Original Article

The efficacy and safety of radial endobronchial ultrasound-guided transbronchial lung cryobiopsy in the diagnosis of lung disease

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Background: Transbronchial lung cryobiopsy (TBLC) is a novel technology in which a cryoprobe is used to obtain large tissue samples from the lungs of patients with interstitial lung diseases (ILDs) and peripheral pulmonary lesions (PPLs). We aimed to determine the efficacy and safety of TBLC in the diagnosis of peripheral lung diseases in the Endoscopy Center of Shanghai Pulmonary Hospital. Further, the application value of radial endobronchial ultrasound (R-EBUS) used to determine the optimal area for cryobiopsy was evaluated in this study.

Methods: In this retrospective study, the data of patients with unclarified ILDs or PPLs who underwent TBLC guided by R-EBUS between April 2020 and December 2021 at Shanghai Pulmonary Hospital in China were analyzed.

Results: A total of 137 patients [72 men, 65 women; median age, 52 years (range, 24–76 years)] were enrolled in the study. Out of the 137 patients included in the study, 123 (89.8%) were diagnosed after multidisciplinary discussions (MDDs), including 105 (85.4%) with ILD, 10 (8.1%) with tuberculosis, and 8 (6.5%) with a malignant tumor. Sixty-five (47.4%) patients had a definitive pathologic diagnosis through TBLC, including 54 (83.1%) with ILD, 5 (7.7%) with tuberculosis and 6 (9.2%) with malignant tumors. The overall pathological diagnosis rate was 47.4%. In addition to clarifying the blood supply situation of the candidate target, R-EBUS detected lesions in 44 (32.1%) patients. Mild and moderate bleeding occurred in 75.2% and 24.8% of patients, respectively. No cases of severe bleeding were observed. Pneumothorax occurred in 6 (4.4%) patients, of which 2 recovered without additional treatment, and 4 (66.7%) needed closed thoracic drainage. Hydropneumothorax and mediastinal emphysema occurred in one patient each. No patients died due to TBLC.

Conclusions: R-EBUS-guided TBLC is safe and effective for the diagnosis of lung diseases, including ILDs and other PPLs. R-EBUS can guide cryobiopsy and avoid the potential risk of severe bleeding as well as radiation exposure. The pathological diagnosis rate of ILDs is relatively low, and MDD plays an important role in the diagnosis of ILDs.

Keywords: Transbronchial lung cryobiopsy (TBLC); radial endobronchial ultrasound (R-EBUS); interstitial lung diseases (ILDs); peripheral pulmonary lesions (PPLs)

Submitted Jun 28, 2023. Accepted for publication Oct 20, 2023. Published online Dec 06, 2023.
doi: 10.21037/jtd-23-1005
View this article at: https://dx.doi.org/10.21037/jtd-23-1005

Introduction

Transbronchial lung cryobiopsy (TBLC) is a novel technique that is increasingly being used in the field of respiratory intervention (1-3). TBLC uses very low temperatures induced by the rapid expansion of gas released at high flow, causing the lung specimen to adhere to the equipment probe. Then, the specimen is removed from the body by rapid probe withdrawal, without increasing the risk of life-threatening complications (4). The value of biopsy for diagnostic purposes is influenced not only by the size of the biopsied tissue itself but also by the absolute and relative content of the alveolar structures and bronchial wall and the neoplastic or reactive changes in the tissue samples (5). TBLC can be used to harvest larger lung specimens and reduce tissue artifacts (6), which markedly improves the diagnostic yield compared with conventional transbronchial lung forceps biopsy (7). These advantages promote diagnostic accuracy and procedural success.

As the gold standard for tissue acquisition, surgical lung biopsy (SLB) is associated with much higher morbidity and mortality rates than TBLC (8). TBLC can be used to obtain significantly large samples with the lower risk of complications, consisting mainly of pneumothorax or bleeding and its diagnostic yield approaches that of SLB (9,10). Therefore, TBLC is a popular method to acquire lung tissue for diagnostic purposes.

Radial endobronchial ultrasound (R-EBUS) can be used to assist TBLC (11). Compared with conventional biopsy forceps, which allow only forward blind advancement, R-EBUS can be used to guide the biopsy procedure directly to the target area, which is initially identified on chest computed tomography (CT) and may encompass peripheral pulmonary lesions (PPLs) or diffuse lung lesions. Abdelghani *et al.* (12) suggested that the use of radial EBUS to locate and select target lung biopsy site before TBLC might increase diagnostic yield for diffuse parenchymal lung diseases (DPLD). Further, R-EBUS is highly sensitive to the presence of blood vessels, and it can thus be used to guide cryobiopsy in areas with a poor blood supply, which may decrease the volume and severity of bleeding (13,14).

Although the guidelines on TBLC in the diagnosis of interstitial lung diseases (ILD) have been released (15), more clinical data are needed to clarify its applicability to the diagnosis of other PPLs and optimize the procedures. In this study, we aimed to determine the efficacy and safety of TBLC in the diagnosis of peripheral lung diseases in the Endoscopy Center of Shanghai Pulmonary Hospital. Further, R-EBUS was mainly used to determine the optimal area for cryobiopsy with the absence of major vessels and the application value of R-EBUS was evaluated in this study. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1005/rc).

Highlight box

Key findings

- Our findings indicated that the optimized procedure of radial endobronchial ultrasound (R-EBUS)-guided transbronchial lung cryobiopsy (TBLC) was safe and effective for the diagnosis of lung diseases, including interstitial lung diseases (ILDs) and other pulmonary lesions.

What is known and what is new?

- TBLC was an appropriate for diagnosing ILDs with larger tissue samples obtained.
- Our study further confirmed the efficiency of TBLC with the optimized procedure.

What is the implication, and what should change now?

- In addition to ILDs, the optimized procedure of R-EBUS-guided TBLC also has potential application value in more lung diseases. More clinical studies are needed to identify the value.

Methods

Patients

This retrospective observational study included patients who underwent R-EBUS-guided TBLC between April 2020 and December 2021 at Shanghai Pulmonary Hospital. The

inclusion criteria were as follows: (I) complete clinical data (including medical history, serology, pulmonary function tests, and high-resolution CT); (II) chest CT suggesting diffuse lung lesions or peripheral lung lesions with bronchial signs; and (III) cases with an unclear pathological diagnosis and having been followed up for at least 6 months. Data on clinical features, anesthesia methods, freezing times, specimen size, pathological diagnosis, MDD diagnostic results, and complications were recorded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. K18-179) and informed consent was taken from all the patients.

Preoperative examinations

All patients underwent high-resolution chest CT, with or without contrast enhancement, before TBLC. Before TBLC, respiratory function; complete blood count; coagulation profile; serum creatinine concentration; arterial blood gases; and serology against human immunodeficiency virus, hepatitis B, and hepatitis C were measured. In addition, spirometry, pulse oximetry, electrocardiography, and echocardiography were performed.

Anesthesia and artificial airways

TBLC was performed under general anesthesia, and an anesthesiologist evaluated the patient's condition before the procedure. While propofol, sufentanil, and rocuronium were administered for anesthesia induction, propofol and remifentanil were administered for anesthesia maintenance. After intravenous anesthesia induction, either tracheal intubation was performed or a rigid tracheoscope was inserted for ventilation, and an anesthesia ventilator or high-frequency jet ventilator was connected for auxiliary ventilation. The patient's vital signs were monitored by intraoperative electrical monitoring. The TBLC operation process was then initiated.

EBUS and biopsy procedure

A flexible bronchoscope (BF-P290; Olympus, Tokyo, Japan) was used to observe the trachea and bronchi in sequence from the healthy side to the affected side. When the bronchoscope was inserted into the target bronchus under direct vision, the R-EBUS probe with an external diameter of 1.4 mm (UM-S20-17S; Olympus) was inserted through the bronchoscope working channel into the bronchi leading to the area suspected of containing the lesions. The blood vessels and lesions of the candidate sampling site were detected by the R-EBUS probe to avoid major vessels adjacent to the target area. Then, the depth of the probe was marked.

After the target cryobiopsy location was determined using the R-EBUS probe, the probe was removed and an endobronchial blocker (C-AEBS-7.0-65-SPH-AS; Cook Medical, Bloomington, IN, USA) was placed into the target lobe with the flexible bronchoscope for the patients with tracheal intubation before TBLC (*Figure 1*).

The cryosurgical unit (ERBECRYO® 2; Erbe Elektromedizin GmbH, Tübingen, Germany) and cryoprobe (1.9-mm diameter; Erbe Elektromedizin GmbH) were prepared for subsequent TBLC. The cooling gas source was carbon dioxide, with the gas pressure ranging from 45–65 bar. The reusable cryoprobe was guided into the sampling location through the working channel of the bronchoscope. The sample location was assessed to be at least 1 cm away from the pleura to minimize the risk of pneumothorax. The probe was cooled for approximately 3–5 seconds. Simultaneously, the bronchoscope and the probe with the frozen lung tissue attached to the tip were pulled out quickly. Then, the Arndt balloon was inflated for prophylaxis of bleeding. The cryobiopsy process was repeated in different lung segments or the same area.

Unless significant bleeding or other serious complications occurred during the operation, at least two lung segments and a total of three times cryotherapy biopsies were repeated.

Pathological examination and final diagnosis

The frozen specimen was thawed in saline and fixed in 4% neutral-buffered formalin. Two senior pathologists conducted the pathological examinations independently. The patients' clinical data, blood test results, chest images, and pathology reports were examined for the final diagnosis.

Complication assessment

TBLC-related complications, including bleeding, pneumothorax, infection, and mediastinal emphysema, were evaluated. Bleeding severity was graded as follows: grade 0, no bleeding; grade 1, bleeding that could be controlled using suction only, without other hemostatic measures;

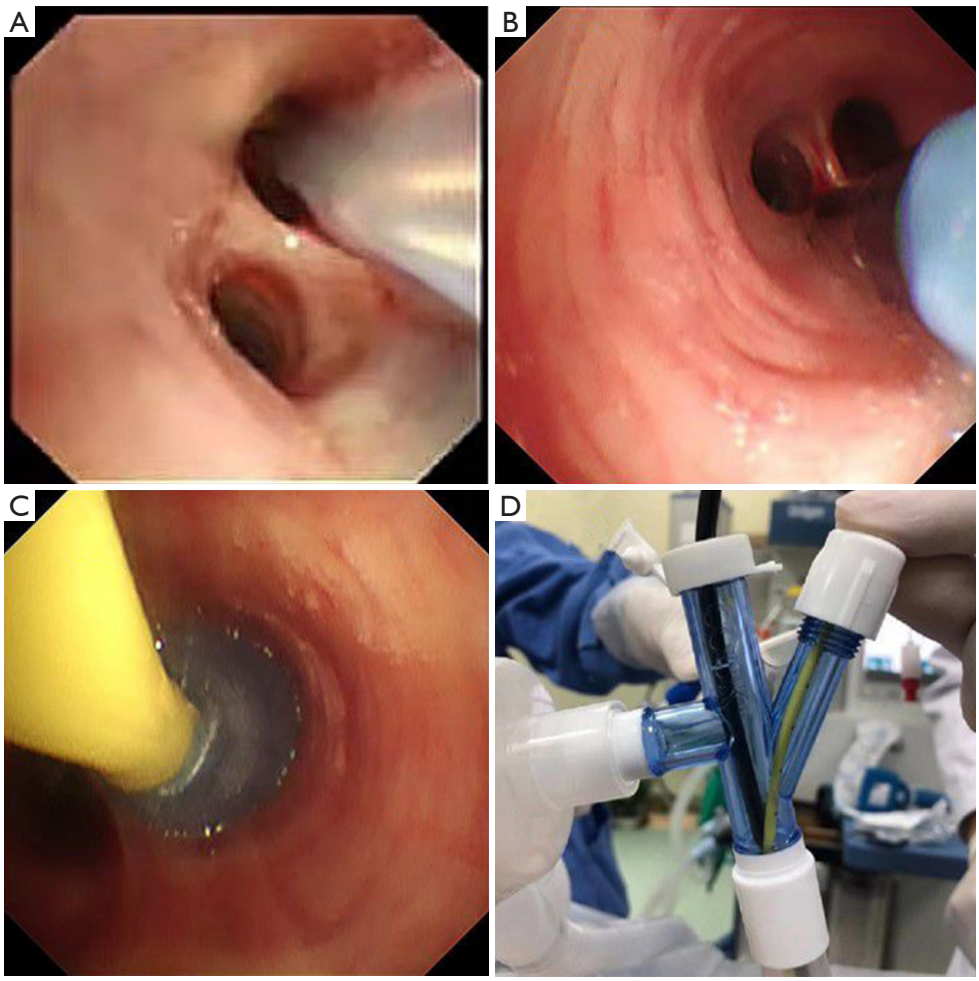

Figure 1 The process of TBLC guided by R-EBUS. (A) The R-EBUS probe was inserted through the bronchoscope working channel into the bronchi. (B) The cryoprobe was guided into the sampling location through the working channel of the bronchoscope. (C) An Arndt endobronchial blocker was inserted into the target lobe with the flexible bronchoscope. (D) A spherical Arndt endobronchial blocker was bound to a flexible bronchoscope. TBLC, transbronchial lung cryobiopsy; R-EBUS, radial endobronchial ultrasound.

grade 2, bleeding that could be controlled using cold saline, hemostatic drugs, balloon occlusion, or maneuvering of the rigid bronchoscope to the contralateral bronchus; and grade 3, bleeding that causes the patient to require blood transfusion or mechanical ventilation. Mild bleeding was categorized as grade 0–1, moderate bleeding as grade 2, and severe bleeding as grade 3 (16).

After TBLC, patients with clinical symptoms or abnormal physical signs further underwent chest X-ray or CT to exclude pneumothorax. All patients were monitored for at least 1 day before discharge. Pneumothorax was defined as mild if <30% of the thoracic volume was lost, moderate if ≥30% but <50% of the thoracic volume was lost, and severe if ≥50% of the thoracic volume was lost.

Statistical analysis

The χ^2 test or Fisher's exact test was used to compare categorical variables. A two-sided P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 software version (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics

A total of 137 patients [72 males, 65 females; median age, 52 years (range, 24–76 years)] were enrolled in the study. Forty-three (31.4%) patients had a history of smoking. The

Table 1 General clinical characteristics of patients (n=137)

Characteristics	Statistic results
Age (year)	
Median [interquartile range]	52 [42–59]
Range	24–76
Sex, n (%)	
Male	72 (52.6)
Female	65 (47.4)
Smoking history, n (%)	
Yes	43 (31.4)
No	94 (68.6)
Comorbidity, n (%)	
Hypertension	19 (13.9)
Diabetes mellitus	6 (4.4)
Chronic kidney disease	7 (5.1)
Rheumatic diseases	6 (4.4)
Asthma	4 (2.9)
Hypothyroidism	5 (3.6)
Hepatic insufficiency	3 (2.2)
Chronic obstructive pulmonary disease	2 (1.5)
Airway, n (%)	
Tracheal intubation	125 (91.2)
Rigid bronchoscope	12 (8.8)
Biopsy location, n (%)	
Left upper lobe	8 (5.8)
Left lower lobe	29 (21.2)
Right upper lobe	33 (24.1)
Right middle lobe	6 (4.4)
Right lower lobe	61 (44.5)
Lesion was detected by R-EBUS, n (%)	
Yes	44 (32.1)
No	93 (67.9)
Mean size of the biopsied sample (mm^2)	3.20±1.06
Number of biopsies	
Median [interquartile range]	3 [2–4]
Range	1–5
Freezing duration (second)	
Median [interquartile range]	5 [4–6]
Range	3–7
Post-TBLC examinations, n (%)	
Chest X-ray	47 (34.3)
Chest CT	9 (6.6)
Complications, n (%)	
Bleeding	
Grade 0	9 (6.6)
Grade 1	94 (68.6)
Grade 2	34 (24.8)
Grade 3	0
Pneumothorax	6 (4.4)
Mild with symptomatic treatment	2 (1.5)
Moderate with closed thoracic drainage	4 (2.9)
Severe	0
Hydropneumothorax	1 (0.7)
Pneumomediastinum	1 (0.7)

R-EBUS, radial endobronchial ultrasound; TBLC, transbronchial lung cryobiopsy; CT, computed tomography.

most prevalent comorbidities were hypertension (13.9%), diabetes mellitus (4.4%), chronic kidney disease (5.1%), rheumatic disease (4.4%), asthma (2.9%), hypothyroidism (3.6%), hepatic insufficiency (2.2%), and chronic obstructive pulmonary disease (1.5%) (*Table 1*).

Information related to TBLC

Out of the 137 patients, 125 (91.2%) received ventilation via tracheal intubation, and 12 (8.8%) by rigid bronchoscope. The right lower lobe was the most frequently biopsied location (61/137, 44.5%). The median freezing duration was 5 seconds (range, 3–7 seconds). In addition to clarifying the blood supply situation of the candidate target, R-EBUS detected lesions in 44 (32.1%) cases. The size of the biopsied samples was measured by pathologists after fixing them with formalin, and the mean size was 3.20±1.06 mm^2.

Complications after TBLC

Chest CT or X-ray was performed after TBLC in 56 cases (40.9%). Pneumothorax occurred in six patients (4.4%); of these, 4 (2.9%) required closed thoracic drainage, and 2 (1.5%) recovered without additional treatment. In addition,

Table 2 Pathologic diagnosis and final diagnosis by MDD

Final diagnosis	Pathologic diagnosis by TBLC (N1=65)	Diagnosis by MDD (N2=123)	Pathologic diagnostic rate (N1/N2)
ILD	54	105	51.4%
Pulmonary sarcoidosis	10	25	40.0%
Pneumoconiosis	8	10	80.0%
Diffuse panbronchiolitis	6	8	75.0%
Idiopathic interstitial pneumonia	6	9	66.7%
Nonspecific interstitial pneumonia	5	15	33.3%
Alveolar proteinosis	4	8	50.0%
Focal organizing pneumonia	4	6	66.7%
Cryptogenic organizing pneumonia	6	8	75.0%
Extrinsic allergic alveolitis	2	3	66.7%
Interstitial pneumonia with autoimmune features	1	2	50.0%
Respiratory bronchiolitis-ILD	1	4	25.0%
Lymphocytic interstitial pneumonitis	1	2	50.0%
Unclassified ILD	0	5	0
Tuberculosis	5	10	50.0%
Malignant tumor	6	8	75.0%
Adenocarcinoma	6	6	100.0%
Lymphoma	0	2	0

MDD, multidisciplinary discussion; TBLC, transbronchial lung cryobiopsy; ILD, interstitial lung disease.

one patient (0.7%) with pneumomediastinum recovered after symptomatic treatment, including oxygen inhalation and rest. One patient (0.7%) with hydropneumothorax recovered after thoracic closed drainage. No serious postoperative complications or deaths occurred. Mild and moderate bleeding occurred in 75.2% and 24.8% of patients, respectively. No cases of severe bleeding were observed. There was no correlation between biopsy location, number of TBLC procedures, disease types, and time of cryobiopsy and bleeding (P>0.5). The clinical characteristics of the patients are summarized in *Table 1*.

Diagnosis of patients

Out of the 137 patients included in the study, 123 (89.8%) were diagnosed after multidisciplinary discussions (MDDs), including 105 (85.4%) with ILD, 10 (8.1%) with tuberculosis, and 8 (6.5%) with a malignant tumor. Sixty-five (65/137, 47.4%) patients had a definitive pathologic diagnosis through TBLC, including 54 (83.1%) with ILD, 5 (7.7%) with tuberculosis and 6 (9.2%) with malignant tumors. The overall pathological diagnosis rate was 47.4% (65/137).

Fifty-four patients were pathologically diagnosed with ILD. The most frequent diagnosis was pulmonary sarcoidosis (10/54, 18.5%), followed by pneumoconiosis (8/54, 14.8%), diffuse panbronchiolitis (6/54, 11.1%), idiopathic interstitial pneumonia (6/54, 11.1%), cryptogenic organizing pneumonia (6/54, 11.1%), nonspecific interstitial pneumonia (5/54, 9.3%), alveolar proteinosis (4/54, 7.4%), focal organizing pneumonia (4/54, 7.4%), extrinsic allergic alveolitis (2/54, 3.7%), interstitial pneumonia with autoimmune features (1/54, 1.9%), respiratory bronchiolitis-ILD (1/54, 1.9%), and lymphocytic interstitial pneumonitis (1/54, 1.9%). Five patients were diagnosed as unclassified ILD after MDD. Fourteen (14/137, 10.2%) patients remain undiagnosed after MDD (*Table 2*).

Discussion

In this study, we discuss our experience using TBLC at a tertiary hospital in China. In the Endoscopy Center of Shanghai Pulmonary Hospital, tracheal intubation is the preferred technique in most TBLC cases, while other centers prefer using rigid bronchoscopy to solve the complications associated with TBLC, such as bleeding (4,17,18). Airway management with rigid bronchoscopy is more difficult compared to tracheal intubation; therefore, rigid bronchoscopy is usually performed by skillful interventional pulmonologists. In addition, glottis edema is more likely to occur after rigid bronchoscopy (19), and the surface of the flexible bronchoscope may be scratched by the edge of the rigid bronchoscope sheath when retracting the flexible bronchoscope and frozen probe.

A previous study considered moderate or severe bleeding, pneumothorax, or death ≤90 days as clinically significant complications for TBLC procedure (17). The mean reported frequency for mild and moderate bleeding was 29.9% (range, 0–96%) and 9.1% (range, 0–56.4%), respectively (8,18). The mean incidence rate of pneumothorax in patients who underwent TBLC was 9.2% (range, 0–26%) (8,20,21). Our study showed that the incidence of moderate bleeding and pneumothorax was 24.8% and 4.4%, respectively. Of 6 patients (4.4%) with pneumothorax, 4 (2.9%) required closed thoracic drainage, and 2 (1.5%) were treated conservatively. The lower incidence of complications in our study may be attributed to the following reasons. First, the use of R-EBUS and preoperative balloon placement played a significant role in preventing bleeding. R-EBUS guided the cryoprobe to the target location to avoid bleeding. In addition, preoperative balloon placement before cryobiopsy was performed in all patients who underwent tracheal intubation, which was another effective solution that prevented bleeding. Finally, the endoscopist had at least 5 years of experience in bronchoscopy, with >2,000 operations performed annually; therefore, the TBLC procedure was standardized in our study.

Although there have been some published studies on R-EBUS-assisted TBLC (12-14), our research has several differences and characteristics. First, for ILDs, we may have found some abnormalities and obtain pathological diagnosis in the histopathological examination which R-EBUS did not show any obvious abnormalities in sampling location. Therefore, in our study, R-EBUS was mainly used to determine the optimal area for cryobiopsy with the absence of major vessels for ILD cases. For other PPLs, the lesions detected by R-EBUS were still necessary. Second, there were several differences of operation method in our study. A flexible thin bronchoscope (BF-P290; Olympus) was used in our study with 2.0 mm bronchoscope working channel and 4.0 mm outside diameter. The R-EBUS probe was inserted through the bronchoscope working channel into the target segment. When the candidate sampling site was detected and confirmed by the R-EBUS probe, the depth of the probe was marked and then the probe was removed. The cryoprobe was guided into the sampling location through the working channel of the bronchoscope and the frozen biopsy program was started. The procedure was relatively simplified and the radiation machines such as fluoroscopy were not used to avoid patient exposure to radiation. Third, a total of 137 patients were included in our study which provided more information for research. Not only ILD, we also included PPLs in the study and expanded the application range of TBLC.

Recently a genomic classifier was developed with machine learning and whole transcriptome RNA sequencing using lung tissue for classification of usual interstitial pneumonia (UIP) (22-25). A systematic review summarized by Kheir *et al.* (26) showed that genomic classifier testing predicts histopathologic UIP in patients with ILD with the specificity of 92% and the sensitivity is only 68%. The testing was not widely available. Based on the review, an official ATS/ERS/JRS/ALAT clinical practice guideline for idiopathic pulmonary fibrosis (an Update) and progressive pulmonary fibrosis showed that no recommendation for or against the addition of genomic classifier testing for the purpose of diagnosing UIP in patients with ILD of undetermined type who are undergoing transbronchial forceps biopsy (27). In China, genomic classifier testing was not routinely applied for diagnosing ILD.

Of the eight patients who were diagnosed with lung cancer pathologically, six were diagnosed by TBLC, and two by EBUS-TBNA (n=1) and thoracoscopy (n=1). Peripheral lesions with bronchus signs were crucial for diagnosis by TBLC. Kho *et al.* (28) reported significantly increased diagnostic yield with cryobiopsy in eccentrically and adjacently orientated lesions of 75.0%, compared to 48.8% with forceps biopsy ($P<0.05$). No difference was found in the yield of concentric lesions (28). Nasu *et al.* (29) reported an increased diagnostic yield with cryobiopsy in the presence of the bronchus sign. In our study, all six cases diagnosed by TBLC had bronchial signs on CT (one case of eccentrical lesion and five cases of adjacent lesions),

while the other two cases of undiagnosed lesions had no obvious bronchial signs. This suggests that TBLC is more advantageous for lesions with bronchial signs that are not concentric. However, a multi-center randomized controlled study is needed to verify this.

Conclusions

Our single-center cohort study showed that R-EBUS-guided TBLC is a safe and effective technique for diagnosing lung diseases, including ILDs and other PPLs. R-EBUS can guide cryobiopsy and avoid the potential risk of severe bleeding as well as radiation exposure. TBLC has great clinical application value. The pathological diagnosis rate of ILDs is relatively low, and MDD plays an important role in the diagnosis of ILDs.

Acknowledgments

We thank all the patients and the investigators.
Funding: This study was supported by the National Natural Science Foundation of China (No. 82002416).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1005/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1005/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1005/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1005/coif). All authors report that this study was supported by the National Natural Science Foundation of China (No. 82002416). The authors have no other conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. K18-179) and informed consent was taken from all the patients.

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Cite this article as: Yang L, Bi S, Wei G, Yu D, Wang H, Dong J, Wang H, Gu Y. The efficacy and safety of radial endobronchial ultrasound-guided transbronchial lung cryobiopsy in the diagnosis of lung disease. J Thorac Dis 2023;15(12):6570-6578. doi: 10.21037/jtd-23-1005