 15, 20). In these eight cases, the cryobiopsy diagnoses appreciably differed from those of SLB and final MDA2 diagnoses. Although some of this discrepancy is explainable on the basis of

overlap of histological features among entities (organizing pneumonia and NSIP or chronic hypersensitivity pneumonitis versus UIP in IPF, issues known to occur even in SLBs), the result of cryobiopsy alone would have led to a significantly different clinical diagnosis unless overridden by MDA. In case 21 (chronic lymphocytic leukemia vs. desquamative interstitial pneumonia), there appeared to be differential representation of lesions in the specimens, the significance of which could not be determined by histological evaluation alone, regardless of specimen type. In some cases, discrepancy was associated with low confidence in the histologic analysis of the samples, and the diagnosis rendered represented what was considered most likely from a list of several possibilities that explain some of the discordances. The UIP pattern was the most frequent pattern, occurring in SLB samples for eight cases, TBLC samples for nine cases, and both TBLC and SLB for only five cases (Table 2).

The kappa-concordance coefficient with the final diagnosis at MDA2 was 0.31 (95% CI, 0.06–0.56) for TBLC (a percentage

agreement of 48% [95% CI, 26–70%]), and 0.51 (95% CI, 0.27–0.75) for SLB (a percentage agreement of 62% [95% CI, 38–82%]) (Table 3). Representative CT scan images and histological slide photos together with the final MDA diagnosis for example concordant and discordant cases are given in Figure 2.

During MDA2, the final diagnosis was concordant with the pathological diagnosis in six (75%) of the eight cases where SLB and TBLC were concordant. In the 13 cases with discordant TBLC and SLB diagnoses, MDA2 was concordant with the TBLC diagnosis in three cases (23%) and with the SLB diagnosis in six (46%). In four cases, MDA2 was concordant with neither (Table 2).

Safety

The mean (±SD) duration of the two procedures was 33.29 ± 8.22 minutes for TBLCs versus 34.57 ± 15.65 minutes for SLBs (paired *t* test *P* = 0.737). The duration between the two procedures was less than 20 minutes for achieving the following sequence of events: rigid bronchoscope removal, reintubation with a two-lumen tube and test of mechanical ventilation with/without single lung exclusion, and installation in lateral decubitus. Only two serious adverse events were reported during the study, consisting of two pneumothoraces after TBLC, found at the VATS procedure (9.5%). The median bleeding volume during TBLC was 35 ml (interquartile range, 20–90 ml). Four cases of oxygen desaturation during surgery were observed: three for TBLC, with oxygen saturation as measured by pulse oximetry at 85%, 75%, and 76%; and one case for SLB with oxygen saturation as measured by pulse oximetry at 79%.

Discussion

This prospective clinical study directly compares the histological yield of TBLC versus video-assisted thoracoscopy SLB for patients with ILD requiring pathological classification. It demonstrates that TBLC and SLB are poorly concordant (with only 38% agreement [95% CI, 18–62%]) for the histologic diagnosis of ILDs when the specimens are reviewed in a blinded fashion for histologic diagnosis only, and that SLBs carry more weight for the final diagnosis, as decided during MDA. To our knowledge, this study is the first to present

Table 2. Blinded Histology and Multidisciplinary Diagnostic Results for each Patient

Patient	Diagnosis Based on Blinded TBLC Samples	Diagnosis Based on Blinded SLB Samples	Diagnosis Based on MDA1	Diagnosis Based on MDA2
1	OP	Subacute HP	NSIP	NSIP
2	UIP	CHP?	NSIP	IPF
3	UIP	UIP	Possible UIP pattern	CHP
4	Nondiagnostic	PLCH	DIP	PLCH
5	UIP	UIP	NSIP	IPF
6	UIP	CHP	NSIP	IPF
7	UIP	NSIP	No classification	NSIP
8	RB-ILD	RB-ILD	RB-ILD	RB-ILD
9	Nondiagnostic	UIP	NSIP	IPF
10	PLCH	UIP	Possible UIP pattern	IPF
11	NSIP	NSIP	Fibrotic NSIP	NOS
12	UIP	UIP	NSIP	IPF
13	Nondiagnostic	ALI	NSIP	NOS
14	NSIP	LP	Sarcoidosis	CVID
15	UIP	NSIP	NSIP	NSIP
16	Nondiagnostic	UIP	CHP	IPF
17	UIP	UIP	Possible UIP pattern	IPF
18	NSIP	NSIP	Possible UIP pattern	NSIP
19	UIP	UIP	Inconsistent UIP pattern	IPF
20	RB-ILD	NSIP	Inconsistent UIP pattern	RB-ILD
21	CLL	DIP	Inconsistent UIP pattern	DIP

Definition of abbreviations: ALI = acute lung injury (including diffuse alveolar damage and organizing pneumonia); CHP = chronic hypersensitivity pneumonitis; CLL = chronic lymphocytic leukemia; CVID = common variable immune deficiency; DIP = desquamative interstitial pneumonia; HP = hypersensitivity pneumonitis; IPF = idiopathic pulmonary fibrosis; LP = lymphoid process; MDA1 = first multidisciplinary assessment; MDA2 = final multidisciplinary assessment; NOS = not otherwise specified; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; SLB = surgical lung biopsy; TBLC = transbronchial lung cryobiopsy; UIP = usual interstitial pneumonia.

At the end of inclusions, SLB and TBLC slides were deidentified and sent to an expert pathologist for blinded interpretation, and a single, favored diagnosis provided. Diagnoses determined during MDA1 and then MDA2 multidisciplinary assessment meetings are also provided.

systematically paired, same-patient comparisons of TBLC and SLB assessed by a blinded external pathology expert. The kappa concordance coefficient between biopsy techniques was low (0.22; 95% CI, 0.01–0.44), indicating that TBLC cannot be

considered as a substitute for surgical lung biopsy. Furthermore, the final diagnosis at MDA2 agreed more with SLB than with TBLC results ($\kappa = 0.51$ [percentage agreement, 62%] compared with $\kappa = 0.31$ [percentage agreement, 48%]) (Table 3),

Table 3. Percentage Agreement and Kappa-Concordance Coefficients for Diagnostic Results after Pathological Review of Biopsy Specimens

Comparison	% Agreement (95% CI)	κ (95% CI)
TBLC vs. SLB	38 (18–62)	0.22 (0.01–0.44)
TBLC vs. MDA2	48 (26–70)	0.31 (0.06–0.56)
SLB vs. MDA2	62 (38–82)	0.51 (0.27–0.75)

Definition of abbreviations: CI = confidence interval; MDA2 = the final multidisciplinary assessment; SLB = surgical lung biopsy; TBLC = transbronchial lung cryobiopsy. Histological interpretations for TBLC and SLB specimens were performed by a blinded, external expert. The final diagnosis was determined during MDA2.

supporting a considerable difference in the diagnostic confidence accorded to SLB over TBLC.

Several previous studies support TBLC as a potentially systematic component of diagnostic histology for ILD (13–17). The purported advantages compared with SLB include a relatively high percentage of diagnostic yield combined with presumably less surgical risk and fewer adverse events (18, 19). Ravaglia and colleagues (16) stated that after the establishment of a definitive diagnosis via TBLC, “the subsequent performance of a surgical biopsy merely results in avoidable morbidity and mortality, without any added diagnostic value.” However, a growing body of literature has challenged the previous stance as well as the generalized confounding between diagnostic “agreement” versus “accuracy” present in the literature (20, 21). The only way to truly evaluate the diagnostic accuracy of TBLC was to perform both TBLC and SBL on the same patients (11) and to incorporate the findings into a multidisciplinary discussion (18, 21–23), as in this article.

Several elements from the literature support the primary result of this study. First, the diagnostic yields of TBLC lag behind those of SLB (23). Second, in a recent study the addition of TBLC histology led to a change in the initial clinical-radiologic diagnosis in 26% of cases, compared with 36% for SLB; simultaneously, 50% of TBLC cases received an IPF diagnosis versus only 39% for SLB, and interpathologist agreement was lower for TBLC than for SLB (18). All the latter confirm that the diagnostic yields from TBLC and SLB samples are not necessarily identical and that the diagnosis of IPF is more accurately made by SLB (21).

Our reported level of agreement between pathology reports (external blinded reports vs. local reports) remains highly variable, with kappa coefficient of 0.5 or less (Table 3), highlighting room for improvement in this domain, although this direct comparison could be questioned because the local pathology reports were not blinded and the TBLCs and SLBs were interpreted together in the local reports. Low rates of interexpert agreement are indeed well established in the literature (24). One study has suggested that, as far as TBLC is concerned, performing only one single tissue sampling in one lobe segment provides inferior results, as compared with

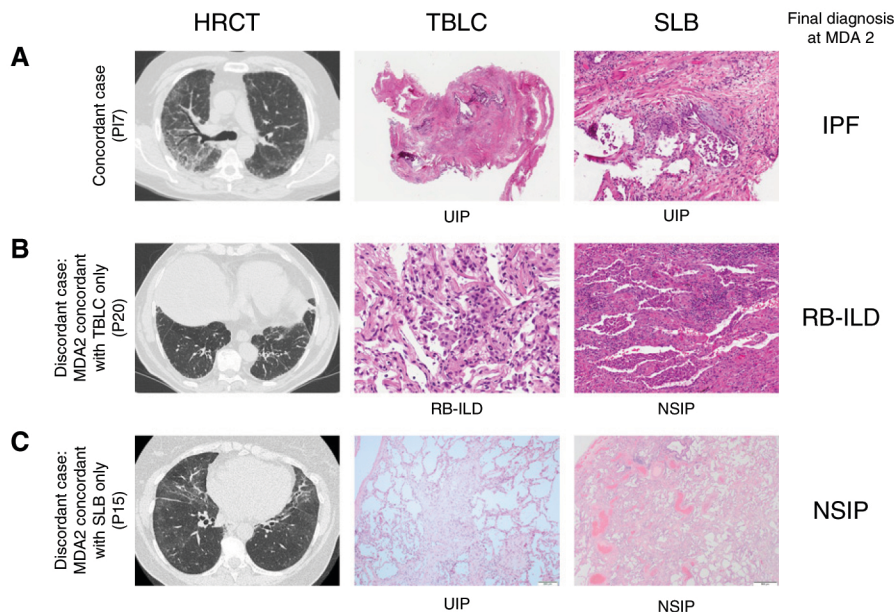


Figure 2. High-resolution computed tomography (HRCT), transbronchial lung cryobiopsy (TBLC), and surgical lung biopsy (SLB) image examples for (A) a completely concordant case with all diagnostic procedures in agreement, (B) a case of discordance between the final diagnosis determined during a multidisciplinary assessment meeting (MDA2) and SLB, and (C) a case of discordance between the MDA2 and TBLC. Preferred diagnoses are indicated as: IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease; UIP = usual interstitial pneumonia.

sampling at least two segments (16). As we took specific care to systematically cryosample in different lobes and different segments within lobes, this concern does not apply to our study. Variation can also arise from biopsy location, and the more central character of TBLC specimens might reduce their diagnostic value (20, 21). Cases 10 and 14 provide good examples of how tissues from the same patient can contain different elementary lesions (or lack thereof) that can imply different diagnoses. The most likely explanation for persistent lack of reproducibility of lung histology interpretation results is that the probability of observing known disease patterns is linked to biopsy size and the degree of lesion patchiness (10). In this study, we used the largest cryoprobe size (2.4 mm) available to maximize the cryosample dimensions. The resulting tissue sample sizes were comparable to other studies (17), with samples more than 0.5 cm in diameter, as recommended (25), and considered to be of good quality (Table E2). It is worth noting that our external expert pathologist (T.V.C.) assessed fully anonymized slides. This is artificial and far from the routine

pathological report built not only on biopsy findings but also on clinical and radiological information. In addition, our protocol allowed for only one diagnosis, irrespective of the level of confidence, whereas in practice multiple options can be proposed and ranked according to their level of likelihood (and the possibilities reassessed and discussed in MDA), and the final MDA aims at selecting the one that best fits clinical-radiologic observations.

Our diagnostic yield results are, finally, mostly in line with the literature, although higher than some reports. The cryobiopsies were nondiagnostic in 19% of cases, versus 0% for SLB (Table 2). However, only eight (out of 21; 38%) cases were fully concordant between TBLC and SLB. Of these, six were also concordant with the conclusion of the final MDA. The three-way (TBLC, SLB, and MDA2) concordance cases involved four UIP patterns, one respiratory bronchiolitis-associated ILD pattern, and one NSIP pattern. For the remaining cases, the type of discordance was variable (and case 5 could be considered having minor discordance), but SLB was clearly more informative than TBLC

(Table 2). For certain cases (e.g., 3, 4), just a bit more clinical/radiological detail would have sorted things out. Importantly, there are clearly cases where TBLC and SLB results correspond to different therapeutic strategies (Table E3) and likely survival expectations, which clearly is of great value for the affected patients. According to the pathology reports for anonymized slides, TBLC would have led to a different treatment if SLB was not performed in 11 of 21 (52%) cases (Table E3).

As concerns safety, only two cases (out of 21) of pneumothorax due to TBLC were noted at the beginning of the VATS procedure, which is comparable to previous studies (26). Other adverse events included one acute worsening of NSIP, although the onset of decline might have occurred before the procedure (increased ground-glass opacities at CT repeated the evening before the procedure compared with the HRCT discussed during initial MDA, 31 d before). One patient who had a pneumothorax was discharged after 10 days of pleural air-leak drainage. Finally, the TBLC procedure was not more rapid than SLB, and the latter allowed observation of almost systematic hematomas (peripheral to Fogarty balloon control) caused by the former. However, the strict selection criteria used should be kept in mind, as the outcomes reported here might not apply to excluded patients, such as patients with significant resting hypoxia while breathing air, decreased DL_{CO} below 35% predicted, and significant pulmonary hypertension. Longer-term complications attributable to TBLC were also impossible to capture in this study, because of the rapid, subsequent performance of SLB.

The limitations of this study include a small sample size. Performing both TBLC and SLB on the same patients was quite complex to organize, and recruitment was challenging (*see* screening losses in Figure 1). Poor feasibility and/or ethics concerns are cited as substantial implementation barriers by other teams (16, 20) and probably explain why our study is the only one of its kind so far. Nevertheless, further, larger studies would reinforce the generalizability of the findings. Two ethics committees approved our protocol without any major concerns, with the exception of one constraint (i.e., that TBLC be performed just before VATS to minimize the risk of pneumothorax). This may represent a

further limitation: if there was no subsequent SLB, the operator might be inclined to more aggressive TBLC sampling to maximize sample quality/extent. However, because our sample sizes/numbers (Table E2) are comparable to other TBLC studies, we do not believe this type of bias affected our study.

Another potential limitation is the fact that the diagnoses from blinded review frequently represented the “mostly likely” at the top of a differential, and MDA discussion might have led to reassessment of the histologic diagnosis, especially in those cases in which a minor discordance was present. In addition, the blinded reviewer had access to full slides and could thus deduce which were TBLC and which were SLB, but not the pairing between them. Finally, the patients involved are highly selected, already difficult cases, and

diagnostic histology in this domain is notoriously arduous. Pending disease-specific diagnostic innovations that move us beyond visual histology pattern interpretation, the reader should keep in mind that interexpert concordance in this difficult domain is generally low (24), and there is much still to accomplish in this challenging field.

In conclusion, this prospective study comparing blinded intrapatient TBLC and SLB tissue samples for the evaluation of ILD for the first time demonstrates poor concordance in terms of pathology results between the two sampling procedures. Although TBLC has been demonstrated to exceed traditional forceps transbronchial biopsy for obtaining useful histological information (27), it falls short of SLB (25) and should not be considered as equal to a surgical lung biopsy under VATS

technique. When the clinical and radiological contexts are not provided to the pathologist as imposed by the design of this study, our results indicate that there is no role for TBLC in the vast majority (two-thirds) of patients where histopathology is required for definitive diagnosis of diffuse ILDs. Reintegrating these data into the full context of routine practice may change these outcomes. Nonetheless, we believe that patients who are able to undergo SLB should be recommended to do so. For those patients in unacceptable condition for SLB, the trade-off between the supposed lower risks associated with TBLC and the case-specific consequences of diagnostic uncertainty require careful consideration.

References

- Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, *et al.*; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188:733–748.
- King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, *et al.*; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–2092.
- Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, *et al.*; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
- Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al.*; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis. Evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
- Miller JD, Urschel JD, Cox G, Olak J, Young JE, Kay JM, *et al.* A randomized, controlled trial comparing thoracoscopy and limited thoracotomy for lung biopsy in interstitial lung disease. *Ann Thorac Surg* 2000;70:1647–1650.
- Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States: 2000 to 2011. *Am J Respir Crit Care Med* 2016;193:1161–1167.
- Griff S, Ammenwerth W, Schönfeld N, Bauer TT, Mairinger T, Blum T-G, *et al.* Morphometrical analysis of transbronchial cryobiopsies. *Diagn Pathol* 2011;6:53.
- Berbesu EA, Katzenstein A-LA, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. *Chest* 2006;129:1126–1131.
- Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, *et al.* Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. *Chest* 2017;151:389–399.
- Lentz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F. Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *J Thorac Dis* 2017;9:2186–2203.
- Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al.*; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–e68.
- R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016 [accessed 2019 Apr 12]. Available from: <https://www.R-project.org/>.
- Casoni GL, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, *et al.* Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014;9:e86716.
- Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, *et al.* Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure. *Respiration* 2018;95:188–200.
- Sriprasart T, Aragaki A, Baughman R, Wikenheiser-Brokamp K, Khanna G, Tanase D, *et al.* A single US center experience of transbronchial lung cryobiopsy for diagnosing interstitial lung disease with a 2-scope technique. *J Bronchology Interv Pulmonol* 2017;24:131–135.
- Ravaglia C, Wells AU, Tomassetti S, Dubini A, Cavazza A, Piciucchi S, *et al.* Transbronchial lung cryobiopsy in diffuse parenchymal lung disease: comparison between biopsy from 1 segment and biopsy from 2 segments: diagnostic yield and complications. *Respiration* 2017;93:285–292.
- Iftikhar IH, Alghothani L, Sardi A, Berkowitz D, Musani AI. Transbronchial lung cryobiopsy and video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse parenchymal lung disease: a meta-analysis of diagnostic test accuracy. *Ann Am Thorac Soc* 2017;14:1197–1211.
- Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, *et al.* Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:745–752.
- Kronborg-White S, Folkersen B, Rasmussen TR, Voldby N, Madsen LB, Rasmussen F, *et al.* Introduction of cryobiopsies in the diagnostics of interstitial lung diseases: experiences in a referral center. *Eur Clin Respir J* 2017;4:1274099.
- Raparia K, Aisner DL, Allen TC, Beasley MB, Borczuk A, Cagle PT, *et al.* Transbronchial lung cryobiopsy for interstitial lung disease diagnosis: a perspective from members of the pulmonary pathology society. *Arch Pathol Lab Med* 2016;140:1281–1284.

21. Patel NM, Borczuk AC, Lederer DJ. Cryobiopsy in the diagnosis of interstitial lung disease: a step forward or back? *Am J Respir Crit Care Med* 2016;193:707–709.
22. Johannson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease: a systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13: 1828–1838.
23. Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciucchi S, *et al.* Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration* 2016;91:215–227.
24. Walsh SLF, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, *et al.* Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. *Lancet Respir Med* 2016;4:557–565.
25. Colby TV, Tomassetti S, Cavazza A, Dubini A, Poletti V. Transbronchial cryobiopsy in diffuse lung disease: update for the pathologist. *Arch Pathol Lab Med* 2017;141:891–900.
26. Cooley J, Balestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasart T, Swank Z, *et al.* Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. *Respir Med* 2018;140:71–76.
27. Pajares V, Puzo C, Castillo D, Lerma E, Montero MA, Ramos-Barbón D, *et al.* Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology* 2014;19:900–906.