CHEST

Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Disease

Retrospective Analysis of 74 Cases

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BACKGROUND: Diagnostic evaluation of patients with diffuse parenchymal lung disease (DPLD) is best achieved by a multidisciplinary team correlating clinical, radiological, and pathologic features. Surgical lung biopsy remains the gold standard for histopathologic diagnosis of idiopathic interstitial pneumonias. Emerging data suggest an increasing role for transbronchial cryobiopsy (TBC) in DPLD evaluation. We describe our experience with TBC in patients with DPLD.

METHODS: We retrospectively reviewed medical records of patients with radiographic features of DPLD who underwent TBC at Mayo Clinic in Rochester, Minnesota from June 2013 to September 2015.

RESULTS: Seventy-four patients (33 women [45%]) with a mean age of 63 years (SD, 13.8) were included. The mean maximal diameter of the samples was 9.2 mm (range, 2-20 mm [SD, 3.9]). The median number of samples per procedure was three (range, one to seven). Diagnostic yield was 51% (38 of 74 specimens). The most frequent histopathologic patterns were granulomatous inflammation (12 patients) and organizing pneumonia (OP) (11 patients), resulting in the final diagnoses of hypersensitivity pneumonitis (six patients), cryptogenic OP (six patients), connective tissue disease-associated OP (three patients), drug toxicity (three patients), infection-related OP (two patients), sarcoidosis (two patients), and aspiration (one patient). Other histopathologic patterns included respiratory bronchiolitis (three patients), acute fibrinous and organizing pneumonia (two patients), desquamative interstitial pneumonia (1 patient), diffuse alveolar damage (one patient), pulmonary alveolar proteinosis (one patient), amyloidosis (one patient), eosinophilic pneumonia (one patient), necrotizing vasculitis (one patient), bronchiolitis with food particles (one patient), and malignancy (three patients). Pneumothorax developed in one patient (1.4%), and bleeding occurred in 16 patients (22%).

CONCLUSIONS: Our single-center cohort demonstrated a 51% diagnostic yield from TBC; the rates of pneumothorax and bleeding were 1.4% and 22%, respectively. The optimal use of TBC needs to be determined. CHEST 2017; 151(2):400-408

KEY WORDS: cryobiopsy; diffuse parenchymal lung disease; lung

ABBREVIATIONS: ANCA = antineutrophil cytoplasmic antibodies; CVID = common variable immunodeficiency; DPLD = diffuse parenchymal lung disease; HP = hypersensitivity pneumonitis; IIP = idiopathic interstitial pneumonia; MDD = multidisciplinary diagnosis; OP = organizing pneumonia; TBC = transbronchial cryobiopsy; UIP = usual interstitial pneumonia

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Diffuse parenchymal lung disease (DPLD) comprises a group of varied processes, which range from acute inflammatory disorders to progressive fibrotic conditions.[1,2] The evaluation of patients with DPLD is best achieved by a multidisciplinary approach combining clinical, radiological, and pathologic features. Surgical lung biopsy may be necessary for a confident clinicopathologic diagnosis in the case of atypical features, despite the risk for serious complications, including acute exacerbation and death.[1,3] Transbronchial lung biopsy is not currently recommended when attempting to histologically confirm idiopathic interstitial pneumonia (IIP)—for example, usual interstitial pneumonia (UIP)—due to its low diagnostic yield.[1,2,4]

Flexible cryoprobes inserted through a bronchoscope are used with increasing frequency to diagnose and manage central airway lesions.[5] Transbronchial cryobiopsy (TBC) has been used more recently for the assessment of parenchymal lung diseases. The major advantage of TBC is larger tissue samples with a higher percentage of alveolar tissue,[6-10] with fewer crush artifacts and less atelectasis.[8-10] The increased tissue volume with a greater portion of alveolar tissue correlates with a better diagnostic yield.[7,11] The downside is the potential for bleeding complications and the high pneumothorax rates (up to 28%), often requiring inpatient admission and chest tube drainage.[6-9,11,12] The role of TBC in the investigation of DPLD is still not well established.

The purpose of this study was to describe our experience with TBC in patients with DPLD at Mayo Clinic in Rochester, Minnesota and compare it with previous studies. We also evaluated the efficacy of TBC in achieving a diagnosis that resulted in a meaningful change in patient management.

Methods

The study was approved by the Mayo Clinic Institutional Review Board (IRB 15-008652). We conducted a retrospective review of the clinical records of patients with DPLD from June 2013 to September 2015 at the Mayo Clinic in Rochester, Minnesota. Over the period examined, 200 cryobiopsies in 187 patients were performed at our institution. The medical records were analyzed, and demographic data, chest CT scans, procedure details and complications, diagnostic results, and pathologic features were recorded.

The indication for TBC was diffuse pulmonary infiltrates of unclear cause. We excluded the 113 patients who required cryosurgical techniques for other indications (eg, airway lesions). All cryobiopsies of lung allografts in lung transplant recipients were also excluded. The request to use cryobiopsy was made by the referring pulmonologist. The proceduralist then made the determination whether to proceed with cryobiopsy or conventional transbronchial biopsy.

Transbronchial Cryobiopsy

The patients were fiberoptically intubated with an 8.0-mm cuffed endotracheal tube using moderate to deep sedation in the bronchoscopy suite. We routinely placed a deflated 7F or 9F Arndt bronchial blocker (Cook Medical) external to the tube in the mainstem bronchus on the side chosen for biopsy to occlude the airway in case of bleeding.[13] The guide loop of a lubricated and deflated Arndt bronchial blocker was secured around the distal tip of the bronchoscope. The patient was intubated, with the bronchial blocker riding alongside the bronchoscope. Once the bronchial blocker was directed into the mainstem bronchus on the side to be biopsied, the guide loop was loosened, releasing it from the bronchoscope, where it remained in position.[13] We advanced the bronchial blocker as close to the opening of the biopsied segment as possible. In patients with advanced pulmonary disease, we blocked the entire lung that was planned for biopsy for approximately 1 min before performing the biopsy to ensure that the patient could tolerate single-lung ventilation in the event of a severe bleeding episode or pneumothorax. All anticoagulants were discontinued before the procedure per guidelines.[14] The bronchoscope (Olympus XT180) was advanced to the segment chosen for biopsy. The Erbe 1.9-mm cryoprobe (Erbe Elektromedizin GmbH) was introduced through the working channel of a flexible bronchoscope and passed into the distal airways under fluoroscopic guidance. The regions that appeared to have the most active disease underwent biopsy, depending on the clinical indication. If chest CT scans showed ground-glass opacities, a biopsy of that particular area was attempted. The cryoprobe was cooled for 3 to 5 s at the desired location and firmly pulled back, separating the frozen biopsy sample from the lung. The bronchial blocker balloon was usually inflated as the bronchoscope and cryoprobe were removed as a single unit. The tip of the cryoprobe was submerged in saline at room temperature to thaw the specimen, which was transferred to formalin. We often inflated the balloon prophylactically to prevent any potential blood from spilling into the airway while the specimen thawed from the tip of the probe. A biopsy was performed on only one side per patient, and three cryobiopsy samples were generally obtained from one to two lobes. The balloon was deflated once the bronchoscope was back in the airway and bleeding was assessed.

Complications

Mild bleeding was defined as bleeding that was easily controlled with suction only. Moderate bleeding was defined as the need to inflate or reinflate the endobronchial blocker, with or without the need for additional interventions. Severe bleeding was defined as any life-threatening bleeding requiring transfusion or escalation of care such as admission to the ICU or surgery consultation.[15]

Statistical Analysis

Descriptive statistics were used to analyze patient characteristics. Normally distributed continuous data were described as means and SD. The categorical variables were reported in percentages of total subjects. The data were analyzed using SPSS software, version 16 (SPSS, Inc.)

Results

Seventy-four patients were included in the study cohort: 33 were women (45%), with a mean age of 63 years (range, 20-89 years [SD, 13.8]) (Table 1). The mean maximal diameter of samples was 9.2 mm (range, 2-20 mm [SD, 3.9]). Most of the patients (59 patients) had biopsy samples obtained from one lobe; the remaining 15 patients had biopsy samples obtained from two lobes. The median number of samples per procedure was three (range, one to seven). Histologic slides were available for review by a pulmonary pathologist in 69 cases. The presence of small airways was observed in 49 cases (66%), components of a large airway were seen in 35 cases (47%), and alveolar tissue was present in 68 cases (92%).

Thirty-three patients (45%) underwent echocardiography before the procedure. The mean right ventricular systolic pressure was 35 mm Hg (range, 18-49 mm Hg [SD, 6.9]).

Correlation of clinical, radiological, and histopathologic findings yielded a definite multidisciplinary diagnosis (MDD) in 51% of subjects (38 of 74 patients). The most frequent histopathologic diagnoses were granulomatous inflammation (12 patients) and organizing pneumonia (OP) (11 patients), resulting in the final diagnoses of hypersensitivity pneumonitis (HP) (six patients), cryptogenic OP (six patients), connective tissue disease-associated OP (three patients), infection-related OP (two patients), drug toxicity (three patients), sarcoidosis (two patients), and aspiration (one patient). Other histopathologic diagnoses and MDDs are listed in Table 2. There were no subsequent surgical lung biopsy procedures in this group. The clinical course was consistent with the MDD.

Thirty-six cases (49%) had nonspecific histopathologic findings or discrepancies between the histopathologic diagnosis and the MDD, as shown in Table 3. Of these patients, 31 had nondiagnostic biopsy results despite adequate lung parenchyma. The remaining five patients had histopathologic diagnoses of extensively necrotic unclassified neoplasm (one patient), respiratory bronchiolitis (one patient), emphysema (one patient), perivascular fibrosis (one patient), and chronic bronchiolitis with lymphocytic inflammation (one patient), but they were discordant with the clinical diagnoses (Table 3). The first two of these five patients underwent surgical lung biopsies that resulted in a specific diagnosis of lymphomatoid granulomatosis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, respectively.

Of those patients with nondiagnostic biopsies (31 patients), the specific diagnosis or possible diagnosis was established by a multidisciplinary approach in 20 patients. Five patients from this group underwent surgical lung biopsies that revealed UIP (two patients), HP (one patient), HP with UIP (one patient), and granulomatous inflammation associated with common variable immune deficiency (CVID) (one patient).

Among the 36 patients who had nonspecific histopathologic findings (31 patients) or discrepancies between clinical and histopathologic diagnoses (five patients), the diagnoses remained unclear in eight patients (11% of entire cohort); these patients refused surgical lung biopsy, preferring observation (Fig 1).

TABLE 1] Baseline Characteristics of the Patients

Variable (N = 74)	No.
Age at diagnosis, mean (SD), y	63 (13.8)
Sex, female (%)	33 (45)
No. of specimens per procedure (N = 74), median (range, SD)	3 (1-7, 1.1)
Diameter (n = 72), mean (range, SD), mm	9.2 (2-20, 3.9)
No. of small airways per biopsy (n = 69)[a], mean (range, SD)	0.9 (0-3, 0.8)
No. of large airways per biopsy (n = 69)[a], mean (range, SD)	0.8 (0-4, 1.0)
Presence of alveoli (n = 69)[a]	68 (92%)

[a]Cryobiopsy samples were available for review in 69 subjects.

Complications

Bleeding complications were observed in 16 cases (22%); seven patients had mild bleeding, and nine patients had moderate bleeding requiring inflation of the bronchial blocker. One patient was discharged after bronchoscopy but was later readmitted with recurrent hemoptysis for observation. This patient was hemodynamically stable and did not need additional intervention.

Pneumothorax developed in one patient (1.4%) after eight attempts, and four cryobiopsy samples were obtained from multiple regions in the right lower lobe.

TABLE 2] Diagnoses Obtained From Transbronchial Cryobiopsy

Histopathologic Diagnosis (n = 38)	Multidisciplinary Diagnosis
Nonnecrotizing granulomatous inflammation (12 patients)	Hypersensitivity pneumonitis (6 patients) Drug toxicity (3 patients) Sarcoidosis (2 patients) Aspiration (1 patient)
Organizing pneumonia (11 patients)	Cryptogenic organizing pneumonia (6 patients) Connective tissue disease associated (3 patients) Infection-related organizing pneumonia (2 patients)
Respiratory bronchiolitis (3 patients)	Respiratory bronchiolitis/interstitial lung disease
Acute fibrinous and organizing pneumonia (2 patients)	Infection related (1 patient) Graft vs host disease (1 patient)
Diffuse alveolar damage (1 patient)	Idiopathic pulmonary fibrosis with acute exacerbation
Desquamative interstitial pneumonia (1 patient)	Desquamative interstitial pneumonia
Necrotizing granulomatous inflammation (1 patient)	Granulomatosis with polyangiitis
Eosinophilic pneumonia (1 patient)	Chronic eosinophilic pneumonia
Pulmonary alveolar proteinosis (1 patient)	Pulmonary alveolar proteinosis
Amyloidosis (1 patient)	Pulmonary amyloidosis
Lymphoma (2 patients)	Lymphoma
Invasive mucinous adenocarcinoma (1 patient)	Invasive mucinous adenocarcinoma
Bronchiolitis with food particles (1 patient)	Aspiration

The patient experienced mild bleeding and was hospitalized for 3 days and required pigtail catheter placement for the treatment of pneumothorax.

Mild pneumomediastinum without concomitant pneumothorax occurred in one patient (1.4%) after cryobiopsy specimens were obtained from the lingula and anterior and lateral and posterior segments of the left lower lobe. No therapeutic intervention was needed for the management of this patient.

One patient tolerated the procedure well without immediate postprocedure complications, but this patient experienced a pulmonary abscess in a segment that had previously undergone biopsy 2 weeks after the bronchoscopy.[16] This patient was treated with systemic antibiotics and had complete resolution of symptoms without further invasive procedures or treatment. There was no mortality associated with the procedures.

Discussion

The role of TBC in DPLD evaluation is still evolving. Previous studies from multiple centers have demonstrated the feasibility of the technique,[6-9,11,12,17-20] but there is a lack of consensus on the indications, contraindications, and diagnostic accuracy. Thus, its role remains controversial.

Our study demonstrated a diagnostic yield of 51% when a positive biopsy result was defined as diagnostic histologic findings, histologic findings that supported a final diagnosis, or histologic findings consistent with the final diagnosis.[21] The diagnostic yield of cryobiopsies was generally lower than that previously reported. The diagnostic yield varied between studies from 70% to 95% with a 2.4-mm probe[7-9,11,12,20] and 79% to 80% with a 1.9-mm probe.[6,17,19] One possible explanation is that the mean diameter of samples obtained might have been smaller than that reported in previous studies, as more alveolar tissue correlates with a better diagnostic yield.[7,11] This likely relates to differing techniques, including shorter freeze times and use of the smaller 1.9-mm probe as opposed to the 2.4-mm probe. The optimal tissue yield with the fewest procedure-related risks needs to be determined. The previous studies of TBC in the DPLD population are summarized in Table 4. The literature search was limited to English-language publications.

The use of TBC appears attractive in the evaluation of patients with DPLD. Previous studies have indicated that TBC has a role in the diagnosis of IIP. Conventional transbronchial biopsy has been reported to identify 9% to 30% of UIP cases,[22-24] whereas cryobiopsy can identify 9% to 75% of these cases.[6-9,11,17] The frequency of a UIP pattern among these studies varied widely,

TABLE 3] Nondiagnostic Biopsy Results and Diagnosis After Multidisciplinary Review

Histopathologic Diagnosis	No. of Patients (N = 36)	Multidisciplinary Diagnosis
Alveolated lung parenchyma with mild interstitial chronic inflammation	12	Unclear (3 cases) Possible IPF (1 case) Connective tissue disease-associated (1 case) HP (2 cases) IgG4 disease (1 case) Post-irradiation fibrosis (1 case) Granulomatous inflammation associated with CVID (1 case, surgical biopsy) UIP (1 case, surgical biopsy) HP (1 case, surgical biopsy)
Alveolated lung parenchyma with mild interstitial chronic inflammation Interstitial fibrosis	8	IPF (4 cases) IPF/HP (1 case) Familial pulmonary fibrosis (1 case) Unclear (1 case) HP with UIP (1 case, surgical biopsy)
Alveolated lung parenchyma with mild interstitial chronic inflammation Organizing pneumonia	2	Unclear (1 case) UIP (1 case, surgical biopsy)
Alveolated lung parenchyma with mild interstitial chronic inflammation Elevated eosinophil levels	2	Rheumatoid arthritis related (1 case) Unclear, sarcoidosis/HP (1 case)
Mild cellular interstitial pneumonia	1	Aspiration NTM infection
Patchy interstitial thickening due to mild interstitial chronic inflammatory infiltrates	1	Drug related
Alveolated lung parenchyma without specific abnormalities	5	HP (2 cases) Aspiration/BOS (1 case) Drug related/amyloidosis (1 case) Resolved eosinophilic pneumonia (1 case)
Extensively necrotic neoplasm	1	Lymphomatoid granulomatosis (1 case, surgical biopsy)
Respiratory bronchiolitis	1	ANCA-associated vasculitis (1 case, surgical biopsy)
Emphysema	1	Possible HP
Perivascular fibrosis	1	Unclear
Chronic bronchiolitis and interstitial lymphocytic infiltrates	1	Unclear Steroid responsive

ANCA = antineutrophil cytoplasmic antibodies; BOS = bronchiolitis obliterans syndrome; CVID = common variable immunodeficiency; HP = hypersensitivity pneumonitis; IgG4 = immunoglobulin G4; IPF = idiopathic pulmonary fibrosis; NTM = nontuberculous mycobacterial; UIP = usual interstitial pneumonia.

depending on the study population, number of patients, and experience of the bronchoscopists and pathologists.

As expected, our series identified the disorders that are centered on terminal and respiratory bronchioles or distributed along the lymphatic routes, such as OP, HP, and sarcoidosis. In contrast to previous studies,[6-9,11,17] our series failed to demonstrate the specific histopathologic patterns of UIP or nonspecific interstitial pneumonia. Selection bias likely played a role in this regard, as the clinicians might not have expected TBC to be adequate in diagnosing these patterns and were more likely to offer surgical lung biopsy to such patients. In addition, biopsy technique likely played a role; more peripheral placement of a larger cryoprobe with longer freezing time would have yielded a higher rate of a UIP diagnosis at the cost of increased pneumothorax (up to 33%) and bleeding rates.

The prevalence of conventional transbronchial biopsy specimens yielding nonspecific inflammation and

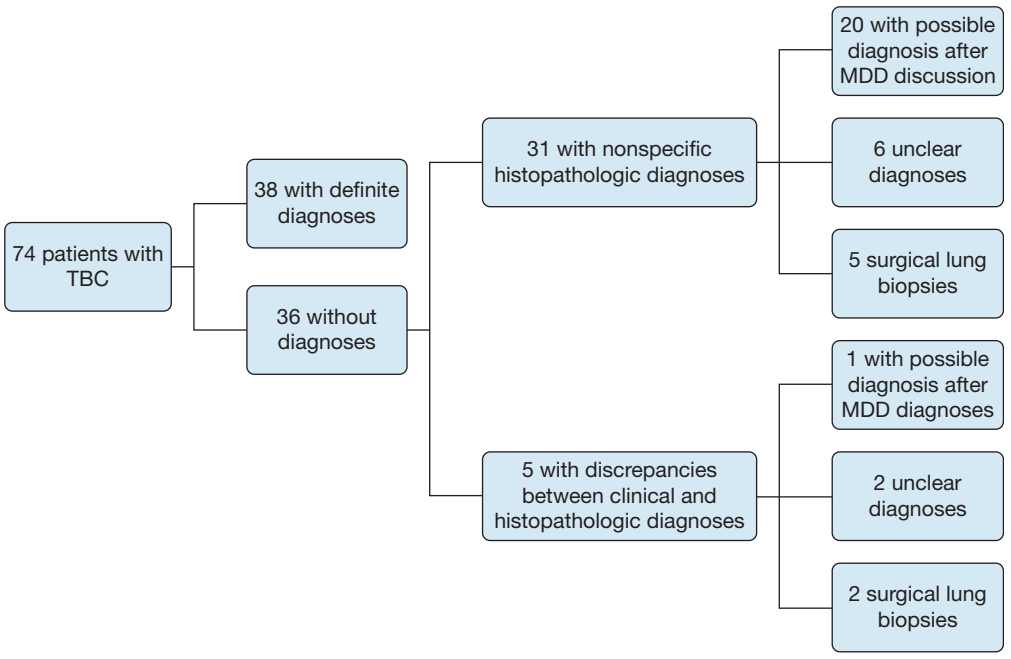

Figure 1 – *Results of transbronchial cryobiopsy interpretation after multidisciplinary discussion. MDD = multidisciplinary diagnosis; TBC = transbronchial cryobiopsy.*

fibrosis has varied from 21% to 48% in prior studies.[25] A previous report from our center described nonspecific inflammation, interstitial thickening, chronic interstitial pneumonitis, nonspecific fibrosis, or pulmonary parenchyma without diagnostic abnormalities in 31% of forceps biopsies (199 of 651 procedures).[21,26] In that study, lung parenchyma was obtained in 92% of biopsies, and "clinically useful histopathologic diagnoses" were attained in 38.2% of the procedures compared with 92% and 52% in the current study, respectively. The current study using TBC surprisingly included a high proportion (42% [31 of 74]) of biopsy specimens demonstrating nonspecific inflammation, fibrosis, or no specific abnormalities. The number of patients and the specific DPLD population undergoing TBC may explain the higher percentage of nonspecific findings. When introducing TBC into our practice, the histopathologic findings were considered helpful in 78% of the biopsies (58 of 74) based on a multidisciplinary approach. The recent study supported the impact of TBC on the MDD process, as the interpretation of TBC increased the diagnostic confidence level in the diagnosis of idiopathic pulmonary fibrosis.[27]

The clinical diagnosis of IIP can be challenging in real clinical practice. The certainty of a diagnosis depends on multiple factors, as the level of agreement between radiologists and pathologists is variable. Reported interobserver agreement between pathologists from multiple series was fair, with a mean kappa coefficient of 0.3 (0 indicating only chance agreement and 1 perfect agreement).[28,29] Tomassetti et al[27] reported that pathologists were less confident in their independent interpretation of TBC compared with surgical lung biopsy, as shown by the higher prevalence of UIP high-confidence diagnoses (85% compared with 52% with TBC) and higher interobserver agreement (0.86 compared with 0.59 with TBC) with surgical lung biopsy. Nevertheless, TBC and surgical lung biopsy had similar impact on the final diagnosis after integration into the MDD discussion.[23] Furthermore, distinguishing a UIP or nonspecific interstitial pneumonia pattern is sometimes difficult, as interlobar histologic variability is common in IIP.[30] Studies of diagnostic accuracy in idiopathic pulmonary fibrosis are performed mostly in tertiary centers. Even in referral centers, however, significant interobserver variability exists.[28]

The decision to perform TBC is often based on clinician or bronchoscopist preference. The advantage of TBC regarding the size and histologic quality of specimens was recognized in multiple series, indicating that it might be able to replace surgical lung biopsy in many cases of DLPD.[6-11,31] Using cryobiopsy, we can obtain better histologic data regarding sample size and quality

TABLE 4] Studies of Transbronchial Cryobiopsy in Patients With Diffuse Parenchymal Lung Diseases

Study/Year	Study Design	Cryoprobe Diameter, mm	No. of Patients	Diagnostic Yield, %	Most Frequent Diagnoses, No.	Size of Specimens	Complications	Deaths
Current study	Retrospective	1.9	74	51	Granulomatous inflammation, 12; OP, 11	Diameter 9 ± 4 mm	Pneumothorax, 1.4%; bleeding, 22%	None
Tomassetti et al[27]/2016	Retrospective	2.4	58	91	UIP, 40; NSIP, 7	NA	Pneumothorax, 33%; "severe" bleeding, 0%	1.7%; in patient with acute exacerbation of IPF
Ravaglia et al[18]/2016	Retrospective, TBC vs SLB	2.4	447 total; 297 TBC, 150 SLB	82.8 for TBC vs 98.7 for SLB	UIP, 92; OP, 31; NSIP, 25; nondiagnostic, 51	NA	Pneumothorax, 20%; bleeding, 0%; transient respiratory failure, 0.7%	0.3%; in patient with acute exacerbation of IPF
Pourabdollah et al[20]/2016	Prospective, forceps followed by TBC	2.4	41	77.5	Granulomatous inflammation, 16	Area, 22 ± 19.1 mm^2	NA	NA
Hernandez-Gonzalez[19]/2015	Retrospective, TBC	1.9	33	79	UIP/probable UIP, 7; Non-UIP, 19	Diameter, 4 ± 1.7 mm	Pneumothorax, 12%; bleeding, 30%	None
Hagmeyer et al[12]/2015	Pooled prospective and retrospective	NA	51	75	NSIP, 14; UIP, 13; OP; 5	NA	Pneumothorax, 26%; bleeding, 78% in prospective cohort	1.9%; 1 patient with acute exacerbation of IPF
Pajares et al[9]/2014	Randomized controlled; forceps vs TBC	2.4	77; 38 forceps, 39 TBC	74.4	NSIP, 12; UIP, 7	Area, 14.7 ± 11 mm^2	Pneumothorax, 7.7%; bleeding, 56.4%	None
Griff et al[17]/2014	Retrospective	1.9	52	79	UIP, 10; sarcoidosis, 10; OP, 8; HP, 6	Diameter, 6.9 ± 4.4 mm	None	None
Casoni et al[11]/2014	Prospective	2.4	69	93	UIP, 47; NSIP, 9; not diagnostic, 5	Area, 43.11 mm^2 (11.94-76.25 mm^2)	Pneumothorax, 28%; bleeding, 1.4%	1.4%; in patient with acute exacerbation of IPF, massive pneumothorax

(Continued)

TABLE 4] (Continued)

Study/Year	Study Design	Cryoprobe Diameter, mm	No. of Patients	Diagnostic Yield, %	Most Frequent Diagnoses, No.	Size of Specimens	Complications	Deaths
Fruchter et al[8]/2014	Retrospective	2.4	75	70	NSIP, 21; OP, 11; UIP, 7	Area, 9 mm^2 (6-18 mm^2)	Pneumothorax, 2.6%; bleeding, 4%	None
Kropski et al[6]/2013	Retrospective	1.9	25	80	UIP, 7; non-UIP, 12; normal, 1	Area, 64.2 mm^2 (1.5-136.7 mm^2)	None	None
Babiak et al[7]/2009	Retrospective; forceps followed by TBC	2.4	41	95	UIP, 15; NSIP, 10; sarcoidosis, 6; HP, 3; DIP, 3[a]	Area, 15.11 mm^2 (2.15-54.15 mm^2)	Pneumothorax, 4.9%; bleeding, 0%	None

DIP = desquamative interstitial pneumonia; IIP = idiopathic interstitial pneumonia; NA = not available; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; SLB = surgical lung biopsy; TBC = transbronchial cryobiopsy. See Table 3 legend for expansion of other abbreviations.

compared with conventional transbronchial biopsy, but this still may not be sufficient to reach a diagnosis by MDD if there is disagreement among clinicians, radiologists, and pathologists, and pathognomonic histopathologic findings are lacking. The result or benefit of TBC might not be applicable to all patients or all centers, and therefore the decision should be based on local expertise, clinical practice patterns, and multidisciplinary discussion.

The current study observed high rates of bleeding complications, but they were generally manageable. We now preemptively place a bronchial blocker for safer performance of TBC and inflate the balloon prophylactically to create a tamponade effect and to prevent spillage of blood into the remaining airway if bleeding occurs. Our center previously reported more procedural complications in association with cryobiopsies than conventional biopsies in patients with lung allografts, although the difference was not statistically significant (cryobiopsy, 7 of 27 patients vs conventional biopsy, 4 of 27 patients; $P = .25$).[32] Delayed complications after TBC, including delayed bleeding, pneumothorax, and lung abscess, can occur, and these patients should be informed and monitored accordingly. The long-term morphologic complications of larger defects in the lung parenchyma and repeated cryobiopsy procedures remain to be clarified.

The main limitation of this study was its retrospective design at a single center. Other limitations include the relatively small number of patients and the lack of surgical lung biopsy confirmation for only a minority of study subjects. Referral bias was another important consideration in the current study, because the cases identified from the specialized center tended to have complex presenting features that could have affected the diagnostic yield and decision for subsequent surgical lung biopsy.

Conclusions

Our single-center cohort demonstrated a 51% diagnostic yield from TBC, which was lower than that of previously published data from other centers. Nevertheless, it was considered helpful in 78% of patients when histopathologic data were integrated with clinical-radiological data in a multidisciplinary approach. Potential bleeding, pneumothorax, and delayed complications remain a concern. Optimal patient selection and the technique of TBC still need to be determined.

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Author contributions: K. U. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. K. U. contributed to the conception and design; collection, analysis, and interpretation of data; drafting and critical revision of the article; and collection/generation of the images. R. M. K. contributed to the experiments, collection of the data, and critical revision of the article. A. C. R. contributed to the collection, analysis, and interpretation of the data and critical revision of the article. J. H. R. contributed to the conception and design, analysis and interpretation of data, and critical revision of the article. E. S. E. contributed to the conception and design, experiments, collection of data, and critical revision of the article. All authors approved the final article.

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