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Transbronchial mediastinal cryobiopsy—literature review and practice recommendations

Arthur Oliver Romero[1]^, Sze Shyang Kho[2]^

[1]Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Nevada Las Vegas, Las Vegas, NV, USA; [2]Division of Respiratory Medicine, Department of Medicine, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia

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Correspondence to: Arthur Oliver Romero, MD, MSc, FCCP, DAABIP. Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Nevada Las Vegas, 1707 W Charleston Blvd #270, Las Vegas, NV 89102, USA. Email: arthur.romero@unlv.edu.

Background and Objective: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is currently the preferred method of mediastinal sampling, due to its wide availability, safety, and ease of use. This technique performs very well in diagnosing thoracic malignancy, but utility is less in lymphoma and granulomatous disease. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TBMC) has been posited as an alternative method with the ability to produce histologic samples and higher diagnostic yield. We evaluated the efficacy and safety of EBUS-TBMC in the diagnosis of malignant and benign lesions and proposed detailed procedure methodology to facilitate adaptation of this novel technique.

Methods: We searched PubMed database for relevant articles published up to December 31, 2023. Subsequently, we conducted a comprehensive bibliographic analysis with a particular emphasis on procedural evolution, safety, efficacy, and practice variation. Articles not published in English were translated.

Key Content and Findings: Our literature review, comprising of 20 published articles, highlights the efficacy EBUS-TBMC for evaluation of both malignant and benign mediastinal lesions. Compared to EBUS-TBNA, the cryobiopsy approach has added diagnostic yield for lymphoma, sarcoidosis, and tuberculosis. There is wide practice variation and no standardized technique.

Conclusions: EBUS-TBMC has demonstrated safety and efficacy in diagnosing malignant and benign lesions. Greater utility may be found in the evaluation of suspected lymphoma and granulomatous disease. Further studies are needed to identify optimal techniques and best practices for case selection.

Keywords: Bronchoscopy; cryobiopsy; endobronchial ultrasound (EBUS); mediastinal lymphadenopathy

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Introduction

Few technologies have revolutionized the approach to tissue acquisition in lung disease more than bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The simplicity with which it allows user real-time guidance has led to it being the preferred approach for biopsy of mediastinal structures such as lymph nodes and masses. It is minimally invasive, safe and has diagnostic yields equivalent to mediastinoscopy (1). Its performance has been demonstrated in multiple trials and it has found its way into consensus

^ ORCID: Arthur Oliver Romero, 0000-0002-5822-9751; Sze Shyang Kho, 0000-0002-1457-9231.

guidelines for staging lung cancer (2). Where EBUS-TBNA falls short is in lymphoma and benign conditions such as sarcoidosis (3,4). The histological pattern is necessary for diagnosis, and this is lost in cytology samples. Furthermore, current treatment paradigms for cancer require tissue for molecular analysis and EBUS-TBNA is not always reliable in producing adequate cellularity.

The flexible cryoprobe has proven to be very useful in diagnostic and therapeutic bronchoscopy. It is a mainstay for ablation of central airway obstructing tumors as well as the removal of pernicious mucus plugs and blood clots. Patients undergoing work up for diffuse parenchymal lung disease have been spared from surgical lung biopsy with the advent of transbronchial cryobiopsy. The meld of cryobiopsy and ultrasound bronchoscopy in the form of endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TBMC) is now presenting as a promising solution to mediastinal tissue sampling without the limitations of needle aspiration. A prerequisite in performing EBUS-TBMC is the ability to create a track in which to pass the cryoprobe through the bronchial wall. Unlike the EBUS needle the cryoprobe has a larger diameter and blunt tip, thus strategies are available to allow passage into the lymph node.

Intranodal forceps biopsy (IFB), is another bronchoscopy technique for mediastinal sampling that can be performed via the EBUS bronchoscopy (5). Several studies including a meta-analysis have shown that adding this complementary technique to standard EBUS increases the diagnostic yield for sarcoidosis and lymphoma (6,7). Although not the topic of this review, technical aspects of EBUS-IFB, regarding track creation, also apply to EBUS-TBMC (8,9).

Botana-Rial *et al.* performed a systematic review of 7 studies comparing the diagnostic yield of EBUS-TBNA and EBUS-TBMC (10). The results describe the selective advantage of using EBUS-TBMC in cases with benign pathologies and other tumor types such as lymphoma. Case reports were not included and missed on reporting a notable adverse effect. Furthermore, there was also no guidance on how to perform the procedure as required for adoption of the technique. Therefore, the objectives of this study are to review the broader published evidence on safety and efficacy of EBUS-TBMC, present the development and historical context, and propose detailed practice recommendations to facilitate proper conduct of the procedure. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-120/rc).

Methods

We conducted a comprehensive literature search of the PubMed database using a predefined protocol. Our search terms included ("endobronchial ultrasound" OR "EBUS" OR "endobronchial ultrasound-guided") AND ("cryobiopsy" OR "mediastinal cryobiopsy" OR "transbronchial cryobiopsy") AND "cryoEBUS". We restricted our search to articles having human subjects up to December 31, 2023. We also manually explored bibliographic references from the chosen papers to capture any additional pertinent studies. Articles in Spanish and German were translated into English. We first identified potentially relevant papers by reviewing abstracts procured from our search. We included clinical trials, case series and case reports to have a comprehensive evaluation of available literature. We excluded conference abstracts and articles with non-human, animal study subjects. The literature search strategy is reported in *Table 1*.

Approach to mediastinal abnormalities

The mediastinum is the anatomical compartment bounded laterally by both lungs and is divided into superior, anterior, middle, and posterior compartments. Surgical approaches such as mediastinoscopy, thoracoscopy and anterior mediastinotomy allow access to all the compartments. These have a high diagnostic yield but were also associated with surgical morbidity and complications. Percutaneous needle biopsy under computerized tomography (CT) guidance allowed easy access to more anterior lesions with 96% diagnostic yield in a series of 45 patients (11). There is an additional risk of pneumomediastinum and pneumothorax especially if the needle trajectory passes through a transpulmonary route. The endoscopic approach through the tracheobronchial tree or esophagus via EBUS-TBNA or endoscopic ultrasound (EUS) is now the preferred approach especially for mediastinal adenopathy owing to the following advantages: (I) high diagnostic yield that is equivalent to mediastinoscopy; (II) ability to access multiple lymph node stations; and (III) ability to detect and sample lymph nodes even those <10 mm in size (12,13).

EBUS-TBNA

TBNA for flexible bronchoscopy allows access to deeper mediastinal structures via the endobronchial approach (14).

Table 1 Literature search strategy

Items	Specification
Date of search	6/1/2023 to 12/31/2023
Databases searched	PubMed
Search terms	("endobronchial ultrasound" OR "EBUS" OR "endobronchial ultrasound-guided") AND ("cryobiopsy" OR "mediastinal cryobiopsy" OR "transbronchial cryobiopsy") AND "cryoEBUS")
Timeframe	Articles published until 12/31/2023
Inclusion criteria	Original articles, case series and case reports
Exclusion criteria	Conference abstracts, articles with animal study subjects
Selection process	Both authors generated a list of prospective studies

EBUS, endobronchial ultrasound.

Conventional TBNA is a blind technique that requires prior review of imaging such as chest CT scan to identify mediastinal targets for biopsy. The diagnostic yield for malignant lesions is greatly dependent on lesion size, only 27.5% if <3 cm and 65.5% if >3 cm diameter (15). EBUS bronchoscopy was introduced in 2002 and when combined with TBNA, allows real-time targeting of mediastinal and hilar structures from the tracheobronchial tree (16). Yasufuku *et al.* reported a series of 140 patients with undiagnosed mediastinal masses, the overall diagnostic yield of EBUS-TBNA is 93.6% (17). This minimally invasive approach has become the mainstay for evaluation of lymphadenopathy and other lesions adjacent to airways and has replaced mediastinoscopy as the recommended initial staging technique for lung cancer.

Limitations of EBUS-TBNA

While EBUS-TBNA has an excellent yield with primary thoracic malignancy and metastatic lesions, its performance with other diagnoses varies. Lymphoma, sarcoidosis, and tuberculosis are among the conditions that present diagnostic challenges to pulmonologists who perform EBUS-TBNA. Particularly in endemic areas, sarcoidosis and tuberculosis, both of which have granulomas on histologic findings, are difficult to differentiate.

Lymphoma

A frequent concern with EBUS-TBNA is the limited sample volume which may not adequately diagnose lymphoma, especially *de novo* disease. The diagnosis of lymphoma requires accurate subtyping to direct treatment options and additional specimens are required for cytomorphology, immunophenotyping, cytogenetics, and molecular features. An early study on EBUS-TBNA for lymphoma demonstrated a sensitivity 91%, but these studies were performed on a small series of patients (18). Grosu *et al.* specifically examined the ability to subtype lymphoma which varied from *de novo* disease at 67% to 81% in recurrent disease (19). Further discrepancies were noted by Moonim *et al.* in subtyping lymphomas with a sensitivity for Hodgkin lymphoma as low as 79% (20).

Sarcoidosis

The diagnosis of sarcoidosis requires demonstration of non-necrotizing granulomas and exclusion of other causes of granulomatous inflammation. Pulmonary sarcoidosis commonly involves bilateral hilar adenopathy, which allows for easy access via an endobronchial approach. Pooled results from two meta-analyses showed an EBUS-TBNA diagnostic accuracy of 79–84% (3,21). Given that diagnosis in about 1 out of 5 patients is missed, expert recommendation includes performing EBUS-TBNA in conjunction with endobronchial and transbronchial biopsy (22).

Tuberculosis

Tuberculous lymphadenopathy accounts for 26–28% of extrapulmonary tuberculosis and is seen in high-risk patients in endemic areas as well as inner-city dwellings (23). The diagnostic yield of EBUS-TBNA varies by setting, from 72% in a single hospital series in India to 94% in a multicenter study in the UK (24,25). A meta-analysis of 684 patients with mediastinal tuberculous lymphadenopathy

who underwent EBUS-TBNA showed a pooled diagnostic yield of 80%, although there was significant heterogeneity among the 14 studies reviewed (26). Employing a composite clinicopathologic diagnosis with culture and histological results with nucleic acid amplification tests can increase the diagnostic accuracy by up to 98% (26).

Development of TBMC

Cryosurgical techniques have been used in the airways since 1968 but the first use of a flexible cryoprobe during bronchoscopy, for palliation of endobronchial tumors, was reported by Mathur *et al.* in 1996 (27). Similar technology was then applied for transbronchial biopsy in diffuse parenchymal lung disease to avoid the crush artifact that results in forceps biopsy (28). Complications include hemoptysis and pneumothorax and safety concerns have been raised at the onset (29,30). This technique is safer with fluoroscopy guidance and the use of endobronchial blockers to tamponade any bleeding (31). Since then, cryoprobes have become popular tools for the evaluation of peripheral lung nodules and diffuse parenchymal lung disease (32).

The feasibility of cryobiopsy to sample mediastinal lymph nodes was first described by Franke *et al.* in 2013 in an *in vivo* porcine model (33). A 21G cryo-needle was advanced via transbronchial approach into a paratracheal lymph node with EBUS guidance. A 2-second freezing time was used, followed by retraction of the needle and biopsy sample into a protective sheath. The cryo-needle was removed from the bronchoscope working channel. Sample analysis showed an adequate number of lymphocytes reflecting a representative lymph node sample. The first reported human use of EBUS-TBMC was not until 2020, reported by Zhang *et al.* in a 19-year-old patient with mediastinal seminoma, after an initial non-diagnostic EBUS-TBNA (34).

Review of literature on EBUS-TBMC

Our literature search resulted in 20 published articles on EBUS-TBMC from 2020 to 2023. The results of all the studies were extracted and summarized for review. All the articles came from centers in Asia and Europe. There are two randomized trials, followed by a small number of prospective cohort studies. Most of these reports are on diagnostic yield and safety. The rest of the studies are case series and case reports. The various methodology used in the review articles, including study design, biopsy techniques and inclusion/exclusion criteria, are listed in *Table 2*.

Efficacy

Among these studies is a large dual-center trial by Zhang *et al.* with 197 subjects presenting with mediastinal lesions ≥10 mm (35). The subjects were randomized using a crossover design starting with EBUS-TBNA then EBUS-TBMC or vice versa. The overall diagnostic yields were 79.9% and 91.8% (P=0.001) for TBNA and TBMC, respectively. The diagnostic yields for lung cancer, both small cell and non-small cell subtypes, were similarly high in both arms (94.1% *vs.* 95.6%, P=0.58). TBMC was more sensitive in cases of uncommon tumors (91.7% *vs.* 25.0%, P=0.001) and benign disorders (80.9% *vs.* 53.2%, P=0.004). Cryobiopsy was also able to diagnose all cases of sarcoidosis and tuberculosis whereas half and one-third were missed by TBNA, respectively. The most sampled lymph node stations were 7, 4R and 4L, but practically all level lymph nodes were represented.

From the same group that published the first trial, Fan *et al.* recruited 271 patients from 3 centers for a follow up trial to assess the safety and added value of combined EBUS-TBNA and TBMC compared to standard EBUS-TBNA alone (36). Subject eligibility and procedural technique were identical to the previous study. Results show that the addition of cryobiopsy to standard sampling increased the overall diagnostic yield from 81% to 93% (P=0.0039). However, subgroup analysis showed already high diagnostic yields for TBNA alone compared to TBMC (99% *vs.* 99%, P=1.00) for mediastinal metastases from lung and extra thoracic primary cancers. The combined approach is also better for diagnosing benign disorders (94% *vs.* 67%, P=0.0009) and collected more samples for molecular and immunological testing for non-small cell lung cancer. The reported diagnostic yields between TBNA *vs.* TBMC, as well as the histologic diagnosis and cancer subtypes, are summarized in *Table 3*.

There is limited data on lymphoma cases in our review of published studies on EBUS-TBMC. Only 8 (out of 197) and 10 (out of 276) lymphoma diagnoses were reported in the two randomized trials, representing just 4% and 3.7% of cases, respectively (35,36). The combined diagnostic yield for lymphoma from TBMC for both trials is 83.33% (15 of 18 cases). Pooling all the reported lymphoma cases identified across the studies, there are 29 cases with diagnostic yield by TBNA of 27.6% (8 of 29) and TBMC 89.7% (26 of 29) (35-38,40,43). TBNA samples were described as deformed atypical cells whereas TBMC provided larger and better-preserved tissue allowing not just

Table 2 Methodology of published TBMC articles

First author	Year	Study site	N	Design	Sampling method	Inclusion	Exclusions
Zhang (35)	2021	Chongqing, China/ Heidelberg, Germany	196	RT	1:1—TBNA or TBMC first	≥1 cm short axis	Mediastinal cysts, abscesses
Fan (36)	2023	Chongqing, China/ Heidelberg, Germany	271	RT	1:1—TBNA *vs.* TBNA + TBMC	≥1 cm short axis	Mediastinal cysts, abscesses
Ariza-Prota (37)	2023	Oviedo, Spain	50	Pro	TBNA + TBMC	≥1 cm	Multiple comorbidities
Gershman (38)	2022	Tel Aviv, Israel	24	Pro	TBNA + TBMC	>1 cm, FDG avid	Not reported
Oikonomidou (39)	2022	Thessaloniki, Greece	63	Pro	TBNA 19/21/22G *vs.* TBMC	1–3 cm	Not reported
Maturu (40)	2024	Hyderabad, India	46	Pro	TBMC after TBNA and ROSE negative	>1 cm	Not reported
Gonuguntla (41)	2021	Hyderabad, India	4	CS	TBNA + TBMC	>1 cm	N/A
Ariza-Prota (42)	2022	Oviedo, Spain	4	CS	TBNA + TBMC	Not reported	N/A
Genova (43)	2022	Genova, Italy	5	CS	TBNA + TBMC	≥2 cm	N/A
Salcedo-Lobera (44)	2022	Malaga, Spain	3	CS	TBNA + TBMC	Not reported	N/A
Zhang (34)	2020	Chongqing, China	1	CR	TBNA + TBMC	N/A	N/A
Huang (45)	2022	Chongqing, China	1	CR	EUS-B FNA + TBMC	N/A	N/A
Ishiguro (46)	2022	Tokyo, Japan	1	CR	TBNA + IFB + TBMC	N/A	N/A
Kho (47)	2022	Kuching, Malaysia	1	CR	TBNA + IFB + TBMC	N/A	N/A
Tamburrini (48)	2022	Ferrara, Italy	1	CR	TBNA + IFB + TBMC	N/A	N/A
Zhang (49)	2022	Chongqing, China	1	CR	TBNA + TBMC	N/A	N/A
Hetzel (50)	2023	Tubingen. Germany	1	CR	TBMC	N/A	N/A
Schwick (51)	2023	Aachen, Germany	1	CR	TBNA + TBMC	N/A	N/A
Takemura (52)	2023	Tokyo, Japan	1	CR	TBNA + IFB-TBMC	N/A	N/A
Zhang (53)	2023	Chongqing, China	1	CR	TBNA + TBMC	N/A	N/A

RT, randomized trial; Pro, prospective; CS, case series; CR; case report; TBNA, transbronchial needle aspiration; TBMC, transbronchial mediastinal cryobiopsy; G, gauge; ROSE, rapid onsite evaluation; EUS-B, endoscopic ultrasound bronchoscopy; FNA, fine needle aspiration; IFB, intranodal forceps biopsy; FDG, fluorodeoxyglucose; N/A, not applicable.

histologic diagnosis but adequate subtyping (45,48,49).

Sarcoidosis presenting as mediastinal adenopathy is easily diagnosed by TBMC. In all the studies, including the two randomized trials, the diagnostic yield of TBMC for sarcoidosis is 100% (52 of 52 cases) (37,38,41). Interestingly, the prospective trials by Ariza-Prota *et al.* (37) (6 of 6 cases) and Gershman *et al.* (38) (11 of 11) also show an EBUS-TBNA diagnostic yield of 100%, showing full concordance between the two sampling techniques. The pooled TBNA diagnostic yield is lower at 76.9% (42 out of 50 cases). This translates to a modest additional diagnostic yield of 23.1% with TBMC.

Cryobiopsy also worked well for tuberculous mediastinal lymphadenitis. There are 43 cases of tuberculosis in the pooled data with low TBNA diagnostic yield at 48.8% (21 of 43 cases) (35,36,40,41,47). This is very low in comparison to TBMC which was able to diagnose tuberculous lymphadenopathy in 100% of the cases with an added diagnostic yield of 51.2%. The presence of acid-fast bacilli from a TBNA smear does not always guarantee enough material for nucleic acid amplification testing for rapid identification and resistance testing, which may be an added benefit of larger cryobiopsy samples (47).

Table 3 Biopsy characteristics, diagnostic yield, and complications of transbronchial mediastinal cryobiopsy

First author	Year	N	TBNA yield, %	Cryo yield, %	Cryo histology	Complications
Zhang (35)	2021	196	79.9	91.8	Lung CA—129; lymphoma—7; sarcoidosis—15; tuberculosis—16	Pneumothorax—2 (1%); pneumomediastinum—1 (0.5%); bleeding—11 (11%)
Fan (36)	2023	271	81	93	Lung CA—63; metastatic CA—5; lymphoma—8; sarcoidosis—16; tuberculosis—19	Pneumothorax—2 (1%); pneumomediastinum—1 (1%); bleeding—19 (14%)
Ariza-Prota (37)	2023	50	82	96	Lung CA—26; metastatic CA—2; lymphoma—4; sarcoidosis—6	Bleeding—2 (4%)
Gershman (38)	2022	24	87.5	83.33	Sarcoidosis—11; malignancy—9; non-diagnostic—4	None
Oikonomidou (39)	2022	63	NA	NA	Not reported	Bleeding—17 (27%)
Maturu (40)	2024	46	41.3	71.7	Lung CA—12; metastatic CA—4; lymphoma—2; granulomatous; inflammation—13	Bleeding—13 (28%)
Gonuguntla (41)	2021	4	100	100	Lung CA; metastatic CA; sarcoidosis; tuberculosis	Bleeding
Ariza-Prota (42)	2022	4	100	100	lung CA (squamous cell, small cell); lymphoma	Bleeding
Genova (43)	2022	5	80	60	Squamous cell lung CA; lymphoma	None
Salcedo-Lobera (44)	2022	3	100	100	Lung CA (squamous cell, small cell); metastatic CA (esophageal CA)	None
Zhang (34)	2020	1	–	+	Seminoma	Bleeding
Huang (45)	2022	1	–	+	Hodgkin lymphoma (nodular lymphocyte predominant)	None
Ishiguro (46)	2022	1	–	+	Esophageal leiomyoma	None
Kho (47)	2022	1	+	+	Tuberculous granuloma	None
Tamburrini (48)	2022	1	–	+	NHL	None
Zhang (49)	2022	1	–	+	NHL	Bleeding
Hetzel (50)	2023	1	–	+	Adenocarcinoma	None
Schwick (51)	2023	1	–	+	Marginal zone lymphoma	Hemomediastinum; respiratory failure, shock
Takemura (52)	2023	1	–	+	SMARCA4-deficient; undifferentiated tumor	None
Zhang (53)	2023	1	–	+	SMARCA4-deficient; undifferentiated tumor	Bleeding

TBNA, transbronchial needle aspiration; CA, cancer; NA, not applicable; NHL, non-Hodgkin's lymphoma.

Safety

Bronchoscopy with EBUS-guided transbronchial needle biopsy is minimally invasive and safe (54). The addition of a cryoprobe biopsy tool may raise the risks due to the larger specimen taken and larger defect created in the airway wall. There is little data on safety from this technology aside from what can be extrapolated from transbronchial cryobiopsy for interstitial lung disease (ILD) (55).

The reported complications from the reviewed articles

are reported in *Table 3*. These include airway bleeding, pneumothorax, pneumomediastinum and mediastinitis. The most common complication reported among all the studies reviewed is bleeding. Reporting of bleeding severity is inconsistent and not standardized across the articles. Bleeding is seen in up to 11–28% of cases. However, most bleeding is mild and only 1–2% have grade 3 bleeding which is not life threatening but required intervention (35,36). Pneumothorax and pneumomediastinum risk are both at 1%, as seen on post procedure chest radiograph. These were self-limited and none required drainage.

Schwick *et al.* (51) reported serious complications in a patient that was evaluated for suspected lymphoma. EBUS evaluation revealed bilateral hilar and subcarinal, vascular lymph nodes 10–20 mm in size. TBNA with G19 needle in the subcarinal node was done followed by dilation of the opening with the needle sheath. There was bleeding that required epinephrine and hemostasis was achieved. Two hours after the procedure, the patient went into respiratory failure, shock and was transferred to the intensive care unit (ICU) requiring vasopressors and blood transfusion. CT chest revealed a large mediastinal hematoma with active bleeding and partially detached parietal pleura. Follow up scans show no increase in hemomediastinum, and patient recovered without a need for intervention. The biopsy showed marginal zone lymphoma.

EBUS-TBMC technique

EBUS-TBMC shares initial procedural steps with EBUS-TBNA. However, there are several caveats to consider, such as the insertion and placement of the cryoprobe, specimen retrieval, and the management of complications. The existing literature primarily reports EBUS-TBMC being performed by experienced bronchoscopists in high-volume centers that specialize in diagnostic and therapeutic bronchoscopy. The authors agree that EBUS-TBMC should be limited to centers with expertise in EBUS-TBNA and transbronchial cryobiopsy until further safety data and technical refinements become available for wider adoption within the pulmonology community. The wide variation in procedure techniques described in the reviewed articles are summarized in *Table 4*.

Pre-procedural assessment

The general assessment of patient planning for EBUS-TBMC closely aligns with that of EBUS-TBNA. Perioperative risk assessment needs to be carried out, especially in patients with unstable heart disease, pulmonary hypertension, and chronic respiratory failure. There are specific considerations that warrant additional attention, particularly regarding the bleeding profile (e.g., platelet count, coagulation factors), to ensure hemostatic stability during the procedure. Additionally, any anticoagulant/antiplatelet medications should be discontinued in accordance with recommended guidelines to minimize the risk of bleeding complications (56).

Airway management, anesthesia and ventilation

Most of the high-volume centers perform EBUS procedures under conscious sedation via the transoral, transnasal routes or with a laryngeal mask airway (35-38,40,57). The choice of using endotracheal tube and general anesthesia may facilitate more rapid removal and insertion of the bronchoscope during cryobiopsy passes. This may also serve to protect the vocal cords from injury. In the two large multicenter trials, the method of anesthesia varied between sites (Germany and China). This adherence to local practice did not affect the diagnostic yield and safety of EBUS-TBMC (35,36). Rigid bronchoscopy for this approach has also been reported but is not needed unless there is anticipation of moderate to heavy bleeding or other therapeutic procedures are planned (47,48).

Target selection

The selection of target site for EBUS-TBMC depends on the specific indication of the procedure. In cases where there is a high probability of lung cancer with concurrent suspicious lung nodule, a standard EBUS approach involves systematic examination and sampling of the mediastinal and hilar lymph nodes. Beginning with the highest nodal station and moving towards the lower station is recommended. This "upstaging" oncological principle should be followed and EBUS-TBMC is only performed sequentially after EBUS-TBNA on a single nodal station that is deemed most likely to be malignant. This is usually characterized by larger size, sharp margins, a rounded shape, and the absence of central hilar structure. Rapid onsite examination (ROSE) is not available in many centers but may be useful in identifying the lymph node target for cryobiopsy.

For patients with isolated hilar or mediastinal lymph nodes without suspicious lung nodules, EBUS-TBNA is initially conducted as per usual practice, followed by TBMC

Table 4 Variability in transbronchial mediastinal cryobiopsy technique

First author	Year	Anesthesia	Airway	Targeted LN	Needle size/ passes	ROSE	Cryo size	Track creation	No. MCB pass	Freezing time (seconds)
Zhang (35)	2021	CS	Transoral	2R/L to 12R/L	22G ×4	No	1.1	EC knife	3	7
Fan (36)	2023	CS	Transoral	2R/L to 13R/L	22G ×4	No	1.1	EC knife	1	7
Ariza-Prota (37)	2023	CS	Transoral	7, 4R mostly	22G ×3–5	No	1.1	TBNA	3	4
Gershman (38)	2022	CS/DS	LMA	7, 4L	19G ×3	No	1.1/1.7	TBNA/Nd YAG/ track dilation	2–4	3–4
Oikonomidou (39)	2022	CS/DS	LMA/ETT + jet vent	N/A	19/21/22G ×4	No	1.1	TBNA + 19G sheath	2	3
Maturu (40)	2024	GA	LMA	7, 4R, 11L, 11R	19G	Yes	1.1	TBNA	4–7	5–6
Gonuguntla (41)	2021	GA	LMA	7, 11L	19/21/22	Yes	1.1	TBNA	1–2	3
Ariza-Prota (42)	2022	CS	Transoral	7,11R	22G ×4	Yes	1.1	TBNA	3	3
Genova (43)	2022	DS	Not reported	7, 10R	19G ×3	No	1.1	TBNA	2	4
Salcedo-Lobera (44)	2022	CS	Transoral	7, retrotracheal mass	22G ×3	No	1.1	TBNA	1-2	8
Zhang (34)	2020	CS	Transoral	10L	22G ×4	No	1.1	EC knife	2	15
Huang (45)	2022	CS	Transoral + esophageal	Paraaortic LN	21G ×4	No	1.1	Air inflation + EC knife	2	7
Ishiguro (46)	2022	N/A	Not reported	Esophageal mass	22G ×3	No	?	TBNA	2	?
Kho (47)	2022	TIVA	RB	7	22G ×4	Yes	1.1	TBNA	2	7
Tamburrini (48)	2022	GA	RB	7	21G	No	1.1	TBNA + forceps	2	4
Zhang (49)	2022	CS	Transoral	7	21G ×4	No	1.1	TBNA + sheath	1	7
Hetzel (50)	2023	Not reported	Transoral	4L	(Not reported) G ×4	Yes	1.1	EC knife	Several	7
Schwick (51)	2023	GA	ETT	7	19G ×2–3	No	1.1	TBNA + sheath	1	5–7
Takemura (52)	2023	Not reported	Not reported	11s	25G ×3	No	1.7	TBNA	4	Not reported
Zhang (53)	2023	CS	Transoral	11L	21G ×4	No	1.1	EC knife	1	7

CS, conscious sedation; DS, deep sedation; GA, general anesthesia; TIVA, total intravenous anesthesia; N/A, not applicable; LMA, laryngeal mask airway; ETT, endotracheal tube; RB, rigid bronchoscopy; LN, lymph node; G, gauge; ROSE, rapid onsite evaluation; EC, electrocautery; TBNA, transbronchial needle aspiration; Nd YAG, neodymium-doped yttrium aluminum garnet laser; MCB, mediastinal cryobiopsy.

at the largest lymph node identified during the EBUS examination. Larger studies used ≥10 mm lymph node (short axis) as criteria on when to perform EBUS-TBMC (35,36). The lymph node stations most frequently biopsied have been stations 7, 4R/4L and 11R/11L. However, experience from larger trials shows that any lymph nodes from stations 2 to 12 have been biopsied via TBMC (*Table 4*). Thorough examination of the overlying mucosa is crucial. Any nodal station with abnormal overlying mucosa should be avoided to mitigate the theoretical risk of poor wound healing which may lead to fistula formation. Additionally, avoid performing EBUS-TBMC over lymph nodes that exhibit necrotic or cystic appearances, as they may suggest a higher pre-test probability for infection, especially

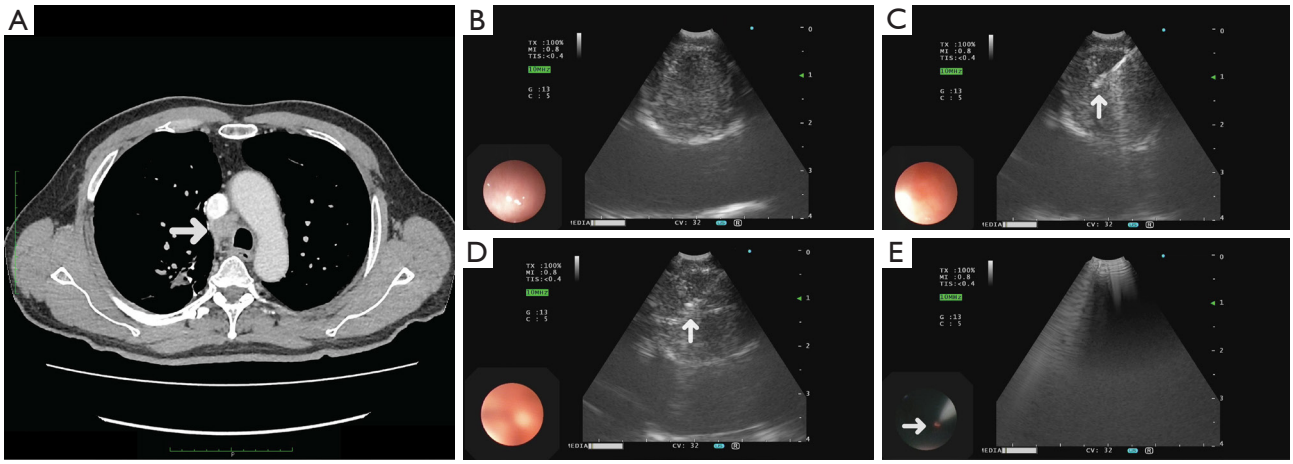

Figure 1 Right paratracheal lymph node. CT chest axial view showing enlarged right paratracheal lymph node (arrow, A). EBUS evaluation revealed a 2 cm heterogeneous station 4R lymph node with loss of central hilar structure (B). Subsequently, an EBUS-TBNA procedure was carried out using a 22G TBNA needle, providing initial biopsy samples (arrow, C). Following this, a 1.1 mm cryoprobe was inserted into the target lesion through the mucosal defect created by the TBNA puncture. The tip of the cryoprobe was clearly visualized under EBUS vision (arrow, D), aiding in precise positioning within the target area. The cryoprobe was then activated for 4 seconds and retrieved *en bloc* with the EBUS bronchoscope, and a substantial specimen was observed adhering to the tip of the cryoprobe (arrow, E). CT, computerized tomography; EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration.

in areas endemic to tuberculosis. Similarly, if purulent material was aspirated during EBUS-TBNA, cryobiopsy is typically avoided in those cases. These recommendations aim to enhance the safety and efficacy of EBUS-TBMC procedures, while minimizing potential complications and optimizing patient outcomes.

Track creation

Several approaches can be used for track creation. The first method is using the prior EBUS-TBNA needle puncture site as the entry point for the cryoprobe, using the same track as the needle (*Figure 1*). The bronchoscopist may consider using a 19G needle, as it can facilitate easier insertion of the cryoprobe by creating a larger track (38,40). However, successful track creation using a 22G needle has been reported (37). During the TBNA procedure, the bronchoscopist should aim to puncture the same site during each puncture attempt, as this can help dilate the track further. The needle sheath can also be advanced into the puncture site to further widen the opening. Additionally, it is helpful to agitate the needle slightly more proximal to the lymph node, rather than just within the core of the lymph node, to break the tougher capsular wall and facilitate later insertion of the blunt cryoprobe.

In cases where track creation proves unsuccessful using the TBNA needle alone, an alternative approach is to employ a 1.9-mm high-frequency needle-knife (KD-31C-1, Olympus) (*Figure 2*). This needle-knife can be inserted into the 2.0 mm working channel of the EBUS bronchoscope to create a mucosal defect at the puncture site. Electrocautery is generally employed in a cutting mode with 15 W power under direct bronchoscopy and EBUS visualization. The goal is to create a track that extends from the airway mucosa through the lymph node capsule, into the core of the lymph node.

Cryoprobe placement and activation

Following successful track creation, the 1.1 mm flexible ultrathin cryoprobe is inserted through the working channel of the bronchoscope to be positioned at the mucosal defect created earlier. It is important to ensure that the cryoprobe is placed perpendicular to the airway wall to avoid inadvertently submucosal placement of the probe. Gentle forward pressure is applied by the bronchoscopist on the cryoprobe, while the assistant provides firm support to the EBUS bronchoscope—this will allow direct visualization of the cryoprobe placement into the target on ultrasound image (*Figure 1*). If resistance is encountered, track dilatation may need to be repeated and excessive forward

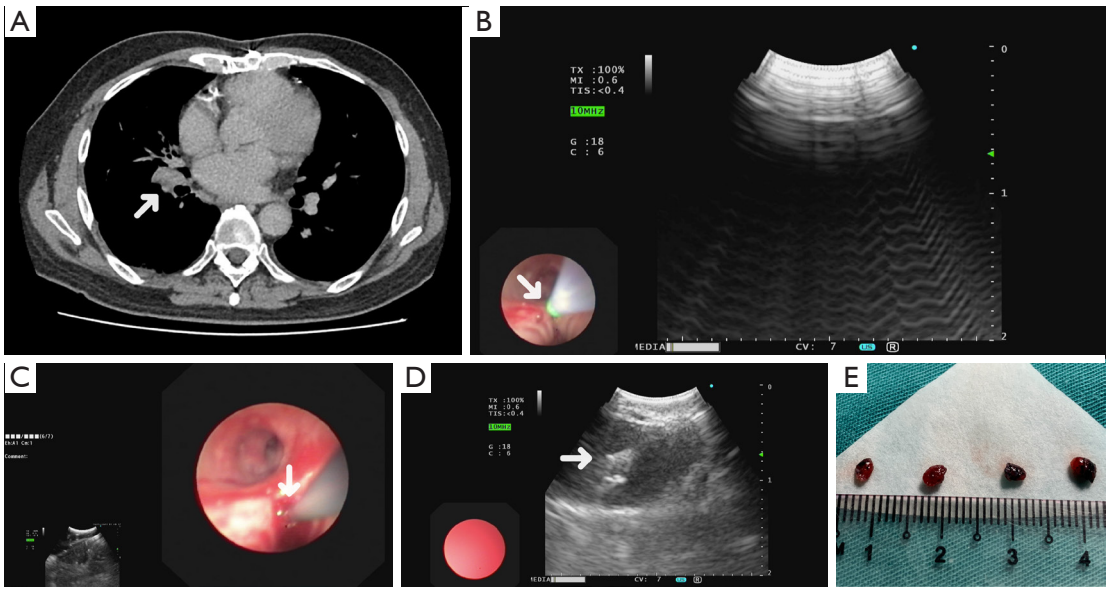

Figure 2 Right hilar lymph node. CT chest axial view showing enlarged right hilar lymph node (arrow, A). EBUS evaluation revealed an enlarged station 11Ri lymph node. The initial TBNA procedure was performed, and subsequently, the track was dilated with an electrocautery needle knife at the secondary carina (arrow, B), which caused interference with the ultrasound image during electrocautery activation. The 1.1 mm cryoprobe was then carefully placed through the mucosa defect and track (arrow, C). The tip of the cryoprobe is clearly visualized throughout the insertion process to prevent overshooting of the target (arrow, D). With four cryobiopsy passes, a good tissue sample of excellent size was obtained from the lymph node (E). CT, computerized tomography; EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration.

pressure should be avoided.

Once the cryoprobe is confirmed to be in the desired position on ultrasound images, Doppler ultrasound is activated to ensure that there are no significant vessels surrounding the probe. The cryoprobe is then activated, and the bronchoscope-cryoprobe assembly is completely removed *en bloc* from the airway. If during retrieval excessive resistance is encountered, the cryoprobe activation should be stopped, and the probe is allowed to thaw. The probe position should be re-checked and repositioned, and a repeat attempt can be carried out with a shorter freezing time. It is worth noting that there is currently no standardized freezing time or number of passes for EBUS-TBMC. The authors recommend starting with a freezing time of 5 seconds, with the option of gradually increasing up to 10 seconds on subsequent passes, if larger specimen size is desired.

Upon successful specimen retrieval, the cryo-specimen is thawed in normal saline and immediately fixed in formalin for histological analysis. The cryoprobe is quickly pulled out of the working channel and the EBUS bronchoscope is reinserted into the airway to assess for any bleeding or other complications. The procedure is repeated for 3–4 passes or until the bronchoscopist deems the specimen to be adequate.

Post-procedural care

Following the procedure, a routine chest radiograph is performed to assess for the presence of pneumothorax and pneumomediastinum. Before discharging the patient, specific inquiries are made regarding throat discomfort, voice changes, chest discomfort, fever, and any worsening cough. These symptoms are monitored to detect any potential signs of vocal cord injury or mediastinitis. Prophylactic antibiotics are not routinely prescribed post-procedure. Once deemed stable, the patient is discharged with instructions on monitoring for evidence of infection or pneumothorax. A follow-up appointment is scheduled in the post-procedural clinic, typically within two to four weeks, for further evaluation and review of the patient's condition.

Discussion

EBUS-TBNA has become the standard of care for mediastinal sampling and lung cancer staging, favored over

mediastinoscopy (58). Needle aspiration has historically performed very well to provide adequate cytology samples for diagnosis of malignancy. The challenge for newer techniques is to overcome the limited diagnostic yield of traditional EBUS-TBNA for sarcoidosis and lymphoma. This has led to development of alternative methods of bronchoscopy-guided, minimally invasive sampling methods.

The idea of passing a biopsy tool inside a lymph node other than the aspiration needle began with EBUS-IFB (5,6). Also known as the mini-forceps, it allows collection of material that could be processed as a histological specimen (8). The combination of EBUS-TBNA and EBUS-IFB improved the overall diagnostic yield and sub analysis demonstrated large benefit in cases of sarcoidosis and lymphoma (7,59). However, the performance of EBUS-IFB is inconsistent, with series reporting 10–20% of malignant cases missed compared to EBUS-TBNA (60,61). EBUS-IFB remains underutilized because of this, alongside factors such as training, availability, and cost (8).

There are no trials directly comparing EBUS-IFB with EBUS-TBMC. We identified four case reports combining both techniques for evaluation of lymphadenopathy (46-48,52). The reports suggest that TBMC offers larger sample collection per pass, less crush artifact and better specimen for histologic diagnosis. Comparing EBUS-IFB with EBUS-TBMC is another area of interest and requires further study.

Determining which patients require EBUS-TBMC and which patients can be managed with only EBUS-TBNA remains a crucial question in the context of this novel technique. Several randomized controlled trials have consistently demonstrated that EBUS-TBNA is highly effective for lesions with a high probability of malignancy, particularly when concurrent suspicious parenchymal lesions are present (35,36,62). Where EBUS-TBMC has added value is in cases of suspected lymphoma, benign processes such as sarcoidosis and tuberculosis and rare tumors. In our practice, we typically limit EBUS-TBMC to a single nodal station during the systematic EBUS-TBNA procedure in these groups of patients. However, whether this approach ensures a better diagnostic yield, especially for molecular analysis, remains uncertain.

The use of ROSE can also serve as a helpful guide in deciding which patients may benefit from EBUS-TBMC. A recent prospective study by Maturu *et al.* revealed that when intra-procedural ROSE was non-diagnostic, the addition of EBUS-TBMC provided an additional diagnostic yield of 43.7% (40). This approach may be useful in resource-limited situations where the bronchoscopist will only need to selectively perform TBMC where ROSE is non-diagnostic or inadequate. Specifically for cases with isolated mediastinal/hilar lymphadenopathy and high pre-test probability for lymphoma or other rare and benign tumors, the threshold for doing EBUS-TBMC should be lower as this may potentially offer valuable insights in reaching a conclusive diagnosis. Further research and clinical experience will contribute to refining the criteria for patient selection and optimizing the diagnostic utility of EBUS-TBMC.

A key aspect of EBUS-TBMC is the creation of a track that allows for the placement of the blunt cryoprobe. In the two largest randomized controlled trials, a 1.9 mm high-frequency needle-knife (KD-31C-1, Olympus) was utilized to create the track (35,36). However, it is unfortunate that this specific reusable needle-knife has been discontinued globally, posing challenges in acquiring the tool. The are other available needle-knives on the market that are compatible with the 2.0–2.2 mm channels of most EBUS bronchoscope. From a logical perspective, initiating track creation using a 19G TBNA needle is a reasonable initial step to allow creation of a larger track (40,43). Interestingly, feasibility has also been demonstrated with 22G TBNA needle for track creation (42,47). Ariza-Prota *et al.* has described in their series the cryoprobe being consistently introduced under ultrasound guidance, following the track left in the lymph node by the previous TBNA needle, to ensure a consistent entry angle (42). Additionally, Gershman *et al.* deliberately dilated the track using the sheath of a 22G TBNA needle, and in some cases, even employed an Nd:YAG laser for track creation to allow for the insertion of a 1.7 mm cryoprobe (38). To address this key issue, the development of a cryo-needle appears to be a reasonable next step in revolutionizing this complex multi-step procedure into a single-step straightforward procedure (63).

Another important consideration is that diseased lymph nodes can exhibit heterogeneity (64). EBUS-TBNA is believed to offer a more representative sampling approach, as each puncture entry point can be different, and by utilizing the fanning method and performing capsule-to-capsule punctures, a larger area of the lymph node can be sampled. This contrasts with EBUS-TBMC, where the biopsy is confined to the same track, with pin-point biopsies being performed only along the trajectory of the track. The potential limitation of EBUS-TBMC in terms of sampling a smaller area of the lymph node is highlighted by Zhang *et al.*, as they reported three lung cancer patients in whom EBUS-TBMC failed to detect malignancy that was

identified by EBUS-TBNA (35). Currently, a sequential approach of EBUS-TBNA followed by TBMC seems to be the preferred combination, as studies have demonstrated a significant increase in the overall diagnostic yield using this approach (36). Exploring the use of more advanced ultrasound imaging techniques, such as elastography, to guide the site of TBMC is an interesting avenue for future exploration.

One of the uncertainties surrounding EBUS-TBMC is determining the optimal activation time and the number of passes required during the procedure. Extensive investigations have been conducted to determine the optimal activation time and passes for the 1.1 mm ultrathin cryoprobe in *ex vivo* and *in vivo* animal models for transbronchial lung cryobiopsy (63,65). However, similar studies specific to mediastinal lesions have not been conducted, possibly due to the challenge of developing adequately sized pathological lymph nodes in healthy animal models suitable for studying with an EBUS bronchoscope (63). The reviewed articles reported majority of the activation times as ranging from 4 to 7 seconds per pass, with a total of 1–3 passes being performed (35-37,40). Preliminary data from the authors' experience indicates a moderate positive correlation between longer activation times and passes with the overall diagnostic yield (66). Specifically, performing 4 or more cryo-passes tends to yield larger specimens, while an activation time of 10 seconds or more tends to result in smaller specimen size. We hypothesize that this may be due to the creation of a relatively small defect that restricts the passage of larger tissue with longer activation time (66). Further prospective trials are highly anticipated to examine and determine the optimal freezing time and number of passes for EBUS-TBMC.

A final consideration is additional cost and procedure time with EBUS-TBMC. Performing cryobiopsy (3 passes) after standard EBUS-TBNA, with and without the use of electrocautery needle knife, adds an approximately 11 and 9 min, respectively (35,37). In the authors' opinion, the additional time required for EBUS-TBMC, when compared to other techniques, is justified to ensure the acquisition of higher quality tissue and achieve a higher diagnostic yield in suitable cases. Lastly, it is worth noting that the 1.1 mm cryoprobe used in EBUS-TBMC is designed for single use. The cost-effectiveness of incorporating this device into the overall EBUS procedure will need to be evaluated in future studies. Considering the potential benefits of EBUS-TBMC, further investigation into the cost-effectiveness aspect will help guide its wider implementation.

This objective of this study is to generate a comprehensive review of all published articles on EBUS-TBMC. The selection process was by design very inclusive to capture as much of available evidence, at the expense of a more robust and systematic approach. As a result, we were able to summarize the major aspects of this novel technique and present a detailed guide to bronchoscopists who wish to adopt EBUS-TBMC in their practice.

Conclusions

EBUS-TBMC is a relatively new procedure which allows for collection of larger mediastinal biopsies under real-time guidance. It builds on the safety and reach of EBUS and the generous sampling ability of cryo-adhesion. EBUS-TBMC has excellent safety profile and high diagnostic yield. There is greater benefit in the evaluation of suspected lymphoma and other benign disorders over malignancy. Accordingly, it may be advantageous to have this available at referral centers or endemic areas. The performance of EBUS-TBMC has many technical aspects and should be performed by advanced bronchoscopists who regularly do EBUS in high volume centers. Having mastery of EBUS-TBNA will facilitate successful adaptation of this technique. Due to wide practice variation, more multicenter randomized trials are needed for standardization of procedure elements and to guide training. EBUS-TBMC has the potential of being the transformative tool in diagnosing mediastinal disease, but current evidence does not support generalized use for all patients with mediastinal abnormalities.

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Footnote

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