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Comparative yield of EBUS-TBNA with EBUS-IFBTLP for diagnosis of mediastinal lymphadenopathy

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Rui Zhang*, Wenping Zhang*, Xiangsong Cheng, Dan Si, Bao Liu, Xingang Hu, Xianliang Chen and Zhuquan Su

Abstract

Background: Patients with mediastinal lymph node enlargement (MLNE) are diagnosed depending on lymph node biopsy. Whereas, how to obtain larger tissue masses from mediastinal lymph nodes and improve the diagnostic yield of the disease remains to be investigated.

Objectives: Aiming to assess the diagnostic value of endobronchial ultrasound-guided intranodal forceps biopsy via transbronchial laser photoablation (EBUS-IFB-TLP) in patients with MLNE.

Design: A prospective, self-controlled study.

Methods: This study was conducted on 67 MLNE patients requiring a lymph node biopsy for diagnosis at the Henan Provincial People's Hospital and the Fuwai Central China Cardiovascular Hospital in China, from January 2020 to December 2022. Each patient underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA group) and EBUS-IFB-TLP (EBUS-IFB-TLP group) on the same mediastinal lymph node for biopsies. The operation time, diagnostic efficiency, and complication rates of the two biopsy methods were compared.

Results: The number of diagnosed patients in the EBUS-IFB-TLP and the EBUS-TBNA groups was 65 (97.0%) and 57 (85.1%), respectively ($p = 0.021$). In the EBUS-IFB-TLP group, 28 cases (96.6%) were diagnosed with lung cancer and were classified into different epithelial types. In the EBUS-TBNA group, there were 27 cases (93.1%) diagnosed with lung cancer, of which 26 (89.7%) were classified into different epithelial types. There were 37 (97.4%) and 30 (78.9%) non-lung cancer patients diagnosed in the EBUS-IFB-TLP and EBUS-TBNA groups, respectively ($p = 0.039$), while 27 cases (96.4%) of sarcoidosis in the EBUS-IFB-TLP group and 20 cases (71.4%) of sarcoidosis in the EBUS-TBNA group were diagnosed ($p = 0.016$). The percentages of intraoperative mild to moderate bleeding complications were 23.9% (16/67) and 14.9% (10/67) in the EBUS-IFB-TLP and in the EBUS-TBNA groups, respectively ($p = 0.109$).

Conclusion: This study demonstrated that EBUS-IFB-TLP could be a feasible and effective method in the diagnosis of patients with MLNE, presenting an analogous safety profile compared with EBUS-TBNA. Further studies are needed to verify the diagnostic performance of EBUS-IFB-TLP for MLNE.

Correspondence to:
Zhuquan Su
Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510145, China
py1011xiaoquan@163.com

Xianliang Chen
Department of Respiratory and Critical Care Medicine, The Henan Provincial People's Hospital, Zhengzhou, Henan 450052, China

Department of Respiratory and Critical Care Medicine, The Fuwai Central China Cardiovascular Hospital, Zhengzhou 450000, Henan, China
13598808035@126.com

Rui Zhang
Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

Wenping Zhang
Bao Liu
Xingang Hu
Department of Respiratory and Critical Care Medicine, The Henan Provincial People's Hospital, Zhengzhou, Henan, China

Xiangsong Cheng
Dan Si
Department of Respiratory and Critical Care Medicine, The Fuwai Central China Cardiovascular Hospital, Zhengzhou, Henan, China
*These authors contributed equally to this work.

Plain language summary

A new way of obtaining a larger biopsy sample in patients with enlarged lymph nodes in the chest

Why was the study done?

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) allows doctors to look at a patient's lungs using a tiny camera (called a bronchoscope). A needle is found at the tip of the bronchoscope and is used to take samples (biopsies) from the lymph nodes in the chest. Lymph nodes are small structures that help filter foreign substances in the body, for example cancer cells. The enlarged (big) lymph nodes are often caused by cancer. Researchers are still trying to work out how to obtain large samples from the lymph nodes which could lead to a better diagnosis.

What did the researchers do?

We explored a new method called endobronchial ultrasound-guided intranodal forceps biopsy based on transbronchial laser photoablation (EBUS-IFB-TLP) to be used in diagnosing patients who have enlarged lymph nodes. EBUS-IFB-TLP is performed under the guidance of endndobronchial ultrasound, the laser fiber is inserted through the bronchoscope to act on the airway wall, creating a hole in the target lymph node, a biopsy forcep was inserted into the lymph node through the biopsy hole. We used both methods on each patient in this study and compared them.

What did the researchers find?

More patients were diagnosed with enlarged lymph nodes when using the EBUS-IFB-TLP method, but there were milder to moderate bleeding complications.

What do the findings mean?

This study shows that EBUS-IFB-TLP could be use in the diagnosis of enlarged lymph nodes.

Keywords: biopsy, diagnostic value, EBUS-IFB-TLP, EBUS-TBNA, mediastinal lymph node enlargement

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Introduction

The diagnosis of mediastinal lymph node enlargement (MLNE) depends greatly on a lymph node biopsy. Transbronchial needle aspiration biopsy (TBNA) is a technique that uses a specially designed biopsy needle, which is inserted into the mediastinal lymph nodes adjacent to the tracheal wall. This procedure allows for obtaining tissue samples under the guidance of a bronchoscope. It is of great clinical value in the diagnosis and staging of lung cancer.[1–3] Although the TBNA operation procedure is simple, it strongly depends on the size and location of the lymph nodes, as well as on the operator's technical expertise.[2,4] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a convex echoendoscope-guided lesion biopsy based on TBNA. Studies have shown that the diagnostic yield of EBUS-TBNA for MLNE is higher than that of traditional TBNA.[5–8] EBUS-TBNA has high sensitivity and specificity in the diagnosis of lung cancers.[9–11] However, some studies have shown that EBUS-TBNA has a lower diagnosis sensitivity for non-tumor lesions,[12–14] which might be correlated with the amount of biopsy specimen. In order to obtain larger tissue masses from

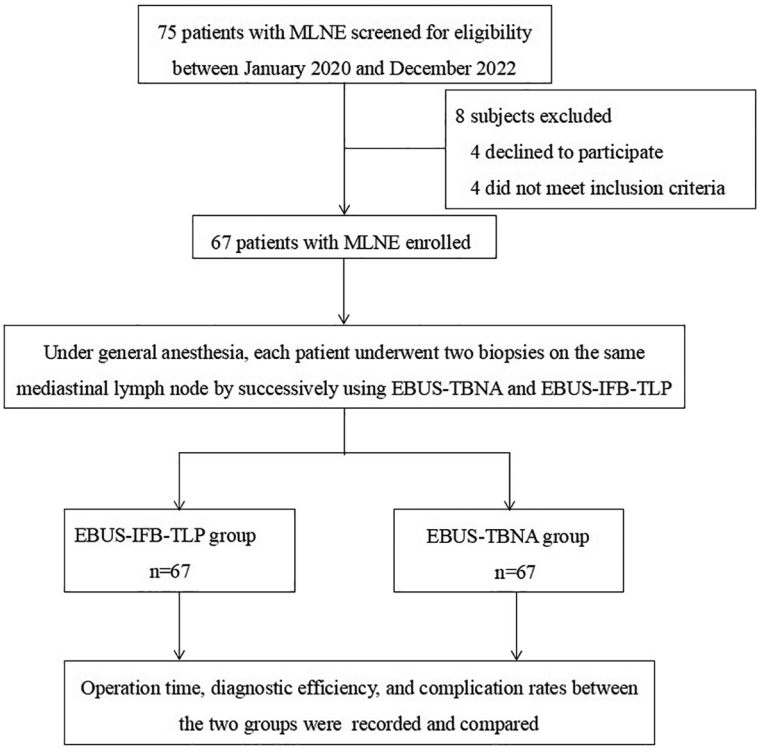

Figure 1. Flow diagram of the study.
EBUS-IFB-TLP, endobronchial ultrasound-guided intranodal forceps biopsy based on transbronchial laser photoablation; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; MLNE, mediastinal lymph node enlargement.

mediastinal lymph nodes and improve the diagnostic yield of the disease, we explored the endobronchial ultrasound-guided intranodal forceps biopsy via transbronchial laser photoablation (EBUS-IFB-TLP) technique. It uses biopsy forceps that are inserted through the hole formed by laser drilling into mediastinal lymph nodes. Here, we conducted a prospective self-controlled study to assess the diagnostic efficiency and safety of EBUS-IFB-TLP in MLNE patients, in comparison with EBUS-TBNA.

Methods

Study design and patients

This prospective self-controlled study was conducted at the Henan Provincial People's Hospital and at the Fuwai Central China Cardiovascular Hospital (Zhengzhou, China), between January 2020 and December 2022, as indicated in the flow diagram (Figure 1). MLNE patients aged over 18 years requiring a lymph node biopsy for diagnosis were consecutively included in this study. Moreover, computed tomography (CT) examination for the enrolled patients showed mediastinal lymph nodes with a short axis diameter more than 10 mm. Pregnant and lactating women, patients who were unable to tolerate general anesthesia or a mediastinal lymph node biopsy were excluded from the study. The demographic and clinical data for all the recruited patients were recorded. Under general anesthesia, each patient underwent two biopsies on the same mediastinal lymph node by successively using EBUS-TBNA and EBUS-IFB-TLP. The operation time, diagnostic efficiency, and complication rates of the two biopsy methods were recorded and compared. Written informed consent was obtained from all the selected subjects. This study was approved by the Ethics Committee of the Henan Provincial People's Hospital and the Fuwai Central China Cardiovascular Hospital (No. 2023-46).

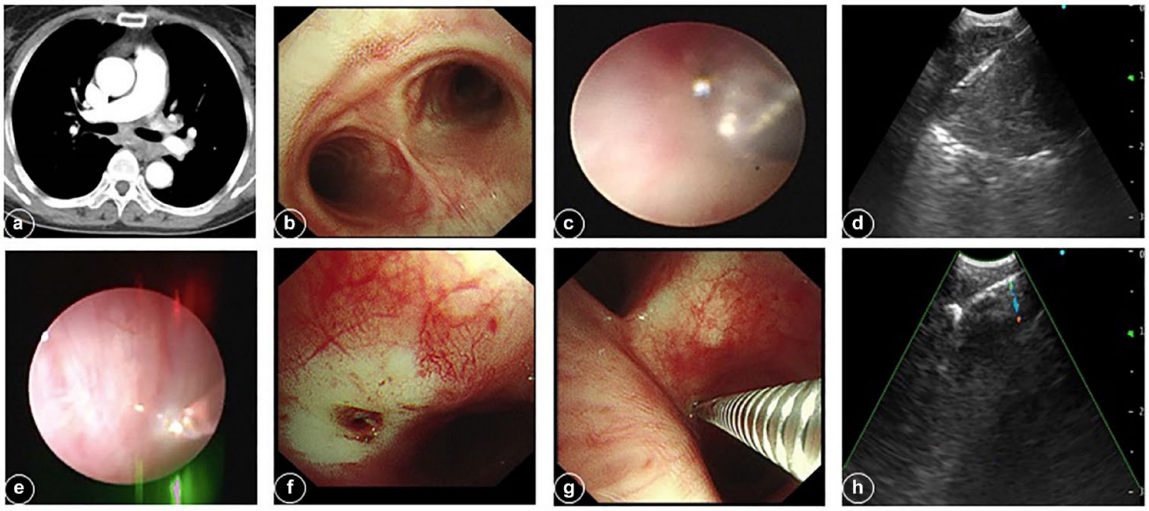

Figure 2. Schematic diagram of the bronchoscopic operations. Panels (a–d) represent the EBUS-TBNA procedure. (a) A preoperative enhanced chest CT scan showed an enlarged subcarinal lymph node, with dimensions 34.17 mm × 19.76 mm. (b) Ultrasound bronchoscopy was used to examine the trachea and bronchi. (c) With the assistance of ultrasound bronchoscopy, a 21G puncture needle penetrated the medial wall of the right main bronchus. (d) To perform the biopsy, the 21G puncture needle was inserted into the subcarinal lymph node. Panels (e–h) represent the EBUS-IFB-TLP procedure. (e) Under the guidance of ultrasound bronchoscopy, an optical fiber was inserted through its working channel. A 1064 nm neodymium-doped yttrium-aluminum-garnet laser irradiation in pulse mode with the power levels of 20–40 W was performed for 15–20 s at a distance of 3–5 mm from the trachea or bronchial mucosal tissue. (f) The hole was formed by laser drilling. (g) A biopsy forceps was inserted into the hole. (h) An ultrasound image showed the biopsy forceps entering the subcarinal lymph node for performing the biopsy.
CT, computed tomography; EBUS-IFB-TLP, endobronchial ultrasound-guided intranodal forceps biopsy based on transbronchial laser photoablation; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Bronchoscopic procedure

Before surgery, each patient received laboratory tests (such as routine blood tests, indicators of inflammation, coagulation, liver and kidney function, and arterial blood gas analysis), electrocardiogram, and chest CT scanning. All patients fasted for 8 h before the operation, and water was prohibited 2 h before the procedure. Each patient underwent a bronchoscopic examination under general anesthesia with a laryngeal mask. EBUS-TBNA was performed following the CHEST guideline and STARD (Supplemental Material) reporting guideline[15]: an EBUS bronchoscope (Olympus BF-UC260FW, Olympus, Japan) was used to observe the trachea and bronchus. For biopsy under real-time ultrasound monitoring, a 21G EBUS-TBNA needle (Olympus ViziShot, model NA-201SX-4021, Olympus, Japan) was used to puncture the target mediastinal lymph node identified by enhanced chest CT scanning. After the EBUS-TBNA procedure, the same lymph node underwent EBUS-IFB-TLP, which was conducted as following: under the guidance of an EBUS bronchoscope, an optical fiber was inserted through the bronchoscopic working channel. A 1064 nm neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser irradiation in pulse mode with the power levels of 20–40 W was performed for 15–20 s at a distance of 3–5 mm from the trachea or bronchial mucosal tissue using an Nd:YAG system (ligenesis, China). The laser thermal ablation vaporized the trachea or the bronchial wall and formed a hole into the target lymph node. Subsequently, biopsy forceps (with a 1.8 mm diameter; Lookmed, Changzhou, China) were inserted into the target lymph node through the biopsy hole. For both EBUS-TBNA and EBUS-IFB-TLP, enlarged mediastinal lymph nodes were aspirated by the needle, or grasped and extracted by the biopsy forceps for four times. The operation processes of EBUS-TBNA and EBUS-IFB-TLP were shown in Figure 2. Samples obtained from the EBUS-TBNA and EBUS-IFB-TLP biopsies were fixed in a 4% paraformaldehyde solution and subsequently stained with hematoxylin and eosin and

immunohistochemistry. Results from pathology and immunohistochemistry of the biopsy specimens were used for diagnosis.

Observed indicators

The operation time of the lymph node biopsy, the total positive rate of diagnosis, and the positive rates of lung and non-lung cancer diagnoses in the EBUS-IFB-TLP and EBUS-TBNA groups were recorded. The complications associated with EBUS-IFB-TLP and EBUS-TBNA during and after bronchoscopic procedures, such as bleeding, pneumothorax, shock, and death, were also recorded. With reference to a previous literature,[16] the severity of intraoperative bleeding complications was graded as grade 0: no bleeding; grade 1: bleeding that could be stopped by negative pressure suction; grade 2: bleeding that could be stopped by a local injection of a cold saline solution, epinephrine, or balloon occlusion; grade 3: severe bleeding that could not be controlled under an endoscope, which might cause instability of hemodynamics and respiratory function. In this condition, vascular or surgical intervention, or even patient admission to the ICU, are needed, in order to stop the bleeding.

Disease diagnostic criteria

For each patient, an accurate diagnosis was made based on the clinical manifestation, the examination results (such as CT scan, Positron Emission Tomography/Computed Tomography (PET-CT) scan, blood tests, and pathology), and the treatment efficacy evaluated through a 6-month follow-up period.

Statistical analysis

The SPSS 23.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. For continuous variables, the values were presented as the mean ± standard deviation or the median (25%–75% percentiles). For categorical variables, values were presented as frequency (percentage). In comparison between the two groups, the paired Wilcoxon rank sum test was used for non-normal distribution data analysis. For two-group comparisons, the rates of diagnosis and bleeding were compared using the McNemar's test. Two-tailed p-values of <0.05 were considered statistically significant.

Results

Clinical characteristics of patients

The present study involved a total of 67 patients, including 35 males and 32 females, aged 18–75 years, with a median age of 62.0 years (51.0–68.0 years) and the body mass index of (23.5 ± 1.7) kg/m^2. The 67 patients were accurately diagnosed based on disease diagnostic criteria, which included 29 patients with lung cancer and 38 patients with pulmonary benign disease. Patients with pulmonary benign disease included 28 sarcoidosis, 9 reactive hyperplasia of lymph nodes, and 1 pulmonary tuberculosis case (Figure 3). A total of 67 target mediastinal lymph nodes were biopsied, including 8 cases (11.9%) in the right lower paratracheal nodes (4R), 2 cases (3.0%) in the left lower paratracheal lymph nodes (4L), 30 cases (44.8%) in the subcarinal lymph node (7), 6 cases (9.0%) in the right hilar lymph nodes (10R), 6 cases (9.0%) in the left hilar lymph nodes (10L), 10 cases (14.9%) in the right interlobular lymph nodes (11R), and 5 cases (7.5%) in the left interlobular lymph nodes (11L). The diameter of the target lymph node was 23.8 mm (22.9–34.2 mm). The operation time of the lymph node biopsy was 7.3 min (7.2–7.4 min) and 8.0 min (7.9–8.3 min) in the EBUS-IFB-TLP and EBUS-TBNA groups, respectively, with a statistically significant difference between the two groups ($p<0.001$). The clinical characteristics of the 67 participating patients were shown in Table 1.

Diagnosis efficiency

In sum, 65 (97.0%) and 57 patients (85.1%) were diagnosed in the EBUS-IFB-TLP and EBUS-TBNA groups, respectively, with a statistically significant difference in the overall positive diagnostic rate between the two groups ($p=0.021$). In the EBUS-IFB-TLP group, 28 cases (96.6%) of lung cancer were diagnosed and determined to be of different epithelial types, including 11 cases of adenocarcinoma, 9 squamous cell carcinoma, and 8 small cell carcinoma. In the EBUS-TBNA group, 27 lung cancer cases (93.1%) were diagnosed and 26 cases (89.7%) were classified into different epithelial types of lung cancer, including 9 cases of adenocarcinoma, 9 squamous cell carcinoma, and 8 small cell carcinoma. There was no statistically significant difference between the two groups in the diagnosis of lung cancer and in the identification of different cell types of lung cancer ($p>0.999$

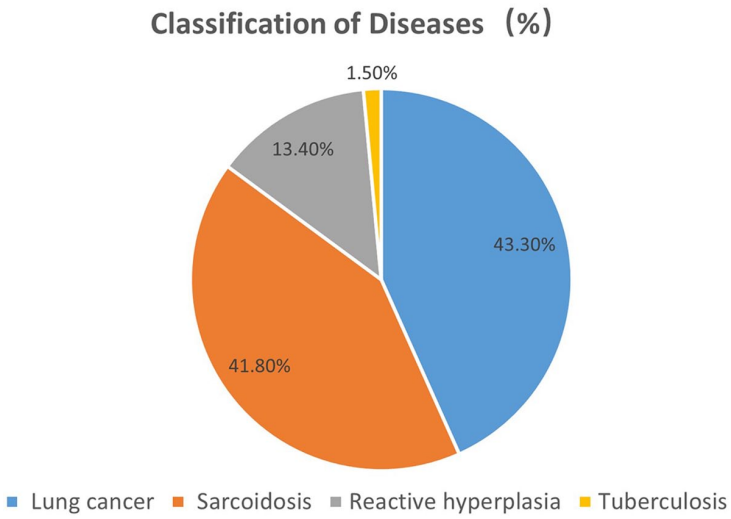

Figure 3. Pie chart of the histopathological findings of endobronchial ultrasound-guided transbronchial needle aspiration biopsy.

Table 1. Clinical characteristics of the 67 enrolled patients.

Clinical characteristics	Value
Male (No.)	35
Female (No.)	32
Smoker (No.)	27
Median age (years)	62.0
BMI (kg/m^2)	23.5 ± 1.7
Target mediastinal lymph nodes (No.)	
Right lower paratracheal nodes (4R)	8
Left lower paratracheal nodes (4L)	2
Subcarinal lymph node (7)	30
Right hilar lymph node (10R)	6
Left hilar lymph node (10L)	6
Right interlobular lymph node (11R)	10
Left interlobular lymph node (11L)	5
Diameter of the target lymph nodes (mm)	23.8 (22.9–34.2)

Data are expressed as *n*, mean ± SD, or median (25%–75% percentiles).
BMI, body mass index; SD, standard deviation.

and $p = 0.500$, respectively). Moreover, 37 (97.4%) and 30 (78.9%) patients with non-lung cancer were diagnosed in the EBUS-IFB-TLP and the EBUS-TBNA groups, respectively, with a statistically significant difference between the two groups ($p = 0.039$). Furthermore, the EBUS-IFB-TLP and EBUS-TBNA groups diagnosed sarcoidosis in 27 cases (96.4%) and 20 cases (71.4%), respectively, with a statistically significant difference in the positive rate of sarcoidosis diagnosis between the two groups ($p = 0.016$). Whereas, 9 cases of reactive lymph node hyperplasia and 1 case of pulmonary tuberculosis were diagnosed in the EBUS-IFB-TLP and the EBUS-TBNA groups, respectively. Comparison of the number of cases diagnosed between EBUS-IFB-TLP and EBUS-TBNA was shown in Table 2.

Safety assessment

The percentage of intraoperative mild to moderate bleeding (grade 1 + grade 2) was 23.9% (16/67) in the EBUS-IFB-TLP group and 14.9% (10/67) in the EBUS-TBNA group, with no statistically significant difference between the two groups ($p = 0.109$). There was no pneumothorax, shock, or death occurred during or after the bronchoscopic examination, in any of the groups.

Discussion

The diagnosis and treatment of MLNE patients rely heavily on pathological tests from lymph node biopsies. The EBUS-TBNA method has been widely used since 2002, being superior to traditional TBNA and having a high diagnostic

Table 2. Comparison of the number of cases diagnosed between EBUS-IFB-TLP and EBUS-TBNA.

Classification of diseases	EBUS-IFB-TLP group, *n* (*n*/*N*)	EBUS-TBNA group, *n* (*n*/*N*)	*p* value
Lung cancer	28 (28/29)	27 (27/29)	1.000
Identified types of lung cancer	28 (28/29)	26 (26/29)	0.500
Non-tumor diseases	37 (37/38)	30 (30/38)	0.039
Sarcoidosis	27 (27/28)	20 (20/28)	0.016
Reactive hyperplasia of lymph nodes	9 (9/9)	9 (9/9)	None
Tuberculosis	1 (1/1)	1 (1/1)	None

In the two-group comparisons, the rates of diagnosis were compared using the McNemar's test. Two-tailed *p*-values of <0.05 were considered statistically significant.
EBUS-IFB-TLP, endobronchial ultrasound-guided intranodal forceps biopsy based on transbronchial laser photoablation; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

yield in patients with mediastinal lymph node metastases.[17–20] EBUS-TBNA has been recommended by the American College of Chest Physicians as the preferred examination method for evaluating tumor-node-metastasis staging of lung cancer, being preferred to mediastinoscopy.[15] Yasufuku et al.[21] used EBUS-TBNA to puncture mediastinal and hilar lymph nodes in 70 patients, demonstrating the sensitivity, specificity, and accuracy of EBUS-TBNA in distinguishing benign from malignant lymph nodes were 95.7%, 100%, and 97.1%, respectively. Using EBUS-TBNA, Herth et al.[11] punctured 572 mediastinal lymph nodes in 502 patients, diagnosing 535 lymph nodes with 93.5% sensitivity. In the present study, we showed that the positive rate of lung cancer in the EBUS-TBNA group was 93.1%, similar to previous studies.[11,21] In addition, 89.7% of lung cancer patients could be classified into different epithelial types.

Although EBUS-TBNA has a high diagnostic yield in the malignant mediastinal lymph node, part of the patients still face the risks of puncture failure, with a decrease in the cell mass extracted, which is insufficient for pathological examination. Moreover, using EBUS-TBNA, the diagnostic yield of sarcoidosis and lymphoma is relatively lower.[12–14] In high burden of tuberculosis country, it was reported that pulmonary tuberculosis in approximately 68% patients who received EBUS-TBNA in diagnosing mediastinal lymphadenopathy with diagnostic yield of 56.9%–87.0%,[22,23] whereas, our study showed that only 71.4% of sarcoidosis patients could be diagnosed using EBUS-TBNA, which was significantly lower than the corresponding diagnostic rate for lung cancer.

To improve the MLNE diagnostic rate, more specimens could be obtained by increasing the number of EBUS-TBNA needle punctures; however, this approach might increase the risk of complications, such as bleeding, bronchial constriction, pneumothorax, and arrhythmia. Expanding the needle diameter is likely a feasible method to improve the diagnostic yield. Although a 19G EBUS-TBNA needle might yield more tissue samples than a 22G EBUS-TBNA needle, studies have revealed the same diagnostic yield of mediastinal lymph node lesions using both needle types.[24] Chaddha et al.[25] found that although the 19G EBUS-TBNA needle had a larger lumen diameter, the obtained samples contained larger amounts of patient blood, which did not bring any diagnostic advantage. Recently, ultrasound-guided endobronchial intranodal miniforceps biopsy (EBUS-MFB) has been used as a new technique for diagnosing MLNE. Some studies have confirmed that EBUS-MFB could improve the MLNE diagnostic yield.[26–29] Moreover, Zhang et al.[30] showed that the diagnostic yield of mediastinal lesions using transbronchial mediastinal cryobiopsy was superior to EBUS-TBNA, especially for the diagnosis of rare lesions.

Nd:YAG laser thermal ablation technology has been mainly used to treat airway obstruction caused by benign and malignant lesions. This technology could immediately reopen the airway and improve the lung function.[31–33] In this study,

we innovatively used EBUS-IFB-TLP to improve the diagnostic yield of mediastinal lymph node lesions. Here, our results indicated that: (1) The operation time of the lymph node biopsy in the EBUS-IFB-TLP group was shorter than that in the EBUS-TBNA group, since the EBUS-IFB-TLP procedure was more available and accessible for obtaining biopsy compared with EBUS-TBNA, making it time-saving and easily achievable after puncturing a hole by transbronchial laser photoablation. (2) The EBUS-IFB-TLP yielded a high diagnostic yield of lung cancer, which was comparable with EBUS-TBNA method. (3) The overall positive rate of the diagnosis of non-lung cancer in the EBUS IFB-TLP group was higher than that in the EBUS-TBNA group, especially for sarcoidosis. The above results suggested that EBUS-IFB-TLP might serve as a time-saving with higher diagnostic yield modality compared with EBUS-TBNA in the diagnosis of MLNE patients.

EBUS-TBNA is a safe technique for the biopsy of mediastinum and hilar lesions. According to a previous study, bleeding, severe cough, and infection are rare complications in patients who received EBUS-TBNA.[34,35] Potential complications in patients undergoing EBUS-IFB-TLP could be related to Nd:YAG laser thermal ablation and lymph node biopsies. These complications can include cough, bleeding, cardiovascular system complications (such as myocardial infarction, cardiac insufficiency, bradycardia, and cardiac arrest), infection, airway combustion, postoperative hypoxemia, respiratory failure, shock, and death.[32] In this study, we found that the main complication in the EBUS-IFB-TLP and EBUS-TBNA groups was mild to moderate intraoperative bleeding. There was no severe bleeding, pneumothorax, or other complications during and after the bronchoscopic procedures. Both methods were safe, which might be related to patients with fewer complications and skilled operators performing the bronchoscopic techniques.

However, this study has the following shortcomings. (1) In this study, the EBUS-TBNA and EBUS-IFB-TLP techniques were sequentially performed in the same target lymph node, which might affect the assessment of any complication. (2) This was a single center study with a relatively small sample size. As such, the diagnostic value of EBUS-IFB-TLP in pulmonary tuberculosis and lymphoma was not fully assessed. (3) This was a pilot study on the novel EBUS-IFB-TLP method, the sample size analysis and calculation was not performed in the current study. Therefore, multicenter and large sample studies are still needed, in order to validate the diagnosis efficiency of EBUS-IFB-TLP in MLNE patients.

Conclusion

In this study, we introduced the novel method of EBUS-IFB-TLP used in the diagnosis of MLNE patients, showing a preferable diagnostic yield and comparable safety with EBUS-TBNA. Hence, EBUS-IFB-TLP could be a feasible and safe biopsy methodology for MLNE in the clinical practice.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Henan Provincial People's Hospital and the Fuwai Central China Cardiovascular Hospital (No. 2023-46). All subjects gave written informed consent.

Consent for publication

Written informed consent was obtained from all the selected subjects.

Author contributions

Rui Zhang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft.

Wenping Zhang: Conceptualization; Data curation; Formal analysis; Resources; Validation.

Xiangsong Cheng: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation.

Dan Si: Conceptualization; Data curation; Resources.

Bao Liu: Conceptualization; Data curation; Investigation; Resources.

Xingang Hu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing.

Xianliang Chen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology;

Resources; Validation; Writing – review & editing.

Zhuquan Su: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID iD

Zhuquan Su https://orcid.org/0000-0002-5583-0349

Supplemental material

Supplemental material for this article is available online.

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