Original Article

# Meta-analysis and systematic review of mediastinal cryobiopsy versus endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of intrathoracic adenopathy

**Roshen Mathew[1], Winnie Elma Roy[1], Elizabel Susan Thomas[1], Nikhil Meena[2], Olesya Danilevskaya[3]**

[1]Department of Pulmonary and Critical Care Medicine, West Virginia University Camden Clark Medical Center, Parkersburg, WV, USA; [2]Department of Pulmonary and Critical Care Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [3]Department of Endoscopy, Pulmonology Scientific Institute under Federal Medical and Biologic Agency, Moscow, Russia

*Contributions:* (I) Conception and design: R Mathew, WE Roy, ES Thomas; (II) Administrative support: WE Roy, ES Thomas; (III) Provision of study materials or patients: R Mathew, WE Roy, N Meena, O Danilevskaya; (IV) Collection and assembly of data: R Mathew, WE Roy, O Danilevskaya; (V) Data analysis and interpretation: R Mathew, WE Roy, ES Thomas, O Danilevskaya; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Roshen Mathew, MD, DAABIP. Director, Interventional Pulmonary Services, Department of Pulmonary and Critical Care Medicine, West Virginia University Camden Clark Medical Center, 800 Garfield Ave, Parkersburg, WV 26101, USA. Email: mathew.roshen@gmail.com.

**Background:** Endobronchial ultrasound (EBUS)-guided mediastinal/hilar cryobiopsy (MedCryoBx) is a relatively new modality, being combined with EBUS-transbronchial needle aspiration (TBNA) to improve yield in the diagnosis of intrathoracic adenopathy. This meta-analysis aims to investigate the diagnostic yield of MedCryoBx versus EBUS-TBNA for intrathoracic adenopathy.

**Methods:** We conducted a systematic search using Google Scholar, Embase, and PubMed/MEDLINE for studies about a diagnosis of intrathoracic adenopathy using MedCryoBx and EBUS-TBNA. Two authors separately reviewed studies for inherent bias using the Quality Assessment Data Abstraction and Synthesis-2 (QUADAS-2) tool. Inverse Variance weighting for random effects methodology was used for meta-analysis. Pooled diagnostic yields overall and for subgroups were estimated. Complications of MedCryoBx were reviewed.

**Results:** Ten studies with 844 patients undergoing either biopsy procedure were in the final analysis. A total of 554 patients underwent MedCryoBx and 704 patients EBUS-TBNA. Meta-analysis showed a pooled diagnostic yield of 91% (504 of 554) for MedCryoBx and 81% (567 of 704) for EBUS-TBNA, with odds ratio (OR) of 2.5 [95% confidence interval (CI): 1.6 to 3.91; P<0.001], with $I^2$ of 20%. Subgroup analysis for benign conditions showed increased diagnostic yield with OR of 7.95 (91% MedCryoBx versus 58% EBUS-TBNA, P<0.001) with an $I^2$ of 25%. Subgroup analysis for lymphoma showed a statistically significant increase in pooled diagnostic yield with OR of 11.48 (87% MedCryoBx versus 29% EBUS-TBNA, P=0.001). Mild bleeding (36.5%) without any intervention was the most common complication. Bleeding requiring intervention (0.7%) was noted in patients. Pneumothorax (0.4%) and pneumomediastinum (0.4%) were less common in this analysis.

**Conclusions:** MedCryoBx is a very promising tool for the diagnosis of intrathoracic adenopathy. It has improved diagnostic yield over EBUS-TBNA in benign and possibly lymphoproliferative diseases, but less so in lung cancer. The complication rates with MedCryoBx are comparable to EBUS-TBNA.

**Keywords:** Cryobiopsy; endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA); interventional pulmonary; mediastinal adenopathy; meta-analysis

Submitted Mar 03, 2024. Accepted for publication May 24, 2024. Published online Jul 18, 2024.
doi: 10.21037/jtd-24-348
**View this article at:** https://dx.doi.org/10.21037/jtd-24-348

## Introduction

Endobronchial ultrasound (EBUS)-guided mediastinal/hilar cryobiopsy (MedCryoBx) is a novel modality gaining traction as a diagnostic method for intrathoracic adenopathy. EBUS-transbronchial needle aspiration (TBNA) has long been accepted as the first approach for a minimally invasive diagnostic method in a sampling of mediastinal and hilar lymph nodes. We have been constantly challenged to obtain sufficient tissue for the diagnosis and testing of various conditions with EBUS-TBNA. This has led to various types and needle gauge sizes for EBUS-TBNA and a plethora of tools such as the intranodal forceps. All these tools have led to some inconsistent specimen yield improvements in this domain.

Flexible cryoprobe transbronchial biopsies were first done by Babiak *et al.* (1) in 2009. In 2013, Franke *et al.* (2) did the first EBUS-guided cryobiopsy in a porcine model using an extended guide sheath. It was technically sound in the study and feasible, however, EBUS-guided MedCryoBx did not take off until again in 2020 when Zhang *et al.* (3) used it for the diagnosis of a mediastinal seminoma. Furthermore, a few good studies and multiple case reports have been done using MedCryoBx for the diagnosis of intrathoracic tumors and adenopathy.

Different variations of technique in performing MedCryoBx have been described. A few small studies and case reports mention using a 19 gauge EBUS TBNA needle and subsequently using the ERBE (Erbe 20402-401, Tübingen, Germany) 1.1 or 1.7 mm disposable cryoprobe through the needle track (4-6). In large, randomized controlled trials (RCTs) by two groups Zhang *et al.* and Fan *et al.* (7,8) describe using a high-frequency hybrid needle knife (HFNK) to make a passage into the lymph node site after EBUS-TBNA. Subsequently, they used an ERBE 1.1 mm disposable cryoprobe to perform MedCryoBx. Another variation of the technique described for MedCryoBx was by using a Nd:YAG (neodymium-doped yttrium aluminum garnet) laser to create a track for the ERBE 1.1 mm disposable cryoprobe (9). The cryofreeze cycle duration in seconds for the cryoprobe use, and the cryoprobe size also varies in studies. The simplest workflow for MedCryoBx in our opinion is using the EBUS-TBNA needle track created by an EBUS-TBNA needle, and then subsequently performing the cryo biopsy with an ERBE 1.1 mm cryoprobe set for a 4–6 second duration freeze cycle (4,6,10).

Most of the studies described in the literature mention the use of MedCryoBx as a complementary tool to the EBUS-TBNA procedure. One study by Soo *et al.* (11) uses MedCryoBx as the only procedure for the diagnosis of intrathoracic adenopathy with good results. Most of these studies also show MedCryoBx to be a feasible procedure with very low complication rates. Our goal from this systematic review and meta-analysis is to investigate the pooled diagnostic yield of MedCryoBx versus EBUS-TBNA and shed some light on its overall safety profile in the biopsy of intrathoracic adenopathy. We present this article in accordance with the PRISMA reporting checklist (12) (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-348/rc).

### Highlight box

**Key findings**

- Endobronchial ultrasound (EBUS)-guided mediastinal or hilar lesion cryobiopsy (MedCryoBx) improves diagnosis yield over EBUS-transbronchial needle aspiration (TBNA) for intrathoracic adenopathy. It has significant diagnostic yield improvements in benign diseases and lymphoproliferative disorders, but not so much in lung cancer diagnosis.
- MedCryoBx has a very low complication profile that is comparable to EBUS-TBNA.

**What is known and what is new?**

- EBUS-TBNA is an accepted less invasive modality for the diagnosis of intrathoracic adenopathy. It has some diagnostic limitations in benign diseases and lymphoproliferative conditions. Various adjunct tools like intranodal forceps and increasing gauge size of EBUS-TBNA needle have made some improvements in this domain.
- MedCryoBx performed under endobronchial ultrasound guidance in various studies included in this meta-analysis denotes an overall improvement in diagnostic yield.

**What is the implication, and what should change now?**

- MedCryoBx is a novel tool with an improvement in diagnostic yield for intrathoracic adenopathy. However larger studies are required for standardization of the procedure itself, and to examine its cost-effectiveness in relation to other adjunct tools that augment the procedure of EBUS-TBNA.

## Methods

We did a systematic review of available literature from online literature databases as described below. A meta-analysis helps us understand a general trend and test the consistency of combined results from multiple studies.

### *Literature search and methodology*

We performed an extensive search of medical literature from Google Scholar, Embase, and PubMed/MEDLINE for articles published until December 1st, 2023. We used the keywords "EBUS-TBNA or endobronchial ultrasound", "transbronchial mediastinal cryobiopsy" and "mediastinal cryobiopsy" mainly to search and identify relevant studies. Multiple studies and abstracts were identified and shortlisted. Conference abstracts presented, and not published were also included if pertinent to the meta-analysis. We also scanned references of included studies to identify any other relevant articles. We also included case series and case reports with 4 or more patients. We excluded studies undergoing MedCryoBx or EBUS-TBNA only. We also excluded studies performing MedCryoBx without EBUS guidance.

A PICO format (Population, Intervention, Comparison, Outcome) to select studies was defined. *Population* was human patients undergoing EBUS TBNA related bronchoscopy. *Intervention* included EBUS-TBNA performed followed by MedCryoBx or vice versa for intrathoracic adenopathy in C*omparison* to EBUS-TBNA procedure alone. *Outcome* focused on the diagnostic yield of MedCryoBx versus EBUS-TBNA and looked at complications related to MedCryoBx.

We aimed to examine as a primary outcome of interest the overall pooled diagnostic yield of MedCryoBx in comparison to EBUS-TBNA alone for intrathoracic lymphadenopathy. Our secondary outcome was focused on ascertaining the pooled diagnostic yield of MedCryoBx in comparison to EBUS-TBNA in the diagnosis of certain subgroup conditions such as lung cancer, benign disease conditions, and lymphoma. Another secondary outcome also evaluated was the safety profile of the MedCryoBx procedure itself.

Complications from bleeding during the procedure were classified as *mild bleeding* (not requiring any intervention) versus *significant bleeding* (requiring some endobronchial intervention to stop the bleeding or resulting in escalation of care). This classification was agreed upon by the authors as the studies used different definitions for complications from bleeding during the procedures.

Two authors (R.M. and W.E.R.) used the Quality Assessment Data Abstraction and Synthesis-2 (QUADAS-2) tool to assess the quality and risk of bias from included studies. Two authors scored each study separately based on the components of QUADAS-2 (13). This included patient selection, index test, reference standard, timing, and flow. The authors then rated the risk of bias and applicability concerns in each category as low, high, or unclear. A third reviewer (N.M.) resolved any disagreement between authors R.M. and W.E.R. and made the final classification of data as per the QUADAS-2 tool.

Institutional Review Board approval from our institutions was not required for this meta-analysis since it was conducting a secondary analysis for already published data.

### *Statistical analysis*

The meta-analysis of chosen studies was performed using RevMan Web (The Cochrane Collaboration, London, UK). We examined the overall diagnostic yield from chosen studies using inverse variance weighting to aggregate diagnostic yield across studies, thus enabling us to calculate a pooled odds ratio (OR). Heterogeneity across studies was measured using $I^2$ index using a random effects model since there was noted to be variance in study characteristics and methodology of selected studies. We also conducted secondary subgroup analyses for various common diagnostic conditions looking at pooled diagnostic yield and OR for lung cancer, benign conditions, other tumors, and lymphoma. The same methodology was also utilized for the subgroup analysis of the categories mentioned above. A funnel plot was also generated for each of the primary and secondary outcome analyses to visualize any publication biases.

## Results

The study selection flow diagram is demonstrated in *Figure 1*. After screening 122 titles from the medical search databases mentioned above, 42 abstracts were screened. Twenty-six were excluded as they were isolated case reports or case series with 1–3 cases only. Sixteen articles were chosen for a detailed evaluation. Of those articles, 6 were excluded. One had overlapping data published by the same author and this was excluded to prevent data duplication. Incomplete data was noted significantly in three of the articles mostly conference abstracts. Two observational studies were excluded as they included only MedCryoBx data. Finally, 10 articles (9 journal articles, 1 conference abstract) of which 2 were RCTs and 8 were observational studies (4-10,14-16) were included in the meta-analysis. All of the supplemental data provided with the articles were evaluated for data breakdown individually for the meta-analysis. One study was in Spanish (14) but had an English translation available to be analyzed. One other study in

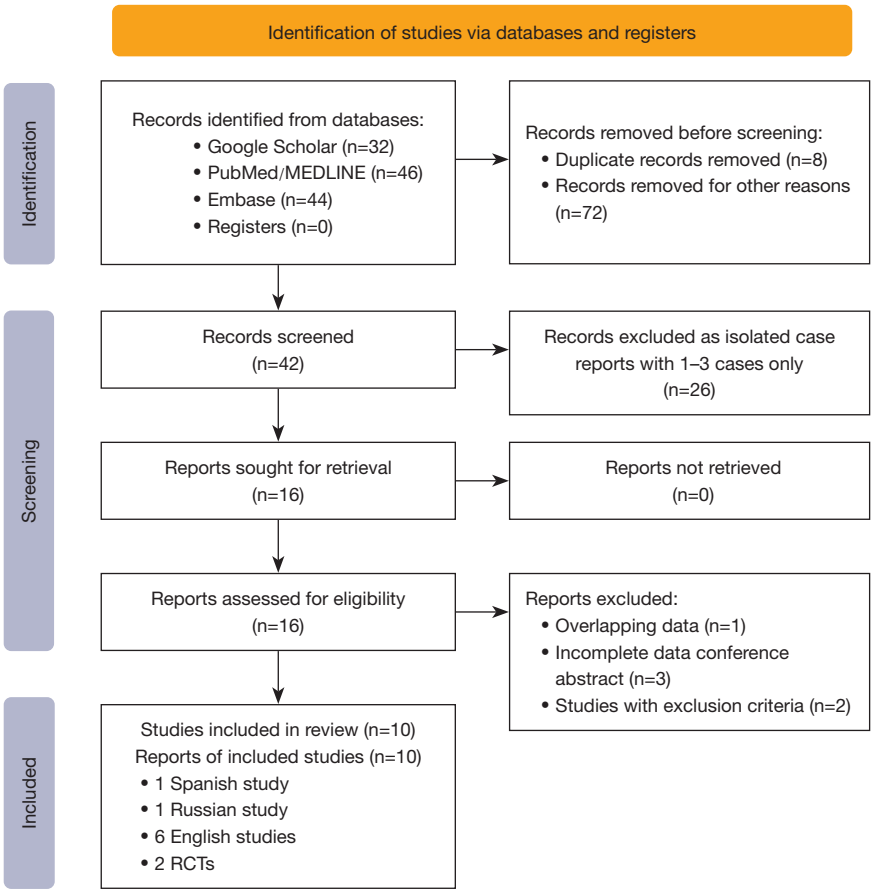


**Figure 1** Flow chart illustrating the study selection process per PRISMA guidelines. RCT, randomized controlled trial.

Russian (16) was partially translated, and the corresponding author was contacted to obtain all the details of the study, including final results and procedure characteristics.

Our quality assessment of study quality as per the QUADAS-2 tool is summarized in *Table 1*. In most studies especially the retrospective studies risk of bias was assessed to be high. This was because of the heterogeneity noted in patient inclusion, varied procedural characteristics of EBUS-TBNA and MedCryoBx, the timing of follow-up for definitive procedures, and the lack of standardization between techniques. The RCTs (7,8) however had a lower risk of bias and applicability concerns overall. The Cohen kappa statistic for interrater agreement for study quality assessment was 0.85.

*Table 2* summarizes data from included studies on the median age of the patients included in the studies, the study design, details on the type of anesthesia or sedation given, access used into the airway, and the type of procedural technique used for MedCryoBx.

*Table 3* gives more specific details on procedural characteristics for EBUS-TBNA and MedCryoBx across the included studies. This table provides insight into the interventions done, the lesion sites involved, the gauge of needle used for EBUS-TBNA, the number of passes done per lesion, and if assessment with Rapid Onsite Evaluation (ROSE) was present. Different brand types and needle gauges of EBUS-TBNA were used in the included studies. This table also offers details on the MedCryoBx procedure with insight into the size of the ERBE cryoprobe used, the cryofreeze time, the number of MedCryoBx taken from sites, and the size of the median specimen size obtained when mentioned in the study. In this meta-analysis, all MedCryoBx was done under direct visualization and guidance with the EBUS scope after passing the cryoprobe through the working channel of the EBUS bronchoscope. Most of the included studies used the disposable ERBE 1.1 mm probe mostly, with few using the 1.7 mm size probe (6,9). One of the studies (16) used a reusable 1.9 mm

**Table 1** Assessment for risk of bias using the QUADAS-2 tool

| Study | QUADAS-2: risk of bias | | | QUADAS-2: applicability concerns | | | |
|---|---|---|---|---|---|---|---|
| | Patient selection | Index test | Reference standard | Flow & timing | Patient selection | Index test | Reference standard |
| Zhang 2021, (7) | Low | Low | Low | Low | Low | Low | Low |
| Fan 2023, (8) | Low | Low | Low | Low | Low | Low | Low |
| Ariza-Prota 2023, (10) | High | Low | High | Low | High | Low | Low |
| Maturu 2024, (6) | Low | Low | Low | High | Low | Low | Low |
| Gershman 2022, (9) | High | Low | Low | Low | High | Low | Low |
| Genova 2022, (5) | High | High | High | Low | High | Low | Low |
| Gonuguntla 2021, (4) | High | High | High | Low | High | Low | Low |
| Ueoka 2022, (15) | High | High | Low | Low | High | Low | Low |
| Salcedo Lobera 2023, (14) | Low | Low | High | High | High | Low | Low |
| Danilevskaya 2023, (16) | High | High | Low | Low | High | Low | Low |

QUADAS-2, Quality Assessment Data Abstraction and Synthesis-2.

**Table 2** Summary of basic characteristics of the included studies

| Study | Country | Design | N | Age, years | Sex (male) | Sedation: airway | MedCryoBx method |
|---|---|---|---|---|---|---|---|
| Zhang 2021, (7) | China, Germany | M-RCT | 197 | 57 | 117 (59%) | MS: TO | HFNK |
| Fan 2023, (8) | China, Germany | M-RCT | 271 | 56 | 165 (60%) | CS: TO | HFNK |
| Ariza-Prota 2023, (10) | Spain | M-Pros | 50 | 63 | 32 (64%) | CS: TO | TBNA trk |
| Maturu 2024, (6) | India | Pros | 196 | 57 | 36 (78%) | GA: LMA | TBNA trk |
| Gershman 2022, (9) | Israel | Pros | 27 | 60 | 17 (70%) | CS, DS: LMA | TBNA trk, Nd:YAG |
| Genova 2022, (5) | Italy | CaS | 5 | 64 | 5 (100%) | MS, DS | TBNA trk |
| Gonuguntla 2021, (4) | India | CaS | 4 | – | – | GA: LMA | TBNA trk |
| Ueoka 2022, (15) | USA | CaS | 9 | – | – | GA: ETT | TBNA trk |
| Salcedo Lobera 2023, (14) | Spain | Pros | 50 | 62 | 37 (74%) | MS: TO | TBNA trk |
| Danilevskaya 2023, (16) | Russia | M-Pros | 35 | 50 | 13 (37%) | LMA ETT | TBNA trk, HFNK |

–, data not available. M-RCT, multicenter-randomized controlled trials; MS, moderate sedation; TO, transoral route; HFNK, high-frequency needle knife; CS, conscious sedation; Pros, prospective observational study; M-Pros, multicenter-prospective observational study; TBNA trk, EBUS-TBNA needle track; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; GA, general anesthesia; LMA, laryngeal mask airway; DS, deep sedation; Nd:YAG, neodymium-doped yttrium aluminum garnet; CaS, case series; ETT, endotracheal tube.

cryoprobe for MedCryoBx through the track created by an EBUS-TBNA needle or a HFNK.

*Table 4* gives a summary of the complications mentioned in the included studies. The most common complication noted was the incidence of mild bleeding 36.5% (202 patients) which was self-limited, without any need for escalation of care or any bronchoscopic intervention. The overall rate of any significant bleeding requiring some bronchoscopic intervention to stop bleeding was reported in 0.7% (4 patients). Overall the rate of pneumothorax was 0.4% (2 patients), and 0.4% (2 patients) for pneumomediastinum respectively. No mention of any patient mortality was noted from the MedCryoBx procedure in the studies.

Our meta-analysis showed an overall pooled diagnostic yield of 91% (504 of 554) for MedCryoBx and 81% (567 of

**Table 3** Procedural techniques and methods across included studies for EBUS-TBNA and MedCryoBx

| Study | Sampling design | ROSE | Lesions | MedCryoBx specimen size, mm | TBNA needle | TBNA passes | Cryo probe size, mm | MedCryoBx passes | Cryo freeze time, s |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2021, (7) | MedCryoBx or TBNA first | No | 2 R/2 L–12 R/L | 4.6 | 22/21G | 4 | 1.1 | 3 | 7 |
| Fan 2023, (8) | TBNA versus TBNA + MedCryoBx | No | 2 R/2 L–12 R/L | 3.8 | – | 4 | 1.1 | 1 | 7 |
| Ariza-Prota 2023, (10) | TBNA + MedCryoBx | No | 2 R, 4 R/L, 7, 10 R, 11 R/L | 4.6 | 22 G | 3 | 1.1 | 3 | 4 |
| Maturu 2024, (6) | TBNA - ROSE/ MedCryoBx | Yes | 4 R, 7, 11 L/R | – | 19 G | 6 | 1.1 | 4–7 | 5–6 |
| Gershman 2022, (9) | TBNA + MedCryoBx | No | 7, 4 L | – | 22 G | 2–4 | 1.1, 1.7 | 2–4 | 3–4 |
| Genova 2022, (5) | TBNA + MedCryoBx | No | 10 R, 7 | 3.5 | 19 G | 3 | 1.1 | 2 | 4 |
| Gonuguntla 2021, (4) | TBNA + MedCryoBx | Yes | 11 L, 7 | – | 19/21/22 G | | 1.1 | 2 | 3 |
| Ueoka 2022, (15) | TBNA + MedCryoBx | Yes | LN | – | 19 G | 3–4 | 1.1 | 2 | 6 |
| Salcedo Lobera 2023, (14) | TBNA + MedCryoBx | No | 7, 10 R, 11 R, 4 R, 11 L, 10 L | 4.7 | 22 G | 2 | 1.1 | 4 | 4 |
| Danilevskaya 2023, (16) | TBNA + MedCryoBx | No | 7, 11 L, 11 R, 4 L, 4 R, 10 R | – | 19 G 22 G | 5–7 | Reusable 1.9 | 3–7 | 3–5 |

–, data not available. EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration; ROSE, rapid on-site exam; MedCryoBx, mediastinal cryobiopsy; L, left; R, right; TBNA + MedCryoBx, EBUS-TBNA followed by MedCryoBx; LN, lymph node.

**Table 4** Complications in patients who underwent EBUS-guided MedCryoBx

| Study | MedCryoBx | Pneumothorax | Pneumomediastinum | Mild bleeding | Significant bleeding |
|---|---|---|---|---|---|
| Zhang 2021, (7) | 194 | 2 | 1 | 169 | 0 |
| Fan 2023, (8) | 134 | 0 | 0 | 0 | 3 |
| Ariza-Prota 2023, (10) | 50 | 0 | 0 | 1 | 0 |
| Maturu 2024, (6) | 46 | 0 | 0 | 13 | 1 |
| Gershman 2022, (9) | 27 | 0 | 0 | 0 | 0 |
| Genova 2022, (5) | 5 | 0 | 0 | 0 | 0 |
| Gonuguntla 2021, (4) | 4 | 0 | 0 | 1 | 0 |
| Ueoka 2022, (15) | 9 | 0 | 0 | 0 | 0 |
| Salcedo Lobera 2023, (14) | 50 | 0 | 0 | 6 | 0 |
| Danilevskaya 2023, (16) | 35 | 0 | 1 | 12 | 0 |
| Total | 554 | 2 (0.4%) | 2 (0.4%) | 202 (36.5%) | 4 (0.7%) |

EBUS, endobronchial ultrasound; MedCryoBx, mediastinal cryobiopsy.

704) for EBUS-TBNA, with an inverse variance weighted pooled OR of 2.50 [95% confidence interval (CI): 1.60 to 3.91; P<0.001], with $I^2$ (heterogeneity index) of 20%. A forest plot for this is denoted in *Figure 2A*. The funnel plot analysis shown in *Figure 2B* denoted no major asymmetry or publication bias.

We also did further subgroup analysis for various conditions. In the subgroup analysis for diagnosis of lung

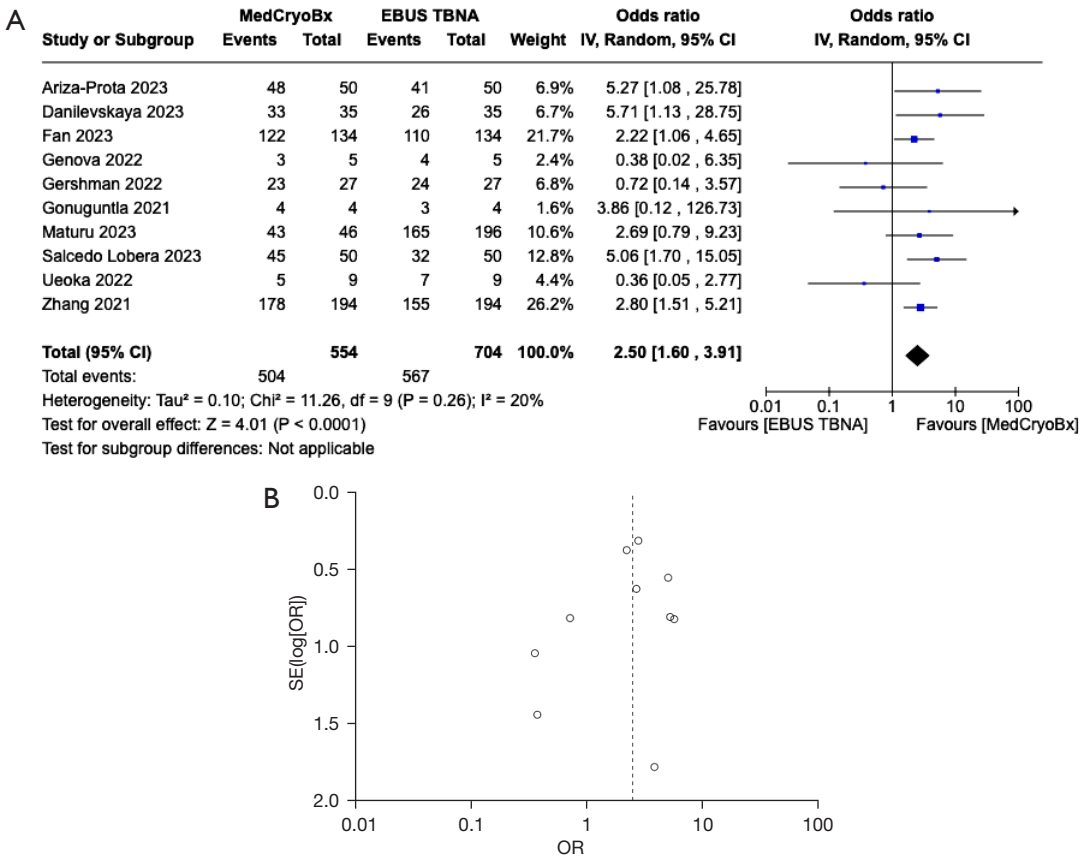


**Figure 2** Overall diagnostic yield of MedCryoBx was better than EBUS-TBNA denoted in (A) forest plot and (B) funnel plot without significant publication bias. CI, confidence interval; IV, inverse variance, OR, odds ratio; SE, standard error; EBUS-TBNA, endobronchial ultrasound-transbronchial needle aspiration.

cancer from seven studies (4,5,7-10,16) with MedCryoBx versus EBUS-TBNA, it showed no statistically significant increase in pooled diagnostic yield 96% (241 of 252) for MedCryoBx versus 92.5% (233 of 252) for EBUS-TBNA, with an inverse variance weighted pooled OR of 1.72 (95% CI: 0.80 to 3.70; P=0.16) with $I^2$=0%. The funnel plot analysis denoted no major publication bias (Figures S1,S2).

We also did a subgroup analysis in the diagnosis of benign disorders. Benign disorders were defined as any granulomatous inflammation from sarcoidosis or other conditions, infections, or any reactive lymph node in the studies. The data from eight studies included (4,5, 7-10,14,16) showed an increase in pooled diagnostic yield of 91% (145 of 160) for MedCryoBx versus 58% (93 of 160) for EBUS-TBNA with an inverse variance weighted pooled OR of 7.95 (95% CI: 3.54 to 17.85; P<0.001) with some heterogeneity $I^2$ of 25%. A funnel plot for this showed asymmetry suggesting possible publication bias (Figures S3,S4), or maybe from wide precision of CI of studies from limited available data.

Subgroup analysis in the diagnosis of lymphoma from five studies (5,7,8,10,16), showed a statistically significant increase in pooled diagnostic yield of 87.5% (21 of 24) for MedCryoBx versus 29% (7 of 24) for EBUS-TBNA, with an inverse variance weighted pooled OR of 11.48 (95% CI: 2.69 to 48.98; P=0.001) with $I^2$=0%. A funnel plot for this showed some asymmetry possibly suggesting some publication bias (Figures S5,S6).

For subgroup analysis in diagnosing other malignant tumors or metastasis, data was available only from 5 studies (7-10,16). This did not show any significant increase in pooled diagnostic yield, 88.5% (23 of 26) for MedCryoBx versus 81% (21 of 26) for EBUS-TBNA, with an inverse variance weighted pooled OR of 2.05 (95% CI: 0.13 to 32.23; P=0.61) with moderate heterogeneity $I^2$=55% in the studies. A funnel plot for this showed some asymmetry

suggesting publication bias (Figures S7,S8).

## Discussion

Our systematic review and meta-analysis of studies show that the overall pooled diagnostic yield of MedCryoBx is higher compared to the EBUS-TBNA procedure for intrathoracic adenopathy, especially for benign conditions and lymphoma. The breakdown of diagnostic yield for lung cancer, benign conditions, other tumors, and lymphoma in the included studies when data was available is shown in Table S1.

There was noted to be a great degree of variability between the studies about the number of EBUS-TBNA passes done and, a gauge of the EBUS needles used. Most of the studies used 21 or 22-gauge needles. Few studies (5,6) used a 19 gauge needle for creating a track before the MedCryoBx procedure. Prior EBUS-TBNA literature studies (17-19) have not shown a difference in diagnostic yield with the needle size for EBUS-TBNA procedures. EBUS-Core needles may have some weak benefits for benign diseases (18,20) such as sarcoidosis. It has been shown in different studies (21-23) that the optimal number of EBUS-TBNA passes for a diagnosis of malignancy or benign granulomatous conditions, and to obtain adequate tissue for molecular cytogenetic profiling is between 3 to 6 passes. The number of EBUS-TBNA passes with most studies included in this metanalysis varied between 2 to 6, with most doing between 4–6 passes. We could not ascertain if any differences in the EBUS-TBNA needle, technique used, or a certain number of needle passes contributed to a mediocre pooled diagnostic yield noted from our meta-analysis. Thus, the technique of EBUS-TBNA used in various studies cannot be statistically evaluated from this meta-analysis.

The technique of performing the MedCryoBx procedure also varies significantly between the studies. Some use an HFNK, some use an Nd:YAG laser to create a track for the cryo-biopsy, and some others use the same needle track created by the EBUS-TBNA for doing the cryo-biopsy. The number of cryo biopsies done also varies between 2–7 biopsies in the studies. Most of the studies used a disposable 1.1 mm size ERBE cryoprobe for the procedure. In one study (9), it used a disposable 1.7 mm size cryoprobe occasionally for cryo-biopsy procedures. Another study (16) used a reusable ERBE 1.9 mm probe with HFNK or needle track for performing the procedure of MedCryoBx. There was also a significant variation in the cryofreeze time between 4–7 seconds for the cryobiopsies done in studies. Do these variations in the technique of the cryo-biopsy play a role in its definitive diagnosis? This is an area again with no specific data available to extrapolate from these included observational and few RCT studies. This will be an area that would require more robust studies in the future with MedCryoBx.

### *Is there a role for MedCryoBx in the diagnosis of lung cancer and other tumor or metastatic lesions?*

For lung cancer diagnosis there was not much of a difference in pooled diagnostic yield or statistical significance noted from the studies (96% MedCryoBx versus 92.5% EBUS-TBNA). This possibly reiterates the fact that EBUS-TBNA when done with at least 3–4 passes was very adequate for sampling and diagnosis of lung cancer. One of the studies by Salcedo Lobera *et al.* (14) did only 2 EBUS TBNA passes. This could explain the lower 60% EBUS-TBNA diagnostic yield in that study. In the diagnosis for other malignant tumors and metastasis MedCryoBx did not show a benefit in this meta-analysis. The studies providing data had lower numbers for other tumor metastasis and malignancy (N=24), thus any meaningful conclusion may not be extrapolated with such small data for MedCryoBx.

### *Is there an improved diagnosis yield with MedCryoBx over EBUS-TBNA for benign conditions and lymphoma?*

MedCryoBx could be a very propitious tool for a diagnosis of benign conditions including granulomatous disease. It showed a statistically significant diagnostic yield of 91% MedCryoBx versus 58% for EBUS-TBNA in our meta-analysis. Similarly, MedCryoBx also showed some favorable benefits in the diagnosis of lymphoma. However, only 24 cases of lymphoma were noted in the included studies. This is again a very small number, and though promising would need further studies proving its results consistently in the future. When MedCryoBx is compared to other tools that are being used alongside EBUS-TBNA, like the intranodal forceps biopsy (IFB), MedCryoBx seems to have improved diagnostic yield (95% for MedCryoBx from this meta-analysis) versus 75–80% with IFB alone in few other studies (19,24,25). A meta-analysis by Agrawal *et al.* (26) using IFB in addition to EBUS-TBNA improved pooled diagnostic yields by up to 92% when compared to EBUS-TBNA alone. A recently published RCT study by Cheng *et al.* (27) also shows an improved diagnosis for MedCryoBx over IFB only for

benign conditions and uncommon tumors.

### *Does MedCryoBx provide larger tissue for additional testing and have a definite role in next-generation sequencing (NGS)?*

Measuring this was not a secondary objective of this study, however, when data was mentioned in the included studies it has been summarized in Table S1. The RCTs (7,8) do mention superior tissue availability for NGS and molecular marker testing with MedCryoBx (95–97%) versus EBUS-TBNA (74–79%). A meta-analysis with 21 studies by Zhao *et al.* (28) mentions a diagnosis yield of 86.5% from EBUS-TBNA for NGS and molecular marker tissue analysis. A recent study from Spain by Velasco-Albendea *et al.* (29) mentions having a tumor percentage of 97% for MedCryoBx versus 26% for EBUS-TBNA specimens, and larger size of cellblocks obtained for non-small cell lung cancer (NSCLC) from 9 patients with a specimen size of 3–4 mm for MedCryoBx. The size of MedCryoBx in millimeters (mm) per sample is comparable to other studies included in this meta-analysis *Table 3*. A study by Oikonomidou *et al.* (30) with 311 patients is so far the largest study with MedCryoBx in our systematic review of the literature. Their study could not be included in this meta-analysis as there was no data relating to specific diagnoses from EBUS-TBNA versus MedCryoBx. Their study focused on cytological analysis and compared specimens obtained from MedCryoBx versus 19-G and 22-G needles. Cellblock slices obtained with the 19-G needle group were superior in their study over MedCryoBx samples for additional tissue (19-G > MedCryoBx > 22-G EBUS TBNA). Another interesting perspective this study provides (30) is a peek at disposable instrument cost for the procedures involved. In Greece, where the study was done the cost of a 19-G EBUS-TBNA needle was 520 euros in place of 1040 euros for the ERBE 1.1 mm disposable cryoprobe. MedCryoBx may have a potential role in providing adequate tissue for molecular markers analysis and NGS as denoted in some studies. However, this needs more potentially blinded randomized studies to be done to reiterate this fact and prove its superiority over existing larger gauge EBUS-TBNA needles which may provide a less costly approach.

### *Does MedCryoBx have a comparable or favorable complication rate over EBUS-TBNA?*

It must be noted that the definition of bleeding after MedCryoBx is not uniform in the included studies. All of the studies mention if bleeding was present and if interventions or escalation of care were needed. Fan *et al.* (8) defined bleeding from a grade 0–4 with mild bleeding being defined as (grade 0–2) and significant bleeding (grades 3 and 4) requiring some intervention to be done for it. A meta-analysis (31) mentions only a small incidence of complications overall for the EBUS-TBNA procedure. *Table 4* shows the incidence of complications from MedCryoBx in the included studies. Overall, 38% (210 of 554) patients had some complications mentioned with MedCryoBx. Most of this 36% (N=202) was mild self-limited bleeding during the procedure not requiring any intervention. When this was compared to complications occurring from EBUS-TBNA from the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) database (32), MedCryoBx has an acceptable, safe comparable profile. There was only a 0.4% rate of pneumothorax for MedCryoBx compared to 0.5% for EBUS-TBNA from the AQuIRE registry. The rate of significant bleeding needing intervention was 0.2% for EBUS-TBNA from the AQuIRE registry compared to 0.7% for MedCryoBx from this meta-analysis. The occurrence of any major complications needing any post-procedure intervention, or escalation of care with MedCryoBx is likely very minimal. However, considering nonuniform definitions for bleeding were used in the included studies this must be interpreted with some caution.

Besides the two RCTs included in this meta-analysis, the other observational studies have a high intrinsic risk of operator and selection bias, even though some have a multicenter study design. None of the included studies in our meta-analysis addresses any interobserver variability. We know from EBUS-TBNA literature there is at least moderate interobserver variability about 70% in the diagnosis of benign conditions and granulomas (32-34), and also in the diagnosis of lung cancer. This is an area that needs to be addressed in future MedCryoBx studies. Since MedCryoBx is a relatively new procedure, the processing of specimens for cytology and histopathology analysis may be again subject to variability, is unaccounted for in these studies, and may affect its diagnostic yield.

There are some limitations to this meta-analysis. Most of the data is from observational studies and retrospective data. The addition of one conference abstract may add some selection bias to the meta-analysis. There is marked variability in the technique of performing MedCryoBx.

Thus, any meaningful recommendations on how to perform EBUS-guided mediastinal cryobiopsy, or the processing of its specimens cannot be determined.

## Conclusions

In conclusion from this meta-analysis and systematic review of the literature, MedCryoBx does have a promising potential role in improving the overall diagnostic yield of intrathoracic adenopathy. This overall yield improvement is mostly limited to benign conditions and may present also for lymphoma, but this needs to be further ascertained with robust studies. It confers no additional benefit, especially in lung cancer diagnosis. There is so much inherent variability and the need for more larger prospective RCT to standardize the technique of MedCryoBx itself. The safety profile of MedCryoBx is comparable to EBUS-TBNA and lower than for surgical mediastinoscopy (35). MedCryoBx need not be used as a first-line diagnostic procedure, or as the only procedure for a diagnosis of intrathoracic adenopathy. A very prudent approach for the use of MedCryoBx in our opinion would be as outlined by Maturu *et al.* (6) as an adjunct tool for nondiagnostic ROSE, and or for cases with a high index of suspicion for lymphoproliferative disorders. A deeper insight into future studies to ascertain its cost-benefit ratio as an adjunct procedure to EBUS-TBNA is also warranted.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-348/rc

*Peer Review File:* Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-348/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-348/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Babiak A, Hetzel J, Krishna G, et al. Transbronchial cryobiopsy: a new tool for lung biopsies. Respiration 2009;78:203-8.
2. Franke KJ, Nilius G, Ruehle KH, et al. The cryo-needle: a new tool for histological biopsies. A feasibility study. Lung 2013;191:611-7.
3. Zhang J, Fu WL, Huang ZS, et al. Primary Mediastinal Seminoma Achieved by Transbronchial Mediastinal Cryobiopsy. Respiration 2020;99:426-30.
4. 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:e00808.
5. Genova C, Tagliabue E, Mora M, et al. Potential application of cryobiopsy for histo-molecular characterization of mediastinal lymph nodes in patients with thoracic malignancies: a case presentation series and implications for future developments. BMC Pulm Med 2022;22:5.
6. Maturu VN, Prasad VP, Vaddepally CR, et al. 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;31:2-12.
7. Zhang J, Guo JR, Huang ZS, et al. Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial. Eur Respir J 2021;58:2100055.
8. 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;11:256-64.

9. Gershman E, Amram Ikan A, Pertzov B, et al. Mediastinal "deep freeze"-transcarinal lymph node cryobiopsy. Thorac Cancer 2022;13:1592-6.
10. 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;9:00448-2022.
11. Soo CI, Kho SS. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy: Insights and technical tips from our early experience with 30 patients. medRxiv 2023. doi: 10.1101/2023.08.06.23293719
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
13. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
14. Salcedo Lobera E, Codeso FMP, Casado Miranda E. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy: series of 50 cases. Rev Clin Esp (Barc) 2023;223:578-81.
15. Ueoka ME, Tome RG, He T, et al. Endobronchial ultrasound-guided intralesional cryobiopsy: a case series. Chest 2022;162:A2127.
16. Danilevskaya OV, Chernikova EN, Esakov YS, et al. Transbronchial cryobiopsy for mediastinal lesions: a pilot study. Khirurgiia (Mosk) 2023;(11):16-24.
17. Kanth S, Pickering EM, Sachdeva A, et al. Endobronchial ultrasound needles: does size matter? Shanghai Chest 2020;4:24.
18. Mathew R, Shah C, Cirino-Marcano MDM, et al. Endobronchial Ultrasound Guided Transbronchial Needle Aspiration: Core vs. Traditional Needle Tissue Acquisition in the Age of Cytogenetics. Chest 2015;148:827A.
19. Darwiche K, Freitag L, Nair A, et al. Evaluation of a novel endobronchial ultrasound-guided lymph node forceps in enlarged mediastinal lymph nodes. Respiration 2013;86:229-36.
20. Biswas A, Wynne JP, Patel D, et al. Comparison of the yield of 19-G eXcelon core needle to a 21-G EBUS needle during endobronchial ultrasound guided transbronchial needle aspiration of mediastinal lymph nodes for the detection of granulomas in cases of suspected sarcoidosis. J Thorac Dis 2017;9:E864-E866.
21. Faber E, Grosu H, Sabir S, et al. Adequacy of small biopsy and cytology specimens for comprehensive genomic profiling of patients with non-small-cell lung cancer to determine eligibility for immune checkpoint inhibitor and targeted therapy. J Clin Pathol 2022;75:612-9.
22. Lee HS, Lee GK, Lee HS, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest 2008;134:368-74.
23. Garwood S, Judson MA, Silvestri G, et al. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 2007;132:1298-304.
24. Radchenko CC, Cho PK, Kang L, et al. Performance of endobronchial-ultrasound guided miniforceps biopsy of targeted mediastinal and hilar lesions. Respir Med 2019;158:92-6.
25. Franke KJ, Bruckner C, Szyrach M, et al. The contribution of endobronchial ultrasound-guided forceps biopsy in the diagnostic workup of unexplained mediastinal and hilar lymphadenopathy. Lung 2012;190:227-32.
26. Agrawal A, Ghori U, Chaddha U, et al. Combined EBUS-IFB and EBUS-TBNA vs EBUS-TBNA Alone for Intrathoracic Adenopathy: A Meta-Analysis. Ann Thorac Surg 2022;114:340-8.
27. 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. [Epub ahead of print]. doi: 10.1016/j.pulmoe.2023.12.002
28. Zhao JJ, Chan HP, Soon YY, et al. A systematic review and meta-analysis of the adequacy of endobronchial ultrasound transbronchial needle aspiration for next-generation sequencing in patients with non-small cell lung cancer. Lung Cancer 2022;166:17-26.
29. Velasco-Albendea FJ, Cruz-Rueda JJ, Gil-Belmonte MJ, et al. The Contribution of Mediastinal Transbronchial Nodal Cryobiopsy to Morpho-Histological and Molecular Diagnosis. Diagnostics (Basel) 2023;13:3476.
30. Oikonomidou R, Petridis D, Kosmidis C, et al. Cryo-Biopsy versus 19G needle versus 22G needle with EBUS-TBNA endoscopy. J Cancer 2022;13:3084-90.
31. Gu P, Zhao YZ, Jiang LY, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer 2009;45:1389-96.
32. Eapen GA, Shah AM, Lei X, et al. Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: Results of the AQuIRE registry. Chest 2013;143:1044-53.

 

33. von Bartheld MB, Dekkers OM, Szlubowski A, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA 2013;309:2457-64.
34. Steinfort DP, Russell PA, Tsui A, et al. Interobserver agreement in determining non-small cell lung cancer subtype in specimens acquired by EBUS-TBNA. Eur Respir J 2012;40:699-705.
35. Czarnecka-Kujawa K, Yasufuku K. The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer. J Thorac Dis 2017;9:S83-97.

**Cite this article as:** 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. doi: 10.21037/jtd-24-348