

Original Article



Transbronchial Mediastinal Cryobiopsy Diagnostic Yield and Perioperative Patient Management: A Single Tertiary Center Experience

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Abstract

OBJECTIVE: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is widely used to diagnose mediastinal lesions; however, small cytology samples from EBUS-TBNA may be inadequate in cases of benign lung diseases, hematologic disorders, and to assess the molecular profile of primary lung cancer (PLC). EBUS-guided transbronchial mediastinal cryobiopsy (TMC) obtains histological samples and potentially implies a higher diagnostic yield (DY) than EBUS-TBNA. The clinical impact of this technique and the perioperative patient management are still unclear. Our aim was to critically analyze our experience with TMC.

MATERIAL AND METHODS: A single center retrospective study was conducted to evaluate TMC DY and perioperative routine over 11 months (February 2023-January 2024).

RESULTS: Forty-one patients were included. The overall DY was 41.5% and 95.1% for EBUS-TBNA and TMC, respectively. TMC provided a higher DY than EBUS-TBNA in cases of hematologic disorders, benign diseases, and uncommon tumors (31% for EBUS-TBNA and 100% for TMC; 95% confidence interval (CI): 52.1-85.8, $P < 0.001$). For PLC, the DY and the assessment of immunohistochemical marker expression did not significantly differ between the two techniques (80% for EBUS-TBNA and 100% for TMC; 95% CI: -4.79-44.8, $P = 0.13$). The management of antithrombotic therapy was the same as that of EBUS-TBNA. Sedatives were administered to achieve deep sedation. After the procedure, no step-up in the level of care was observed, either in outpatients or in patients with a Charlson Comorbidity Index ≥ 5 .

CONCLUSION: TMC had a better DY than EBUS-TBNA in hematologic disorders, benign lung disease, and uncommon tumors, with an optimal tolerability profile.

KEYWORDS: Bronchoscopy, diagnostic methods, endobronchial ultrasound-guided transbronchial needle aspiration, lung cancer, mediastinal diseases, perioperative care

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INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique with a broad capability of obtaining cytologic samples from mediastinal lesions. However, some controversies about its diagnostic yield (DY) remain unsettled. Firstly, the sensitivity of EBUS-TBNA in mediastinal restaging of primary lung cancer (PLC), after induction treatment with chemoradiotherapy, is lower (67-76%) compared with the sensitivity for the initial staging (81-93%). Therefore, confirmation of negative EBUS-TBNA with surgical mediastinoscopy is advised for a conclusive diagnosis.^{1,2} Secondly, for PLC staging, the likelihood of malignant nodal involvement after negative EBUS-TBNA \pm transesophageal bronchoscopic ultrasound-guided fine needle aspiration (EUS-B-FNA) is

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13-15%. Both American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) Guidelines suggest additional mediastinoscopy before surgery.^{1,3,4} Thirdly, the DY for lymphoproliferative disorders is between 31-65%, and the 2011 statement of British Thoracic Society guidelines, “insufficient evidence to recommend EBUS-TBNA for routine use in the diagnosis of lymphoma,” remains valid.^{5,6} Lastly, the sensitivity of the technique in benign mediastinal diseases is around 60%. Further resource-consuming efforts are commonly needed due to the clinical overlap of benign disorders, which demand completely different therapies (i.e., infective versus autoimmune diseases).⁷ Transbronchial biopsy with a cryoprobe of large outer diameter (1.9/2.4 mm), has been widely used for sampling lung parenchyma in the diagnosis of diffuse lung diseases, a setting in which the DY of traditional forceps biopsy is limited by crushing artifacts. Similarly, EBUS-guided transbronchial mediastinal cryobiopsy (TMC) is a minimally invasive technique, allowing to obtain large, architecturally preserved histology samples from mediastinal lesions, using a thin cryoprobe (outer diameter 1.1 mm). Data from published literature suggest that EBUS-TMC has a better DY than EBUS-TBNA in hematologic diseases, benign lung disorders, and typically, but not always, in uncommon tumors, potentially addressing diagnostic limitations with cytology samples.⁸⁻¹¹ Despite its growing use, a clear indication for TMC application is still subject to ongoing debate, and the technical aspects are not standardized. We hypothesized that TMC implementation may favorably impact cases in which the diagnostic performance of EBUS-TBNA is suboptimal, potentially improving patient outcomes (i.e., avoidance of repeated procedures and/or mediastinoscopy, with their associated morbidity), ultimately enhancing the cost-effectiveness of the procedure. In this study, we aimed to evaluate the DY of TMC and describe the periprocedural management of patients undergoing TMC.

MATERIAL AND METHODS

Study Design and Participants

We retrospectively evaluated all patients who consecutively underwent TMC at our large tertiary facility, the Interventional Pulmonology Unit of Cardarelli Hospital, Naples, Italy, over 11 months from February 17, 2023, to January 31, 2024. The primary outcome was the DY of TMC, defined as a conclusive diagnosis obtained from histological samples. Analogously, EBUS-TBNA was considered conclusive if the specimens provided a formal cytological or histopathological diagnosis. All patients provided written informed consent before bronchoscopy. Subject characteristics, including age, sex,

Charlson Comorbidity Index, antithrombotic therapy (ATT), type of hospital admission, and reason for bronchoscopy, were traced using the hospital's electronic medical records. Chest computed tomography (CT) with contrast was performed in all patients, and the ultrasonographic characteristics of the target lesion(s) were reviewed. All patients undergoing TMC were routinely provided multimodal intravenous analgo-sedation with midazolam + propofol±fentanyl, administered by an interventional pulmonologist not directly involved in the procedure, for patients categorized as American Society of Anesthesiologists (ASA) class I-III, or by an anesthesiologist for patients ASA III-IV. Sedation was maintained to target a Ramsay sedation scale score of 4-5 [that is, deep sedation (DS)]. Furthermore, for breathing support, all patients were connected to the ventilator through a Mapleson C circuit after placement of a laryngeal mask airway (LMA). One highly experienced interventional pulmonologist performed three passes of EBUS-TBNA using a convex probe ultrasound bronchoscope (BD UC180F, Olympus, Tokyo, Japan) at the point where the target lesion had the closest contact (≤ 1 cm) to the tracheobronchial wall. The choice of needle size (19G or 21G, ViziShot 2, Olympus, Tokyo, Japan) was at the operator's discretion. All passes were performed at the same angle as the first TBNA, aiming to facilitate the tunnelling process and widen the airway puncture. At the end of the third needle pass, needle length was progressively shortened, and the needle sufficiently agitated at every proximal retraction. This technique created a continuous pathway through the tracheobronchial wall and the capsule of the node, finally allowing for the insertion of the 1.1 mm cryoprobe (Erbecryo 20402-401, Tubingen, Germany). After ensuring in Doppler mode, that intralesional vessels were avoided, the cryoprobe was cooled down for 4 seconds, and the frozen biopsy tissue was retracted en bloc with the scope and probe.¹² All patients had a post-procedural chest X-ray (CXR). The collected adverse events (AEs) were: pneumothorax, pneumomediastinum, mediastinitis, bleeding (mild: no intervention other than intermittent suctioning±cold saline instillation; moderate: need for continuous suctioning±blockade balloons; severe: any other additional intervention, including bronchoscopic intervention, blood product administration, or change in level of care), and death. AEs were monitored 2 hours after bronchoscopy and after 24 hours (via phone call for outpatients). To ensure that any difference in DY by technique (TMC and EBUS-TBNA) did not depend on patient characteristics or target lesion echo features, we examined multiple variables according to the outcome of EBUS-TBNA (that is, the diagnostic EBUS-TBNA group and the non-diagnostic EBUS-TBNA group). After verifying the homogeneity of the sample, the DY of each technique was analyzed to distinguish between neoplastic and non-neoplastic diseases.

Statistical Analysis

Continuous variables are presented as mean and standard deviation (SD), and categorical variables as frequencies and percentages. ANOVA test for continuous variables and Pearson's chi-square test for categorical variables were performed. The primary outcome was analyzed using Pearson's chi-square test. A $P < 0.05$ level of significance was used. All tests were performed using the Jamovi software, version 2.3 (The Jamovi Project 2024, Sydney, Australia).

Main Points

- Transbronchial mediastinal cryobiopsy (TMC) obtains diagnostic tissue both in benign and malignant lung diseases.
- TMC is safe in comorbid patients and in outpatient setting.
- Management of antithrombotic therapy may be the same as with endobronchial ultrasound-guided transbronchial needle aspiration.
- Deep sedation allows for a smooth procedure.

Ethical Considerations

The study received approval from the Research Ethics Committee of Cardarelli Hospital (Campania 3, AORN_063) (approval number: 00023093, date: 10.10.2024). The requirement for consent was waived owing to the retrospective nature of the study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, as revised in 2013.

RESULTS

The study included 41 subjects (20 males, 21 females), of whom 23 were outpatients and 18 inpatients. The reasons for bronchoscopy were suspicion of PLC (n = 12, 29.3%), hematologic disorders and benign lung diseases (n = 18, 43.9%), recurrence of known solid cancer (n = 6, 14.6%), and recurrence of known hematologic malignancy (n = 5, 12.2%). Nineteen patients were on ATT (antiplatelet and/or anticoagulant therapy), but the therapy was discontinued

in preparation for bronchoscopy, only in seven cases. The management of ATT was the same as that of EBUS-TBNA: both low-dose aspirin (primary and secondary prevention of cardiovascular events) and low-molecular-weight heparin (prophylaxis of venous thromboembolism) were not discontinued.^{13,14} Oral anticoagulants were stopped, however, when the thromboembolic risk outweighed the procedural risk of bleeding (i.e., pulmonary embolism, thrombosis of large venous vessels), parenteral anticoagulants were continued. The descriptive characteristics of the sample and target lesion(s) according to EBUS-TBNA DY are reported in Table 1. In brief, the average diameter of the lesions was 2.4 cm ± 1; the most biopsied lymph node station was 7 (n = 28, 65.1%); in 3 cases, EBUS-TBNA + TMC was performed directly on centrally-located mass (hilo-perihilar), with a mean diameter of 7 cm ± 3.2; the mean number of cryoprobes per station was 2.7±0.6. Thirty-nine patients (95.1%) had a definite diagnosis based on the mediastinal specimens: PLC (n = 10, 24.4%), uncommon

Table 1. Descriptive characteristics of the sample by EBUS-TBNA diagnostic yield

	Diagnostic EBUS-TBNA n = 15	Non-diagnostic EBUS-TBNA n = 26	Overall n = 41	P
Age, years	61.1±14.2 (30.0-75.0)	59.1±13.9 (19.0-80.0)	59.8±13.9 (19.0-80.0)	0.65
Sex				0.27
Male	9 (60.0%)	11 (42.3%)	20 (48.8%)	
Female	6 (40.0%)	15 (57.7%)	21 (51.2%)	
Charlson Comorbidity Index				0.067
≤5	6.0 (40.0%)	18 (69.2%)	24 (58.5%)	
5+	9 (60.0%)	8 (30.8%)	17 (41.5%)	
Number of cryobiopsies				0.72
2	4 (26.7%)	9 (34.6%)	13 (31.7%)	
3	8 (53.3%)	14 (53.8%)	22 (53.7%)	
4	3 (20.0%)	3 (11.5%)	6 (14.6%)	
Largest EBUS-TBNA needle, G				0.21
21	11 (73.3%)	23 (88.5%)	34 (82.9%)	
19	4 (26.7%)	3 (11.5%)	7 (17.1%)	
Diagnostic group				0.017
N miss	0	2	2	
Non-PLC	8 (53.3%)	21 (87.5%)	29 (74.4%)	
PLC	7 (46.7%)	3 (12.5%)	10 (25.6%)	
Final diagnosis				0.26
PLC	7 (46.7%)	3 (11.5%)	10 (24.4%)	
Sarcoidosis	3 (20.0%)	7 (26.9%)	10 (24.4%)	
Other lung granulomatosis	2 (13.3%)	4 (15.4%)	6 (14.6%)	
Rare solid malignant tumor	1 (6.7%)	3 (11.5%)	4 (9.8%)	
Benign reactive lymphadenitis	0 (0.0%)	4 (15.4%)	4 (9.8%)	
Castleman disease	1 (6.7%)	2 (7.7%)	3 (7.3%)	
Lymphoma	1 (6.7%)	1 (3.8%)	2 (4.9%)	
Non-diagnostic	0 (0.0%)	2 (7.7%)	2 (4.9%)	

Table 1. Continued

	Diagnostic EBUS-TBNA n = 15	Non-diagnostic EBUS-TBNA n = 26	Overall n = 41	P
Target size on CT (short axis), cm	2.7 (0.8) (1.6-4.2)	2.2 (1.0) (0.9-5.5)	2.4 (1.0) (0.9-5.5)	0.11
Lymph node shape				0.39
Irregular	13 (68.4%)	12 (48.0%)	25 (56.8%)	
Round	4 (21.1%)	8 (32.0%)	12 (27.3%)	
Oval	2 (10.5%)	5 (20.0%)	7 (15.9%)	
Echogenicity				0.51
Homogenous	8 (42.1%)	14 (51.9%)	22 (47.8%)	
Heterogeneous	11 (57.9%)	13 (48.1%)	24 (52.2%)	
Calcifications				0.58
No	15 (78.9%)	23 (85.2%)	38 (82.6%)	
Yes	4 (21.1%)	4 (14.8%)	8 (17.4%)	
Target station				0.32
7	11 (57.9%)	17 (70.8%)	28 (65.1%)	
11R	6 (31.6%)	1 (4.2%)	7 (16.3%)	
10L	1 (5.3%)	1 (4.2%)	2 (4.7%)	
11L	1 (5.3%)	2 (8.3%)	3 (7.0%)	
4R	0 (0.0%)	2 (8.3%)	2 (4.7%)	
10R	0 (0.0%)	1 (4.2%)	1 (2.3%)	

Patient characteristics and target lesion sonographic features according to EBUS-TBNA diagnostic yield. Data are presented as n (%) or mean±SD. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, PLC: primary lung cancer, CT: computed tomography, SD: Standard deviation

tumors (n = 4, 9.8%), hematologic disorders (n = 9, 22.0%), and benign lung diseases (n = 16, 39.0%). In two patients, neither technique established a definite diagnosis. The overall DYs were 41.5% for EBUS-TBNA and 95.1% for TMC. TMC showed a DY comparable to EBUS-TBNA for patients with PLC (80% for EBUS-TBNA and 100% for TMC, 95% confidence interval (CI): -4.79-44.8, $p=0.13$), however, TMC showed a significantly better DY in case of non-PLC pathologies: uncommon tumors (25% for EBUS-TBNA and 100% for TMC, 95% CI: 32.5-100, $P < 0.02$), hematologic disorders (28.6% for EBUS-TBNA and 100% for TMC, 95% CI: 50.6-100, $P < 0.001$), and benign lung diseases (37.5% for EBUS-TBNA and 100% for TMC, 95% CI: 38-70, $P < 0.001$) (Table 2). In nine subjects with a history of previous non-diagnostic EBUS-TBNA, EBUS-TBNA continued to result non-diagnostic, whereas TMC was diagnostic in all cases. AEs were mild bleeding (n = 4, 9.7%), nonspecific chest discomfort (n = 2, 4.8%), and dysphonia (n = 1, 2.4%), which regressed after a short course of oral corticosteroids. No higher incidence of bleeding was observed in patients on ATT than in patients who did not receive ATT, or those who discontinued ATT.

DISCUSSION

In this retrospective analysis, we found that TMC provided a higher DY than EBUS-TBNA in cases of hematologic disorders (benign or malignant), benign lung diseases, and uncommon tumors. The DY was 31% for EBUS-TBNA and 100% for TMC (95% CI: 52.1-85.8, $P < 0.001$). For PLC, the DY, as well as the assessment of immunohistochemical marker expression, did not significantly differ between the two techniques (80% for

EBUS-TBNA and 100% for TMC; 95% CI: -4.79-44.8, $P = 0.13$) (Figure 1). The DY of EBUS-TBNA samples may be hampered by blood and bronchial cell contamination, crushing artifacts and necrosis; furthermore, the diagnostic discordance between cytologic and histologic specimens and the fact that cytological findings of different lesions often resemble one another (i.e., granulomatous components are present in lymphoma, tuberculosis and sarcoidosis) are the main limiting factors to the use of EBUS-TBNA in hematologic disorders as well as in benign lung diseases.^{15,16} Since TMC obtains intact histology samples, cryobiopsies could definitively overcome the cytopathology issues of EBUS-TBNA, giving a conclusive diagnosis in these conditions, as the results of this study confirm, in accordance with literature.^{8-11,17,18} In our sample, in case of suspicion of relapsed/refractory (R/R) hematological malignancies after chemoradiotherapy (n = 5, 12.2%), TMC established a diagnosis in four patients thanks to the high-quality specimens (one patient: confirmation of R/R disease, with biopsy adequate both for subtyping and determining the histologic grade; three patients: benignant lymphadenitis, no R/R disease), with no need of further sampling procedures (negative follow-up after six months of radiological surveillance). Conversely, also in real-life scenarios, when EBUS-TBNA is negative for R/R hematological malignancies, it is deemed insufficient for a reliable result; thus, invasive histologic confirmation is required. Future research should address the role of TMC as a decision support tool in this specific patient population. In the group finally diagnosed with PLC, the sensitivity of EBUS-TBNA was slightly lower than the existing literature (80% versus 91-93%), probably due to a high

Table 2. EBUS-TBNA and TMC diagnostic yields by pathologies

Diagnostic yield by pathologies	EBUS-TBNA n = 41	TMC n = 41	Overall n = 82	P
Overall	17 (41.5%)	39 (95.1%)	56 (68.3%)	<0.001
PLC	8 (80.0%)	10 (100%)	18 (90.0%)	0.13
Non-PLC	9 (31.0%)	29 (100%)	38 (65.5%)	<0.001
Uncommon tumors	1 (25.0%)	4 (100%)	5 (62.5%)	0.028
Hematologic disorders	2 (28.6%)	9 (100%)	11 (61.1%)	<0.001
Lung granulomatosis	6 (37.5%)	16 (100%)	22 (68.8%)	<0.001

Data are presented as n (%).

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, TMC: transbronchial mediastinal cryobiopsy, PLC: primary lung cancer

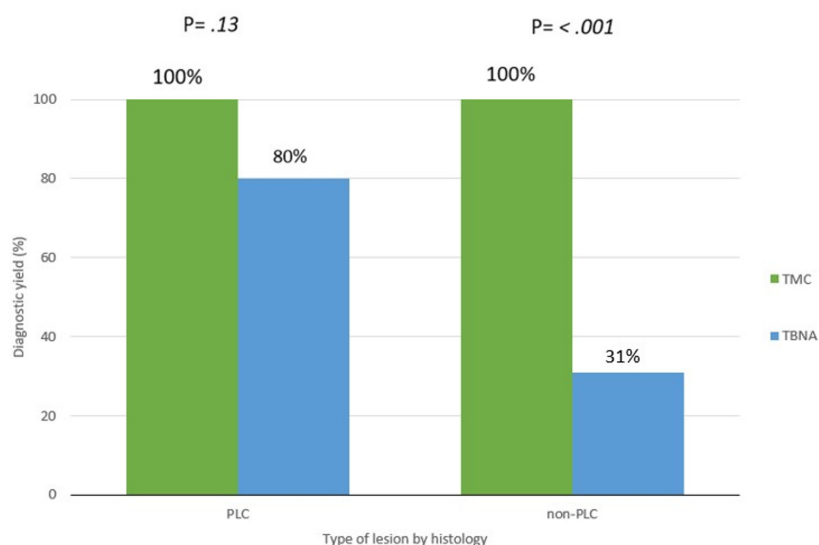


Figure 1. Diagnostic yield by technique in case of PLC and non-PLC diseases (uncommon tumors, hematologic disorders and benign lung disorders): TMC provides 69% a higher diagnostic yield than EBUS-TBNA in case of non-PLC diseases [31% for EBUS-TBNA and 100% for TMC; 95% confidence interval (CI): 52.1-85.8, $P < 0.001$]; for PLC, the diagnostic yield does not significantly differ between the two techniques (80% for EBUS-TBNA and 100% for TMC; 95% CI: 4.79-44.8, $P = 0.13$)

PLC: primary lung cancer, TMC: transbronchial mediastinal cryobiopsy, EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration

prevalence in our cohort, of patients ($n = 8$, 80%) with extensively necrotic lymph-nodes on CT scan.^{3,4} Furthermore, we found the sensitivity of EBUS-TBNA for the diagnosis of granulomatous disorders below the range reported in the literature (37.5% versus 60%).⁷ This result also deviates from our practice as regular EBUS-endoscopists (EBUS-TBNA DY for lung granulomatosis at our interventional pulmonology unit is 57%, unpublished data); factors that may have negatively impacted the DY in this group were history of previous non-diagnostic EBUS-TBNA ($n = 6$, 27.2%) and recent course of steroids administered for other reasons, ($n = 5$, 22.7%) possibly partially attenuating inflammation. However, given the retrospective nature of the study, there were unmeasurable variables that may have introduced a bias toward the null hypothesis (more diagnostically challenging procedures were performed with EBUS-TBNA + TMC, given its theoretical advantage). Furthermore, we could not assess any eventual improvement in the DY for non-malignant lung diseases when utilizing a 19G needle versus TMC. Indeed, among the seven

patients in whom the procedure was performed with the larger needle, only one had a final diagnosis of benignancy (sarcoidosis) on the TBNA specimen. Also if the choice of the needle size was at the operator's discretion, we tended to use a 19G needle only at the beginning of our learning curve with TMC to facilitate the insertion of the cryoprobe by creating a larger entry point rather than on the basis of suspected benign disease; this is in accordance with guidelines on EBUS-TBNA, suggesting using either a smaller (21G) or a larger (19G) needle in patients with suspected benign disease.²⁰ However, studies comparing the DY of the two techniques, in which EBUS-TBNA was performed using only 19G needles, reported that TMC overcame EBUS-TBNA in cases of benign disorders, including infection and sarcoidosis.^{21,22} It is noteworthy that in all our patients who repeated bronchoscopy because of diagnosis initially missed by EBUS-TBNA, the latter continued to be non-diagnostic, while a diagnosis was reached by cryobiopsy in all cases, suggesting that TMC could be the investigation of choice in this population. In two patients, neither EBUS-TBNA nor

TMC could establish a diagnosis: one underwent bronchoscopy for suspicion of relapsing gray zone lymphoma after chemotherapy, the other one, for restaging of primary lung adenocarcinoma after induction chemoradiotherapy; in these clinical scenarios, lymph nodes undergo fibrosis and necrosis, and residual malignant cells may be heterogeneously distributed within the node (center as well as subcapsular zone).^{23,24} This aspect could be particularly relevant because, unlike EBUS-TBNA, which allows a bronchoscopist to extensively sample different zones of the target lesion (“fanning technique”), cryobiopsies may be performed only along the track originally created by the EBUS needle.²⁵ Future research could explore how to increase DY in these patients (i.e., higher number of cryo-passes, use of elastography, creation of more tracks within the nodes). The ACCP guidelines released on September 2024, on the acquisition and handling of EBUS-TBNA samples, recommend performing four or more needle passes over three or fewer needle passes in patients with suspected malignant and non-malignant diseases: a greater number of passes provides adequate specimens for molecular and immunological assessments of malignancies and facilitates the recognition of the characteristic pathology of benign diseases.²⁰ However, when we introduced TMC in our practice (February, 2023) and for all the study period (February, 2023-January, 2024), we complied with the guidelines on EBUS-TBNA in force at that time, and performed three separate needle passes per sampling site, so we cannot exclude the possibility that this factor favored cryobiopsy’s DY.²⁶ However, the number of EBUS-TBNA passes to execute before TMC is not standardized across the studies, ranging from two, to three, to four.^{8,9,12,27,28} Only one study reported up to five passes of EBUS-TBNA before cryobiopsy, and even so TMC outperformed EBUS-TBNA in the diagnosis of uncommon tumors and benign disorders;²⁹ a uniform methodology should be employed in this matter. The minimum number of cryobiopsies that should be conducted on each target lesion is not yet well established and can range between one and four. Kho et al.²⁹ found that the DY of TMC plateaued after 2-3 cryo-passes; accordingly, in our study, we found that the DY of two cryo-passes was the same as that of three or more cryo-passes. The ideal cryoprobe activation time is undefined, ranging from three to seven seconds.^{8-12,25,30} In our experience, cooling down the cryoprobe for no more than four seconds allowed for an easy retraction of the scope from the airway, a longer time may translate into a progressive ascending cooling down of the probe, beyond the blunt tip, with increased resistance opposed by the tracheobronchial wall to the removal of the scope. We did not face technical difficulty with TMC performed on hilar (10R/L) and lobar (11R/L) lymph-nodes. In general, TMC is smoother when the cryoprobe enters the needle track at a near-perpendicular angle (i.e., stations 4R and 7), preventing the sliding of the probe in the sub-mucosal layers above the lesion. Soo et al.³¹ described that cryobiopsy may present some difficulties for posterior tracheal lesions, and Ariza Prota et al.¹² ranked the lymph node stations accessibility for TMC, from easiest to most challenging, as follows: 11L, 11Ri, 7, 11Rs, 4R, 2L, 2R, 10R, 10L, 3p, and 4L. However, experience from larger studies shows that any station, from 2 to 12, may be safely biopsied via TMC.³⁰ In other studies, TMC has been performed through an oral bite under conscious sedation, or through an endotracheal tube under general anesthesia

(GA), respectively.^{8-10,17,18} However, GA, has some critical drawbacks, including pronounced hemodynamic and respiratory impact, prolonged recovery phase, and high costs. These drawbacks could be disproportionate to the relatively simple technical needs of the procedure. Meanwhile, conscious sedation, in which verbal contact with the patient is possible at all times, may not always be ideal for both the patient’s tolerance and the operator’s comfort.³² In our patients, anesthetics were titrated to target a state of DS. Since the heart of the procedure lies in the insertion of the cryoprobe into the target lesion through the tunnel created by the EBUS needle, DS helped the operator to maintain the same angle in which the initial puncture was made by reducing cough and excessive transpulmonary swings, causing access limitation. By manually squeezing the bag of the Mapleson circuit connected to the LMA, episodes of inadequate spontaneous ventilation due to DS were easily corrected. LMA placement could be particularly advantageous in patients undergoing TMC when compared with oral bite, because it allows smooth, fast, and repeated entrances of the scope owing to better laryngeal exposure and avoids contact between the cooled cryoprobe with the attached frozen biopsy and the pharynx. Furthermore, the use of the LMA, compared to the endotracheal tube, makes TMC easier to perform on the upper paratracheal lymph nodes. In our study, there was no pneumothorax or pneumomediastinum, and the overall low incidence of these two AEs in the literature might call into question the appropriateness as well as the cost-effectiveness of performing CXR after the TMC.^{33,34} No instances of mediastinitis were observed, and antibiotics were not routinely administered after the procedure, except in the case of necrotic target lesion(s); notably, the use of LMA could be advantageous in this regard, reducing the contamination of the bronchoscope and, by inference the cryoprobe as well, by oropharyngeal pathogens. In all observed cases, bleeding post TMC was mild and easily controlled; our findings suggest that the management of ATT could be similar to EBUS-TBNA, traditionally considered a procedure with a low relative bleeding risk.¹³ However, at our center, in case of severe airway bleeding, it is possible to convert the procedure to rigid endoscopy: while waiting for further evidence, the capabilities of the center in managing uncontrolled bleeding should be taken into account when considering ATT discontinuation for patients undergoing TMC. TMC was safe even in the presence of a Charlson Comorbidity Index ≥ 5 , and no patient needed a step-up in the level of care after the procedure, delineating a good tolerability profile in the outpatients. In light of the findings of this study, the following recommendations could be implemented for use in daily practice: combined EBUS-TBNA and TMC is preferable to EBUS-TBNA alone in cases of suspected hematologic diseases, lung granulomatosis, CT features suggestive of uncommon lung tumors, history of diagnosis initially missed by EBUS-TBNA, and largely necrotic lesion(s) on CT scans. The decision to perform TMC as the first step in the diagnosis of PLC, in order to ensure adequate tissue acquisition for advanced molecular testing, should be weighed according to the local joint expertise of both interventional pulmonologists and pathologists (i.e., acquisition, handling and processing of the sample, trained personnel, availability of reliable novel tests).

Study Limitations

This study has several limitations: importantly, it is a retrospective, single-center study with a relatively small sample size that allows for indication bias, thus making it unclear when TMC should be used. Furthermore, TMC was performed only by expert interventional pulmonologists; however, the technique is not intuitive and requires a learning curve.

CONCLUSION

In conclusion, TMC appears to be a valuable option for all diseases burdened by a low DY from EBUS-TBNA, probably leading to cost savings in specific diagnostic scenarios. The good tolerability profile makes TMC suitable for outpatients and patients with multiple comorbidities.

Ethics

Ethics Committee Approval: The study received approval from the Research Ethics Committee of Cardarelli Hospital (Campania 3, AORN_063) (approval number: 00023093, date: 10.10.2024).

Informed Consent: The requirement for consent was waived owing to the retrospective nature of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.C., A.P., S.C., G.F., Concept: N.C., A.P., G.F., Design: N.C., A.P., A.F., G.F., Data Collection or Processing: N.C., A.P., A.F., S.C., G.F., Analysis or Interpretation: N.C., A.P., A.F., L.Z., G.F., Literature Search: N.C., A.P., S.C., L.Z., G.F., Writing: N.C., A.P., A.F., S.C., L.Z., G.F.

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REFERENCES

- Vilman P, Clementsen PF, Colella S, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). *Endoscopy*. 2015;47(6):545-559. [\[Crossref\]](#)
- Jiang L, Huang W, Liu J, et al. Endosonography with lymph node sampling for restaging the mediastinum in lung cancer: A systematic review and pooled data analysis. *J Thorac Cardiovasc Surg*. 2020;159(3):1099-1108.e5. [\[Crossref\]](#)
- Rami-Porta R, Call S, Doores C, et al. Lung cancer staging: a concise update. *Eur Respir J*. 2018;51(5):1800190. [\[Crossref\]](#)
- Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e211S-e250S. [\[Crossref\]](#)
- Erer OF, Erol S, Anar C, Aydoğan Z, Özkan SA. Diagnostic yield of EBUS-TBNA for lymphoma and review of the literature. *Endosc Ultrasound*. 2017;6(5):317-322. [\[Crossref\]](#)
- Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax*. 2013;68(Suppl 1):i1-i44. [\[Crossref\]](#)
- Santos LM, Figueiredo VR, Demarzo SE, Palomino ALM, Jacomelli M. The role of endobronchial ultrasound-guided transbronchial needle aspiration in isolated intrathoracic lymphadenopathy in non-neoplastic patients: a common dilemma in clinical practice. *J Bras Pneumol*. 2020;46(2):e20180183. [\[Crossref\]](#)
- Zhang J, Guo JR, Huang ZS, et al. Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial. *Eur Respir J*. 2021;58(6):2100055. [\[Crossref\]](#)
- Ariza-Prota M, Pérez-Pallarés J, Fernández-Fernández A, et al. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: safety, feasibility and diagnostic yield - experience in 50 cases. *ERJ Open Res*. 2023;9(2):00448-2022. [\[Crossref\]](#)
- Fan Y, Zhang AM, Wu XL, et al. Transbronchial needle aspiration combined with cryobiopsy in the diagnosis of mediastinal diseases: a multicentre, open-label, randomised trial. *Lancet Respir Med*. 2023;11(3):256-264. [\[Crossref\]](#)
- Ramarmuty HY, Oki M. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy: a narrative review. *Mediastinum*. 2023;8:2. [\[Crossref\]](#)
- Ariza Prota MA, Pérez Pallarés J, Barisione E, et al. Proposal for a standardized methodology for performing endobronchial ultrasound-guided mediastinal cryobiopsy: a four-step approach. *Mediastinum*. 2024;8:30. [\[Crossref\]](#)
- Abuqayyas S, Raju S, Bartholomew JR, Abu Hweij R, Mehta AC. Management of antithrombotic agents in patients undergoing flexible bronchoscopy. *Eur Respir Rev*. 2017;26(145):170001. [\[Crossref\]](#)
- Pathak V, Allender JE, Grant MW. Management of anticoagulant and antiplatelet therapy in patients undergoing interventional pulmonary procedures. *Eur Respir Rev*. 2017;26(145):170020. [\[Crossref\]](#)
- Das DK, Francis IM, Sharma PN, et al. Hodgkin's lymphoma: diagnostic difficulties in fine-needle aspiration cytology. *Diagn Cytopathol*. 2009;37(8):564-573. [\[Crossref\]](#)
- Monaco SE, Schuchert MJ, Khalbuss WE. Diagnostic difficulties and pitfalls in rapid on-site evaluation of endobronchial ultrasound guided fine needle aspiration. *Cytojournal*. 2010;7:9. [\[Crossref\]](#)
- Gonuguntla HK, Shah M, Gupta N, Agrawal S, Poletti V, Nacheli GC. Endobronchial ultrasound-guided transbronchial cryo-nodal biopsy: a novel approach for mediastinal lymph node sampling. *Respirol Case Rep*. 2021;9(8):e00808. [\[Crossref\]](#)
- Cheng TL, Huang ZS, Zhang J, et al. Comparison of cryobiopsy and forceps biopsy for the diagnosis of mediastinal lesions: A randomised clinical trial. *Pulmonology*. 2024;30(5):466-474. [\[Crossref\]](#)
- Bandyopadhyay D, Panchabhai TS, Mehta AC. EBUS-TBNA for the diagnosis of lymphoma. Still an achilles heel. *Ann Am Thorac Soc*. 2015;12(9):1263-1264. [\[Crossref\]](#)
- Gilbert CR, Dust C, Argento AC, et al. Acquisition and handling of endobronchial ultrasound transbronchial needle samples: an American College of Chest Physicians Clinical Practice Guideline. *Chest*. 2024:S0012-3692(24)05276-0. [\[Crossref\]](#)
- Maturu VN, Prasad VP, Vaddepally CR, Dommata RR, Sethi S. Endobronchial ultrasound-guided mediastinal lymph nodal cryobiopsy in patients with nondiagnostic/inadequate rapid on-site evaluation: a new step in the diagnostic algorithm. *J Bronchology Interv Pulmonol*. 2024;31(1):2-12. [\[Crossref\]](#)

22. Annema JT, Rozman A. Endobronchial ultrasound-guided cryobiopsy-when it is indicated? *Lancet Respir Med*. 2023;11(3):e23. [\[Crossref\]](#)
23. Cetinkaya E, Usluer O, Yılmaz A, et al. Is endobronchial ultrasound-guided transbronchial needle aspiration an effective diagnostic procedure in restaging of non-small cell lung cancer patients? *Endosc Ultrasound*. 2017;6(3):162-167. [\[Crossref\]](#)
24. Kurimoto N, Osada H, Miyazawa T, Nishisaka T, Murayama M. Targeting area in metastatic lymph nodes in lung cancer for endobronchial ultrasonography-guided transbronchial needle aspiration. *Journal of Bronchology*. 2008;15(3):134-138. [\[Crossref\]](#)
25. Romero AO, Kho SS. Transbronchial mediastinal cryobiopsy – literature review and practice recommendation. *AME Med J*. 2024;9:35. [\[Crossref\]](#)
26. Wahidi MM, Herth F, Yasufuku K, et al. Technical aspects of endobronchial ultrasound-guided transbronchial needle aspiration: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(3):816-835. [\[Crossref\]](#)
27. Ariza-Prota MA, Pérez-Pallarés J, Fernández-Fernández A, et al. Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lymph nodes: a case series - how to do it. *Arch Bronconeumol*. 2022;58(10):718-721. [\[Crossref\]](#)
28. Zhang J, Huang ZS, Wu XL, et al. Primary mediastinal large B-cell lymphoma achieved by non-cautery assisted transbronchial mediastinal cryobiopsy. *Respiration*. 2022;101(7):683-687. [\[Crossref\]](#)
29. Kho SS, Tan SH, Soo CI, et al. An explorative analysis on the optimal cryo-passes and freezing time of the ultrathin cryoprobe in endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy. *Sci Rep*. 2024;14(1):18653. [\[Crossref\]](#)
30. Mathew R, Roy WE, Thomas ES, Meena N, Danilevskaya O. Meta-analysis and systematic review of mediastinal cryobiopsy versus endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of intrathoracic adenopathy. *J Thorac Dis*. 2024;16(7):4217-4228. [\[Crossref\]](#)
31. Soo CI, Huan NC, Kho SS. Technical tips, diagnostic yield and safety of endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy. *Med J Malaysia*. 2024;79(4):490-493. [\[Crossref\]](#)
32. Bergbower EAS, Hong C, Gibbons M, Sachdeva A, Rock P, Anders MG. A Retrospective analysis of respiratory complications under general anesthesia during EBUS-TBNA. *J Community Hosp Intern Med Perspect*. 2022;12(1):19-27. [\[Crossref\]](#)
33. Zhang Z, Li S, Bao Y. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy versus endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal disorders: a meta-analysis. *Respiration*. 2024;103(7):359-367. [\[Crossref\]](#)
34. Chalhoub M, Joseph B, Acharya S. A review of endobronchial-ultrasound-guided transbronchial intranodal forceps biopsy and cryobiopsy. *Diagnostics (Basel)*. 2024;14(9):965. [\[Crossref\]](#)