General Principles of Mediastinal Cryobiopsy

Yong-Jia Qi and Ye Fan

Contents

Abstract

Guidelines recommend endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) as the initial technique for mediastinal lymph node staging in lung cancer. However, EBUS-TBNA can be limited by insufficient tissue samples, which may restrict its diagnostic accuracy for certain mediastinal pathologies. Recently, endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TBMCB) has been introduced as an alternative for mediastinal lymph node sampling. This technique offers advantages of obtaining larger tissue samples while maintaining a good safety profile. EBUS-TBMCB involves using an ultrasound bronchoscope to guide the procedure. A high-frequency needle-knife creates an access, after which a cryoprobe is inserted into the mediastinal lymph node for tissue sampling and subsequent diagnostic evaluation. Based on current research findings, EBUS-TBMCB is a safe and novel mediastinal biopsy technique that significantly enhances the diagnostic yield for mediastinal diseases and improves subsequent molecular diagnosis compared to EBUS-TBNA. EBUS-TBMCB is anticipated to complement EBUS-TBNA in future clinical practice.

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Keywords

EBUS · Mediastinal cryobiopsy · Transesophageal cryobiopsy · Diagnostic yield

1 Introduction

The mediastinum is the central compartment of the thoracic cavity situated between the two pleural cavities, containing essential structures such as the heart, thymus, esophagus, and major blood vessels. Due to its complex anatomy, mediastinal diseases have diverse causes, including benign and malignant tumors, autoimmune disorders, infections, and other conditions. Pathological evaluation is the gold standard for diagnosing mediastinal diseases, providing essential evidence for clinical management and prognosis assessment. Traditionally, sampling of mediastinal tissue has been achieved using surgical techniques such as cervical mediastinoscopy, extended cervical mediastinoscopy, and thoracoscopy. However, these invasive procedures are associated with high costs and a 2–3% risk of serious complications, including mediastinal infection, pneumothorax, and esophageal injury—thus limiting their widespread clinical use [1].

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive procedure that uses ultrasound imaging during bronchoscopy to guide the aspiration of lymph nodes or masses in the mediastinum for histological and cytological analysis. Compared to traditional surgical sampling approaches, EBUS-TBNA offers comparable diagnostic efficiency for detecting and staging mediastinal diseases, with additional benefits such as lower invasiveness, reduced risk of complications, and real-time imaging guidance to sample deeper lymph nodes and masses [13–16]. The current evidence-based guidelines by the European Respiratory Society, the American Thoracic Society, and the American College of Chest Physicians recommend needle-based techniques as the preferred initial approach to lung cancer staging [1, 2, 18]. Nevertheless, the small amount of tissues obtained by EBUS-TBNA may lack sufficient cells or tissue architecture, making it difficult to meet the requirements for histopathological and molecular testing, thus hindering its ability to provide a definitive diagnosis of uncommon tumors or benign mediastinal disease [7, 20]. To obtain larger, intact samples containing more diagnostic information for mediastinal diseases, endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TBMCB) has been recently developed as a novel, safe, efficient, and minimally invasive technique for acquiring mediastinal tissue. In this chapter, we will discuss the advantages and drawbacks of EBUS-TBMCB in detail, as well as its clinical applications.

2 Overview

Cryoprobe has been applied in regular bronchoscopy and radial EBUS-guided lung tissue acquisition, proving to be both safe and efficient [3, 4]. Compared to traditional forceps biopsy, this technique is superior in its capacity to harvest a sufficient sample volume with improved quality for pathological evaluation [4]. The advantages of cryoprobe use for pulmonary tissue acquisition have led to the technical integration of endobronchial ultrasound with cryobiopsy for sampling abnormal mediastinal lymph nodes. In 2020, Zhang et al. firstly reported EBUS-TBMCB for mediastinal sampling, where TBMCB was performed with the guidance of linear EBUS. It involves preprocedural thin-section chest CT and real-time EBUS guidance to precisely locate the lesion. After needle aspiration, a bronchial window is created near the lesion using a high-frequency needle-knife, establishing a channel between the bronchus and the mediastinum. Under ultrasound guidance, a cryoprobe is then inserted through the pathway to harvest tissue samples from the lesion. The integration of real-time ultrasound guidance with the sampling advantages of cryobiopsy ensures both the safety and effectiveness of tissue acquisition from mediastinal lesions. In 2021, the first randomized controlled trial recruiting 197 cases was performed to evaluate the clinical value of EBUS-TBMCB. Compared to EBUS-TBNA, mediastinal cryobiopsy has demonstrated a higher overall diagnostic yield, which significantly improved the diagnosis of benign diseases, and the detection of uncommon tumors. Additionally, the procedure was generally safe and well-tolerated, with only minor adverse events encountered [5].

3 Equipment

EBUS-TBMCB can be performed in a bronchoscopy suite (Fig. 1). Similar to EBUS-TBNA, EBUS-TBMCB requires a convex probe endobronchial ultrasound system and an ultrasound processor to provide real-time imaging guidance. Here, we will focus exclusively on the equipment required for TBMCB.

3.1 High-Frequency Operation System and Electric Needle-Knife

The high-frequency operating system consists of two main components: a high-frequency surgical device (Erbe VI0® 3, Erbe) and a high-frequency needle-knife (Olympus KD-31C-1, Olympus) (Fig. 2). The needle-knife is designed for precise cutting and coagulation. When connected to the

Fig. 1 Mediastinal cryobiopsy can be performed in a regular bronchoscopy suite

surgical device system, it generates heat at the needle tip (Fig. 2c) through the application of high-frequency voltage and current. This minimizes bleeding and provides precise control over cutting depth and energy application.

3.2 Cryoprobe

There are usual two types of diameters of cryoprobe in mediastinal cryobiopsy: 1.1 mm or 1.7 mm. There is no conclusive evidence regarding the impact of probe diameter on diagnostic accuracy. The tip of the cryoprobe is introduced into the mediastinum through the window created by high-frequency knife. When connected to cryogenic equipment (ERBECRYO® 2, Erbe) (Fig. 3a), cryoprobe rapidly releases refrigerant, which absorbs surrounding heat and thus freezes and solidifies the tissue around the probe (Erbe 20,402-401,

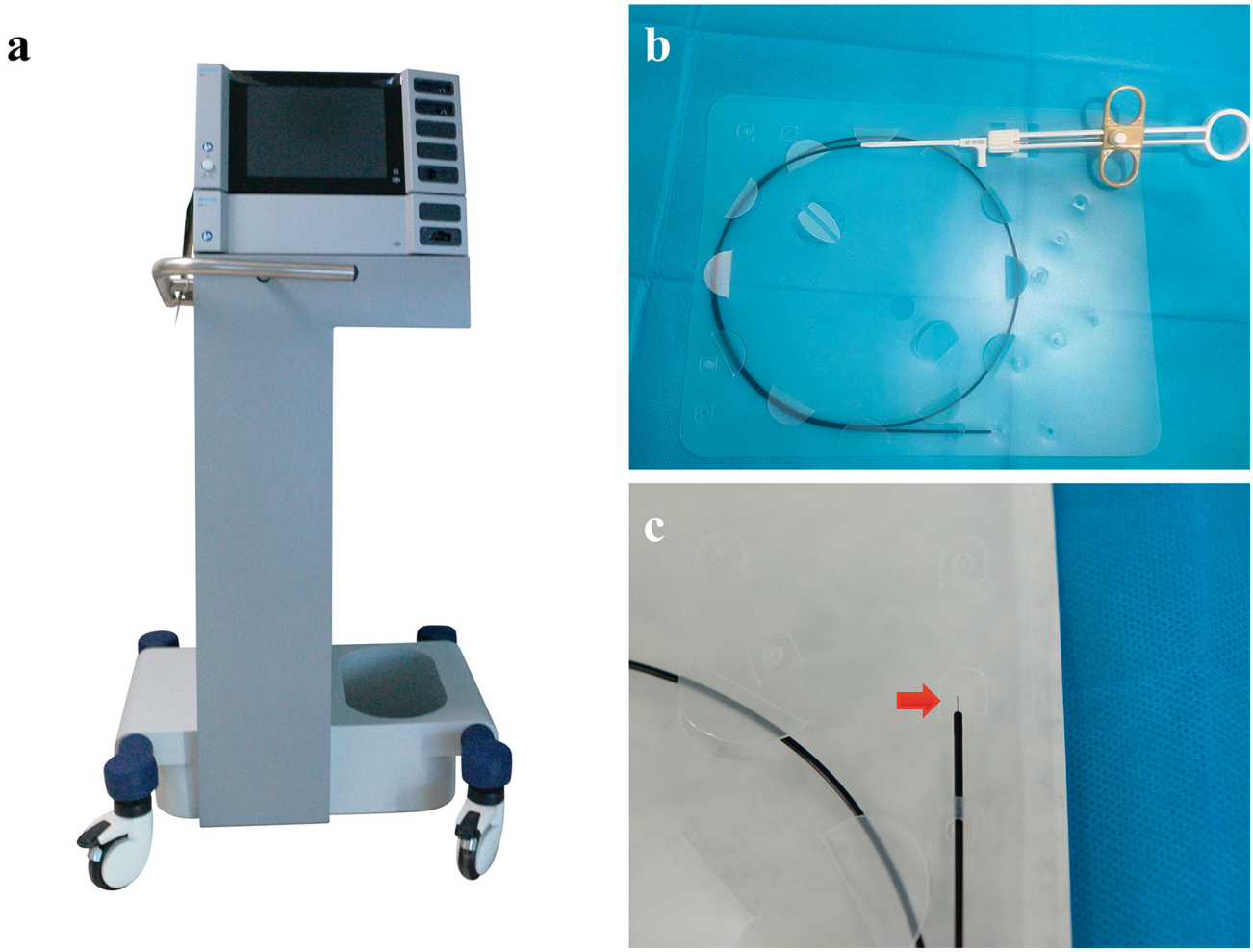

Fig. 2 Cryobiopsy system. High-frequency surgical equipment (Erbe VI0® 3, Erbe) (**a**). A high-frequency needle-knife (Olympus KD-31C-1, Olympus) (**b**, **c**). The red arrow points to the tip of the needle-knife

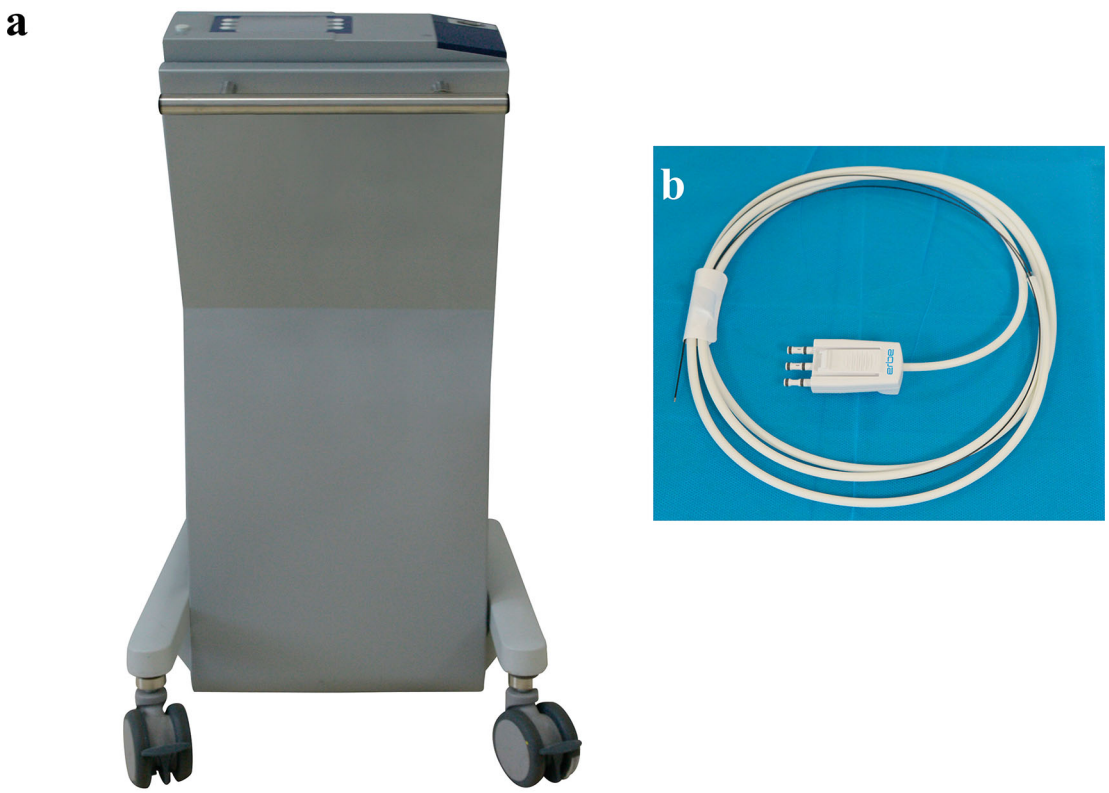

Fig. 3 The cryogenic equipment (ERBECRYO® 2, Erbe) (**a**) and cryoprobe (Erbe 20,402-401, Erbe, Tübingen, Germany) (**b**)

Erbe, Tübingen, Germany) (Fig. 3b). The probe's adhesion to the frozen tissue enables the extraction of the surrounding frozen tissue, thereby facilitating the harvesting of the target mediastinal tissue.

4 Procedure

4.1 Indications and Contraindications

Similar to EBUS-TBNA, the goal of EBUS-TBMCB is to sample and diagnose mediastinal and hilar lymph nodes and lesions. According to published clinical trials, the indications for EBUS-TBMCB include: patients with at least one mediastinal lesion with a short-axis diameter ≥ 1 cm detected by thoracic imaging; patients with newly discovered mediastinal lesions; and patients presenting with clinical respiratory symptoms such as cough, expectoration, thoracalgia, apnea, or complicated lung lesions that require biopsy to determine the etiology. Patients should have undergone necessary preoperative laboratory and imaging examinations, including cardiac ultrasound or CTA when indicated, to exclude potential contraindications. Contraindications for EBUS-TBMCB include: severe cardiopulmonary diseases, coagulation disorders, intolerance to anesthesia or endoscopic procedures, psychiatric disorders, or severe neurosis.

4.2 Anesthesia

Patients are in supine position. The upper airway topical anesthesia is achieved by 2% lidocaine, and conscious sedation is achieved by intravenous injection of midazolam and fentanyl. Oxygen is initially administrated at 1–2 L/min and increased when oxygen saturation is lower than 90%. Patients' vital signs and pulse blood oxygen saturation are continuously monitored. A bronchoscopist performs a mediastinal cryobiopsy under anesthesia.

4.3 EBUS Examination

An EBUS bronchoscope is inserted into the trachea through the nose (if the nose is too narrow for the EBUS bronchoscope to pass through or there are other contradictions, the oral way can be the alternative option). As the EBUS bronchoscope has been inserted in the glottis and the trachea, the bronchi are probed in turn. After the examination of the airway, the EBUS bronchoscope is then contacted with

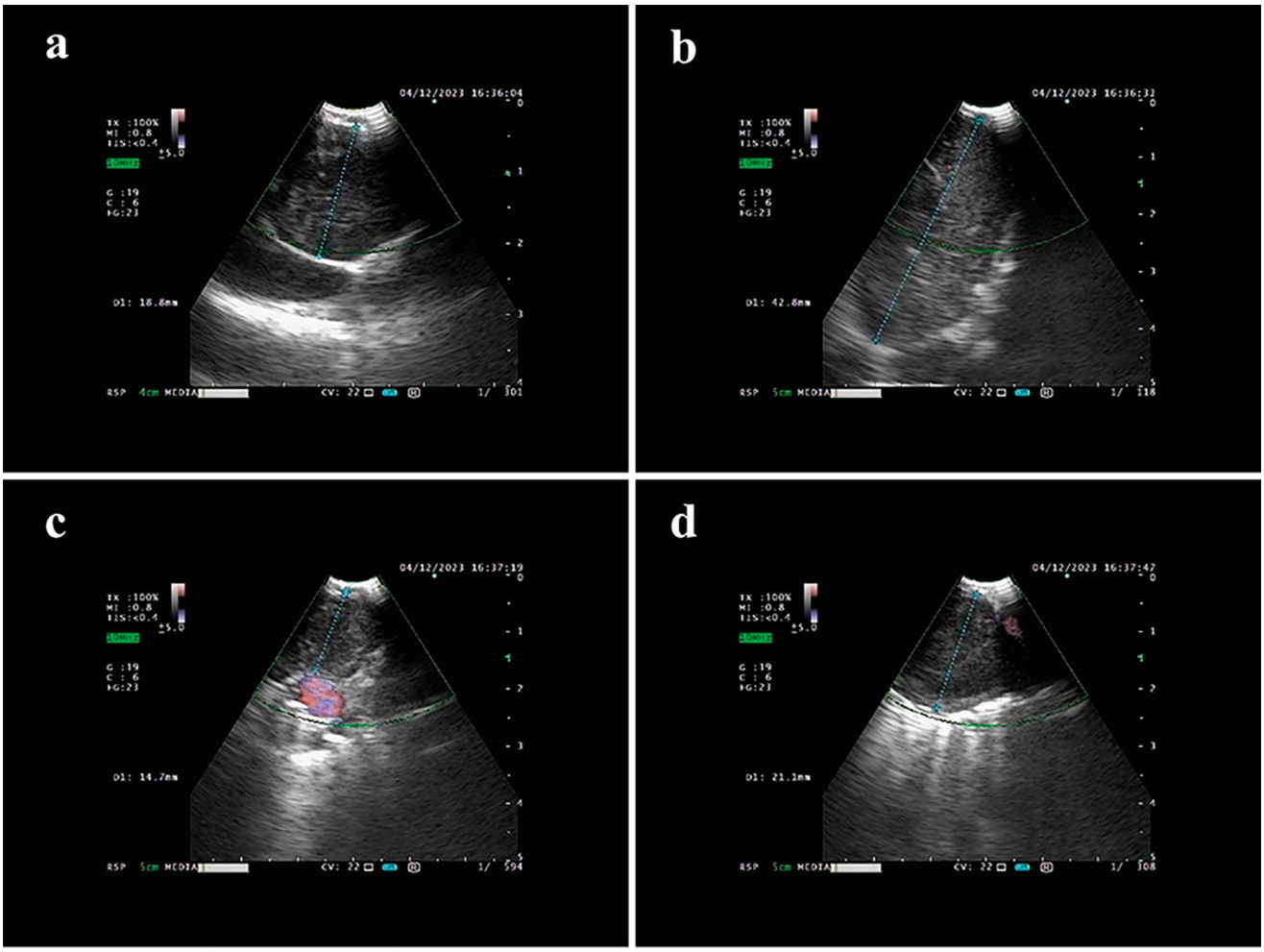

Fig. 4 Endobronchial ultrasound is revealing lymph node soft tissue shadows in groups 4R (**a**), 7 (**b**), 11R (**c**), 12R (**d**), with maximum long diameters of approximately 18.8 mm, 42.8 mm, 14.7 mm, and 21.1 mm, respectively

the airway wall, and a systematic examination of all mediastinal and hilar lymph node stations is sequentially performed according to the Mountain-Dressler lymph node map. For each lesion, the blood supply is identified by the Doppler Ultrasound and the size is measured by its long axis and short axis (Fig. 4). The most suspicious lesion implicated by imaging data (e.g., thoracic CT, PET-CT, ultrasound, etc.) with relatively less biopsy risk is selected as the target for biopsy sampling.

4.4 Opening a Window on the Airway Wall

The target lesion is supervised by ultrasound, and a high-frequency electric needle-knife is inserted through the working channel of the EBUS bronchoscope (Fig. 5a and b), and a cut is then made (about 2–3 mm) on the airway wall adjacent to the target lesions. The knife is thereafter advanced into the lesion under real-time ultrasound visualization, avoiding area with abundant blood flow or massive necrosis. After being confirmed within the lesion and its insertion depth is measured, the needle-knife is then withdrawn. In addition to electric needle-knife, the laser thermal ablation has also been reported to be used in the windowing process [24]. Opening a window is not always necessary. Some researchers have reported the process that after performing the initial puncture with the TBNA needle, a cryoprbe is introduced into the working channel of the EBUS bronchoscope and the cryoprobe is advanced towards the puncture site and gently inserted through the previously created puncture point by the needle into the lymph node [21].

4.5 Cryobiopsy

An appropriate frozen probe is then passed through the working channel of the EBUS bronchoscope, and advanced through the window on the airway wall into the lesion under

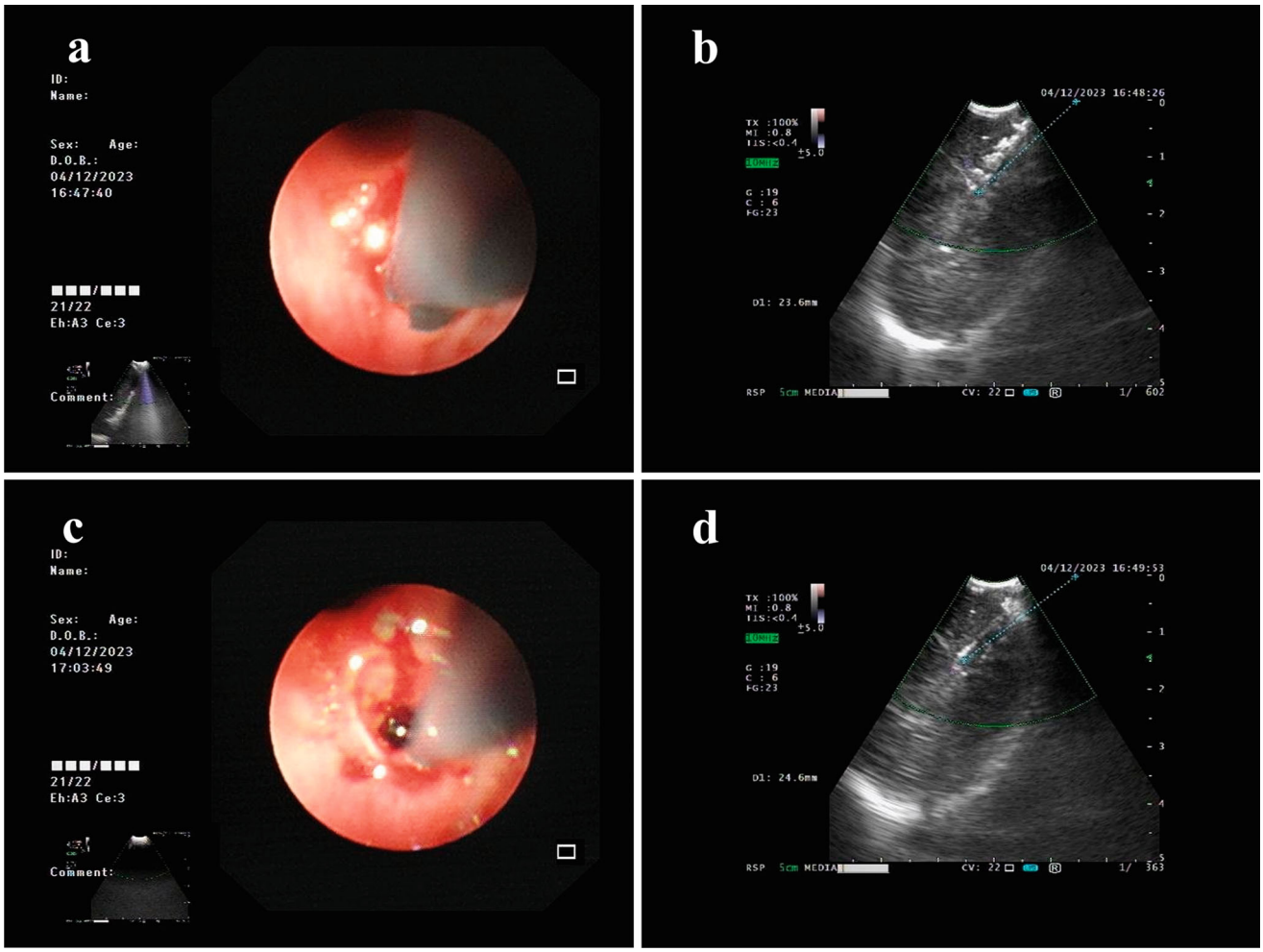

Fig. 5 The procedure of EBUS-TBMCB: Under ultrasound guidance, high-frequency needle-knife fenestration (**a**, **b**) and cryobiopsy (**c**, **d**) were performed on the soft tissue shadow of the group 7 lymph node at the left lateral wall of the protuberance. EBUS-TBMCB, endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy

real-time ultrasound visualization (Fig. 5c and d), avoiding area with abundant blood flow or massive necrosis. After measuring the insertion depth of the cryoprobe, the probe is activated to cool down with nitrous oxide for around 7 s. Thereafter the bronchoscopist gently extracts the cryoprobe tip with rapidly frozen biopsy specimen attached to it, and then withdraws the bronchoscope and the cryoprobe. The frozen specimen is released from the cryoprobe by thawing in saline and fixed in formalin. All the obtained specimens are sent to the Department of Pathology and appropriately processed. Cryoprobe yields intact samples with greater volume compared with TBNA needle or forceps (Fig. 6).

4.6 Postprocedure Check

Check whether there is hemorrhage within the airway through the bronchoscope, especially in the biopsy site. The procoagulants are locally used when necessary. Chest X-ray or other imaging examinations are required within 24 hours to detect whether there is pneumothorax, pneumomediastinum, or mediastinitis. 24 hours after operation, a follow-up is conducted and the symptoms are recorded, including fever, cough, hemoptysis, chest pain, dyspnea, and so on. Perioperative severe adverse events include moderate-severe bleeding (Grade 3 or 4: bleeding requiring topical instillation of epinephrine or ice cold saline or bleeding requiring hemodynamic support, transfusion of blood products, selective mainstem intubation, bronchial blocker, hospital admission, or surgical intervention) [22, 23] oversedation requiring ventilatory support or sedation reversal, pneumothorax with persistent air leak (> 5 days), unplanned hospital readmission, and death. ICU transfer within 48 hours after the procedure is also considered a severe adverse event. 1 month later, a second follow-up is conducted and the complications relative to the operation are recorded.

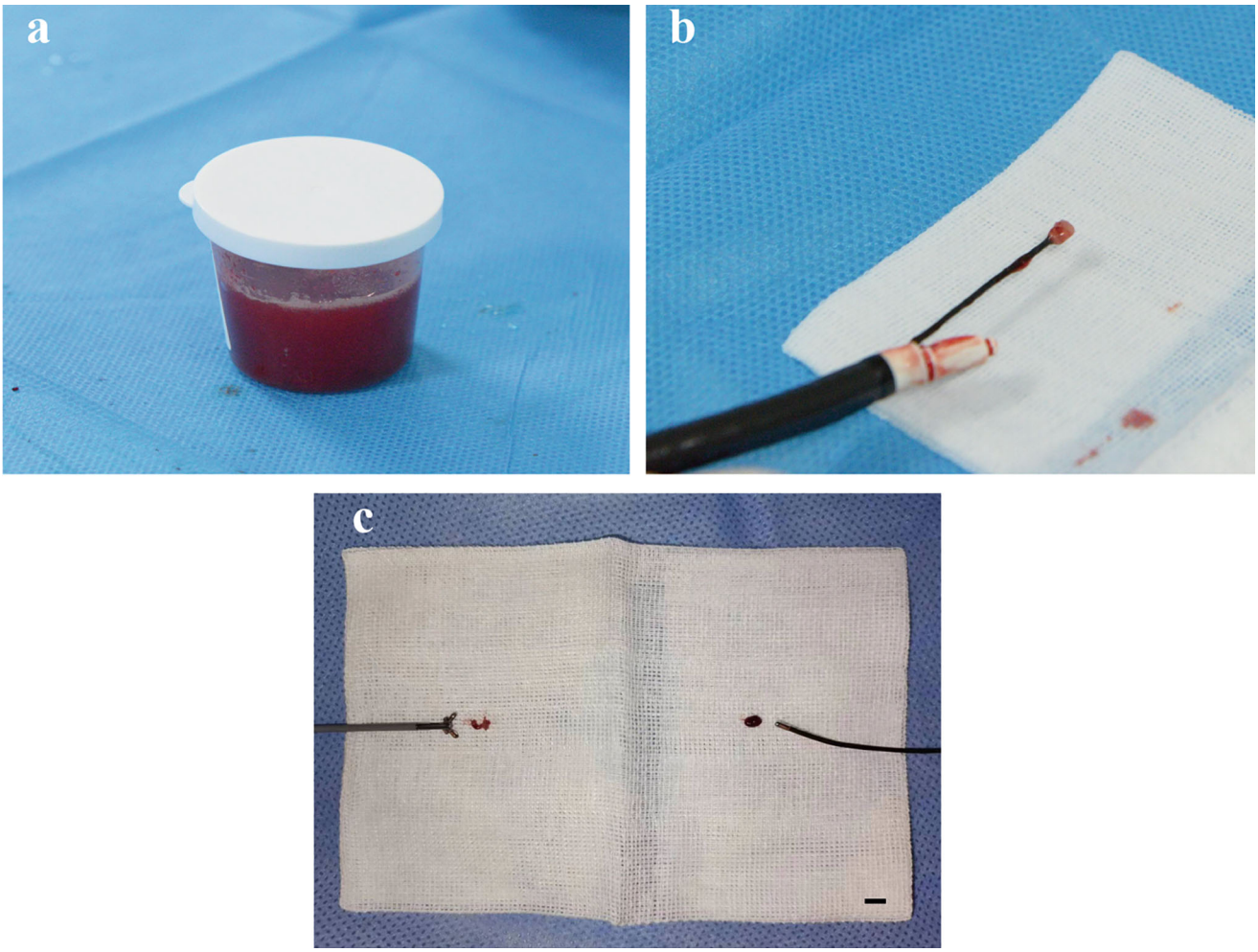

Fig. 6 The tissue volume obtained by EBUS-TBMCB compared with that by EBUS-TBNA and forceps biopsy. Tissue obtained by EBUS-TBNA (tissue suspended in formalin) (**a**). Tissue obtained by EBUS-TBMCB (**b**). Comparison of tissue size obtained by EBUS-TBMCB with a 1.1mm cryoprobe (1time) and EBUS forceps biopsies with a 1.9mm forceps (3 times together) (**c**). Scale bar = 5 mm. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration. EBUS-TBMCB, endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy

5 Diagnostic Yield

According to the published clinical trials, the cryoprobe can be successfully introduced into mediastinal and hilar lesions in all cases, yielding adequate material approximately three times the size of that obtained using standard forceps. The large-scale study has demonstrated that EBUS-TBMCB has a similar safety profile and an improved diagnostic yield compared to standard EBUS-TBNA [5]. It is reasonable to cautiously attribute the diagnostic advantage of TBMCB to intact samples with greater volume.

In Zhang's study, EBUS-TBMCB, but not needle biopsy, resulted in misdiagnosis in three patients with NSCLC (3/135), despite the significantly increased amount of material yielded by transbronchial cryobiopsy [5]. The cause might be that cryobiopsies were always conducted at the same location of the lesion, and as such may have missed the diseased tissue. Nevertheless, the significantly improved diagnostic yield of EBUS-TBMCB for non-lung cancer lesions, along with its benefits in molecular assessment for lung cancer, highlight its potential as a complementary technique to conventional biopsy. This postulate was verified in a multicenter, open-label, randomized trial conducted by Fan and Herth, which determined the safety and diagnostic yield of combining needle aspiration and cryobiopsy as a new sampling strategy for mediastinal lesions and hilar lymphadenopathy. The results indicated that the combination of EBUS-TBNA with cryobiopsy showed similar accuracy in detecting mediastinal metastases compared to standard needle aspiration alone, while providing a superior diagnostic yield for benign disorders. Furthermore, the specimens obtained from the combined biopsies were more suitable for molecular testing and immunological profiling (Fig. 7). These benefits were not accompanied by an increased incidence of procedural complications [6]. Based on the above

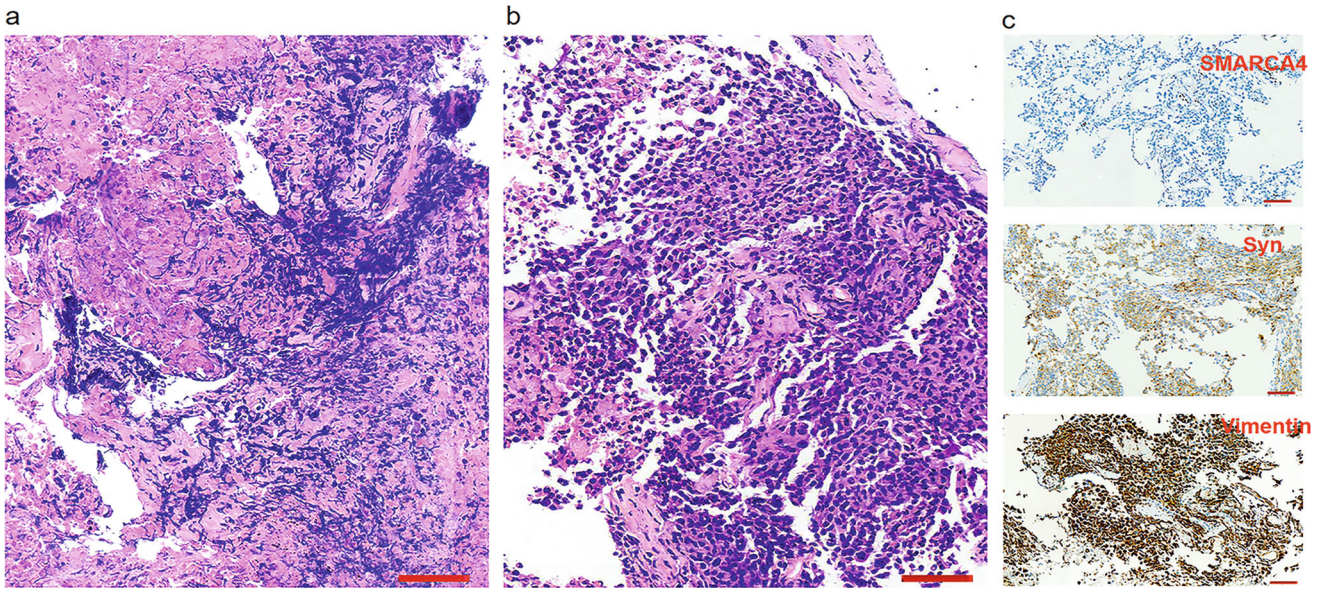

Fig. 7 H&E staining of the specimen from EBUS-TBNA (**a**). H&E staining of the specimen from EBUS-TBMCB (**b**). Immunohistochemistry staining of a specimen from EBUS-TBMCB (**c**). Scale bar, 30 μm. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration. EBUS-TBMCB, endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy

evidence, the combined use of TBNA and cryobiopsy may be the optimal approach for mediastinal diseases.

Forceps biopsy performed under real-time EBUS guidance, a relatively new technique for obtaining more mediastinal tissue, demonstrates enhanced sample quality and improved diagnostic yield compared to EBUS-TBNA, particularly for sarcoidosis and lymphoma [7]. Prior studies have shown that both forceps biopsy and cryobiopsy provide additional diagnostic benefits [6, 8]. Cheng and his colleagues compared these two emerging techniques to determine which one is more compatible with conventional needle biopsy in terms of additional diagnostic benefit relative to the associated risks [9]. In direct head-to-head comparisons, cryobiopsy samples were larger than those obtained from three biopsies using a 1.9 mm standard-sized forceps, directly translating into a superior overall diagnostic yield. Yet, this difference was no longer significant when both techniques were applied as complementary methods to needle aspiration, yet lung cancer patients may benefit from combined needle aspiration and cryobiopsy due to the increased suitability of the obtained tissue for molecular testings. As such, TBMCB might be a valuable adjunct to conventional needle-based biopsy.

6 Safety

EBUS-TBMCB is generally safe. Similar to needle biopsy, bleeding is the most common complication during TBMCB, requiring no additional interventions in most cases. Other adverse events include pneumothorax and mediastinal emphysema, which are much less frequent. Postprocedural chest X-rays or other imaging examinations are useful for the early detection of potential adverse events.

7 Procedural Time

Compared with routine EBUS-TBNA alone, adding cryobiopsy may extend the procedure time by approximately 10 minutes, potentially increasing patient discomfort. However, TBMCB provides more intact tissue samples, enhancing diagnostic utility and potentially reducing the need for additional invasive examinations or unnecessary surgical procedures.

8 Transesophageal Mediastinal Cryobiopsy

For mediastinal lesions that cannot be accessed via the tracheal way, obtaining lymph node samples through the esophageal route—using techniques such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or endoscopic transesophageal fine-needle aspiration with a convex endobronchial ultrasound probe (EUS-B-FNA)—is an alternative option. Guidelines recommend combining EUS-FNA with EBUS-TBNA to increase the number of biopsy samples and enable multiple lymph node biopsies [2, 10]. Consistent with EBUS-TBNA, both EUS-FNA and EUS-B-FNA use fine-needle aspiration for tissue sampling, which may result in inadequate specimens that are unsuitable

for a definitive diagnosis. In 2021, Huang et al. reported the first application of endoscopic transesophageal cryobiopsy, which successfully diagnosed a para-aortic mediastinal lesion as mediastinal nodular lymphocyte predominant Hodgkin lymphoma [11] (Fig. 8). Compared to EUS-B-FNA, transesophageal mediastinal cryobiopsy may provide larger tissue samples with more histopathological information, allowing for additional molecular and immunological testing. However, a major technical challenge of this procedure is obtaining a clear view of the digestive tract with the EBUS scope, which requires repeated inflation of air into the esophagus. Another case series with a larger sample size (30 patients) further demonstrated the advantages of transesophageal mediastinal cryobiopsy. The diagnostic yield for EUS-FNA was 61%, while EUS-TBMCB achieved a 100% yield with no significant complications observed during the procedure [12]. However, larger prospective studies are needed to further validate the diagnostic superiority and safety of cryobiopsy via the esophageal route.

9 Limitations

One of the major limitations of using mediastinal cryobiopsy solely is the risk of misdiagnosing lung cancer, which a combined biopsy strategy may help mitigate. Additionally,

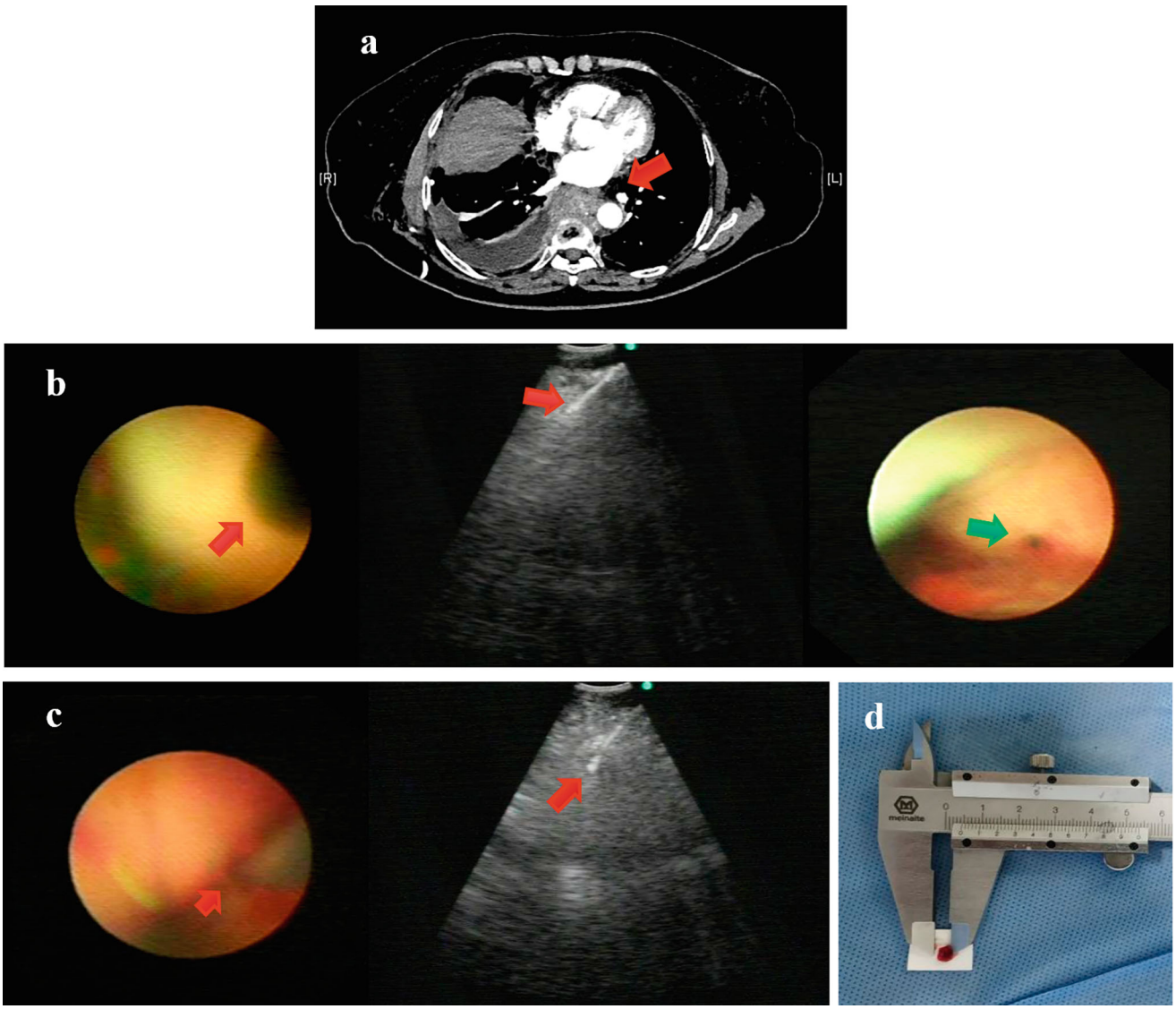

Fig. 8 Transesophageal mediastinal cryobiopsy. CT image showing a posterior mediastinal lesion (red arrow) (**a**). A cut (green arrow) was made through the esophageal wall by the needle-knife (red arrow) under real-time visualization (**b**). EUS-B-guided penetration of the cryoprobe (red arrow) into the mediastinal lesion (**c**). Sample (red arrow) obtained from endoscopic transesophageal mediastinal cryobiopsy (**d**). EUS-B, esophageal endoscopic ultrasound using a convex endobronchial ultrasound probe

current trials have only sampled the most suspicious lesions, leaving the efficiency of multiple-node cryobiopsy unassessed. Furthermore, TBMCB procedure is relatively more complex than needle aspiration, typically requiring skilled bronchoscopists proficient in EBUS techniques.

10 Conclusions

Mediastinal cryobiopsy may serve as a promising complementary technique to standard needle aspiration. It has an acceptable safety profile and provides a significant improvement in overall diagnostic yield for mediastinal lesions when used in conjunction with traditional needle biopsy.

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