

# Mediastinal Cryobiopsy: Bridging the Histology Gap in Endoscopic Thoracic Nodal Sampling

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## Abstract

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the standard minimally invasive technique for mediastinal and hilar evaluation but as a cytologic specimen, is limited when histologic architecture or larger tissue volume is required. EBUS-guided mediastinal cryobiopsy (EBUS-MCB) extends diagnostic capability beyond TBNA by retrieving intact, architecturally preserved tissue cores through the same bronchoscope.

Since introduction into clinical practice in 2020, cryobiopsy combined with standard TBNA has been adopted widely, recognised by many as a significant advance in endoscopic mediastinal diagnosis. Several studies show that MCB has higher diagnostic yield than corresponding TBNA, with the greatest benefit seen in benign granulomatous and lymphoproliferative disorders. MCB has also shown superior performance for molecular profiling in non-small-cell lung cancer as a secondary endpoint in several studies. Complications are uncommon, usually limited to minor bleeding, with serious adverse events reported in fewer than 2% of procedures.

EBUS-MCB added in stepwise fashion to standard TBNA appears to be of greatest utility when paucicellular or non-diagnostic sampling is determined at rapid onsite cytological evaluation (ROSE) or at prior EBUS-TBNA procedure. In cases where there is high pre-test probability for lymphoma, EBUS-TBNA-MCB may reasonably be performed without ROSE feedback, potentially avoiding the need for more invasive and costly diagnostic procedures.

Integration of MCB into selected EBUS procedures has the potential to meaningfully improve diagnostic yield and refine disease subtyping, with downstream implications for treatment selection and patient outcomes. Its use should be tailored to centre-specific resources, expertise and local disease epidemiology to maximise benefit and ensure appropriate implementation.

## Introduction

Linear (or convex probe) endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) has revolutionised mediastinal diagnostic evaluation since its clinical adoption in the early 2000s, replacing mediastinoscopy for lung cancer staging due to comparable sensitivity, reduced morbidity, and superior cost-effectiveness<sup>1,2</sup>. In non-small-cell lung cancer (NSCLC), EBUS-TBNA has reported diagnostic yield exceeding 90%<sup>3</sup>. Yet cytology alone may not suffice when architectural detail is critical, such as with confirmation of granulomatous and lymphoid disorders. High-integrity cellular samples for molecular and immunohistochemistry profiling may also support MCB for comprehensive lung cancer evaluation, increasingly relevant in the era of oncogene-targeted and immune checkpoint inhibitor therapies<sup>4,5</sup>.

Cryobiopsy is already guideline-endorsed for interstitial lung disease diagnosis<sup>6</sup>, producing large, well-preserved histopathology cores through tissue cryo-adhesion to the probe tip. Adaptation of this technique for mediastinal tissue sampling under EBUS guidance offers a route to histologic diagnosis without associated surgical morbidity. Over the past five years, a growing body of evidence from case series, multicentre trials, and systematic reviews has confirmed the feasibility and safety of the EBUS-MCB technique while defining potential clinical settings in which it offers clear advantages as an adjunct to conventional TBNA.

### Evidence and Literature Review

We performed a comprehensive literature search,

including all PubMed publications generated with search terms (“endobronchial ultrasound” OR “EBUS” OR “EBUS-TBNA”) AND (“cryobiopsy” OR “mediastinal cryobiopsy” OR “CRYO”). Findings from the highest quality publications are summarised herein.

EBUS-MCB has been demonstrated as both technically feasible and diagnostically valuable through a rapidly expanding literature base and widespread clinical uptake. Since its introduction in 2020, studies have consistently shown that cryobiopsy combined with standard EBUS-TBNA improves diagnostic yield, particularly in benign conditions and lymphoma where cytology alone often proves inadequate<sup>7</sup>. A summary of key studies is shown in Table 1.

**Table 1:** Key prospective studies in mediastinal cryobiopsy.

Study	N	Study design	Diagnostic yield	Complications	Detail
Zhang, 2021 <sup>8</sup>	197	RCT: 1:1 randomisation EBUS-MCB then TBNA or EBUS-TBNA then MCB	91.8% vs 79.9%, p=0.001	Mild bleeding; Pneumothorax (n=2), Pneumomediastinum (n=1)	Nodes ≥1cm <sup>a</sup> Tunnelling: Needle-knife Cryoprobe: 1.1mm Samples: 4 TBNA, 3 MCB/ patient ROSE: Not used
Fan, 2023 <sup>9</sup>	271	RCT: 1:1 randomisation to EBUS-TBNA then MCB or EBUS-TBNA alone	TBNA-MCB vs TBNA alone: 92.6% vs 80.7%, p=0.004	Mild bleeding; Pneumothorax (n=6, incl 4 from control group); Pneumomediastinum (n=1)	Nodes ≥1cm Tunnelling: Needle-knife Cryoprobe: 1.1mm Samples: 4 TBNA, 1 MCB/ patient ROSE: Not used
Mangold, 2024 <sup>10</sup>	137	Multicentre cohort: EBUS-TBNA + MCB (retrospective consent obtained from all patients who underwent both during EBUS, at proceduralist discretion)	TBNA-MCB vs TBNA alone: 91.2% vs 56.2%, p<0.001	Moderate bleeding <sup>b</sup> (n=8 with 1.7mm probe, n=2 with 1.1mm probe); Pneumothorax and pneumomediastinum (n=1)	Nodes ≥1cm Tunnelling: Needle-knife or 19/21/22G needles Cryoprobe: 1.1, 1.7mm Samples: 3 TBNA, 4 MCB/ patient ROSE: Not used
Todisco, 2025 <sup>20</sup>	91	Multicentre prospective cohort: EBUS-TBNA + MCB (patients with low pre-test probability of primary lung cancer)	MCB <sup>c</sup> vs TBNA: 78.0 vs 60.4%, p=0.016 TBNA-MCB: 84.6%	Mild-moderate bleeding <sup>b</sup> (n=7); not attributed to specific technique	Node size not recorded Tunnelling: 19/21/22G needles Cryoprobe: 1.1mm Samples: 2 MCB/ node, TBNA data NA ROSE: Not used
Ariza-Prota, 2023 <sup>11</sup>	50	Prospective case series: EBUS-TBNA + MCB in all subjects	MCB <sup>c</sup> vs TBNA: 96% vs 82%	Moderate bleeding (n=2) attributed to TBNA rather than MCB <sup>d</sup>	Nodes >1cm Tunnelling: 22G needle Cryoprobe: 1.1mm Samples: 3 MCB/ node, TBNA data NA ROSE: Not used
Salcedo Lobera, 2023 <sup>12</sup>	50	Prospective case series: EBUS-TBNA + MCB in all subjects	MCB <sup>c</sup> vs TBNA: 90% vs 64%	Mild bleeding (n=3), vocal cord haematoma (n=1)	Nodes >1cm Tunnelling: 22G needle Cryoprobe: 1.1mm Samples: 2 TBNA, 4 MCB/ patient ROSE: Not used
Cheng, 2024 <sup>18</sup>	155	RCT: 1:1 randomisation EBUS-TBNA-forceps then MCB or EBUS-TBNA-MCB then forceps	Forceps vs MCB: 85.7% vs 91.6%, p=0.106	Moderate bleeding (n=3); Pneumothorax (n=2, 1 per subgroup)	Nodes ≥1cm Tunnelling: Not stated Cryoprobe: 1.1mm Samples: 4 TBNA, 3 forceps, 1 MCB/ patient ROSE: Not used

<sup>a</sup>Measured by short axis; <sup>b</sup>Moderate bleeding: bronchoscopy wedged into biopsied segment and/or use of adrenaline or cold saline; <sup>c</sup>MCB sample diagnoses independent of paired TBNA diagnoses; <sup>d</sup> Moderate bleeding: 10–40 mL blood during procedure.

Abbreviations: RCT – randomised controlled trial; EBUS – endobronchial ultrasound; MCB – mediastinal cryobiopsy; TBNA – transbronchial needle aspiration; ROSE – rapid on-site evaluation of cytology.

The first randomised controlled trial (RCT) by Zhang et al. in 2021 established proof of concept, comparing EBUS-MCB with EBUS-TBNA in 197 patients from two centres in a crossover design, with reported diagnostic yield of 91.8% versus 79.9%, ( $p=0.001$ )<sup>8</sup>. Cryobiopsy samples were larger and better preserved than cytology cell block material, providing superior histologic characterisation of sarcoidosis, tuberculosis, and lymphoma cases, noting small subgroup numbers of each within larger study populations. No major complications were observed. Findings were supported in a larger randomised trial conducted by the same group, including 271 patients across three centres<sup>9</sup>. In this study (by Fan et al), subjects were randomised to combined EBUS-TBNA-MCB or EBUS-TBNA alone, with increased diagnostic yield in the EBUS-TBNA-MCB group (92.6% versus 80.7%,  $p=0.004$ ), and greatest incremental benefit in benign disease. Adverse events occurred in <2% of cases. Analysis of each biopsy method in the combined procedure subgroup ( $n = 134$ ) revealed similar findings, with an overall diagnostic yield of 82% for EBUS-TBNA and 91% for cryobiopsy (RR 1.11 [95% CI 1.01–1.22];  $p=0.032$ ).

Real-world reproducibility has been demonstrated in a large pragmatic cohort in which patients undergoing EBUS biopsies received combined modality biopsy at the proceduralists' discretion, with retrospective written consent obtained. Mangold et al. analysed 137 patients across four European centres, reporting 91.2% overall yield in those having EBUS-TBNA plus MCB versus 56.2% for EBUS-TBNA alone, with 2% clinically-significant complications<sup>10</sup>. The relatively low EBUS-TBNA yield likely reflects selection bias, with decision to proceed to MCB possibly reserved for more diagnostically challenging cases. High diagnostic yields for EBUS-MCB have been reported in smaller prospective case series by Ariza Protá et al. and Salcedo Lobera et al., with diagnostic ranges of 90-96% and minor bleeding as the predominant complication<sup>11,12</sup>.

Early feasibility reports have also expanded the procedural scope of MCB. Genova et al. demonstrated successful sampling from mediastinal nodes as small as 8-10mm with high-quality histologic cores and no major bleeding<sup>13</sup>, while Gonuguntla et al. described safe retrieval of diagnostic tissue from a 9mm node in a patient with Hodgkin lymphoma<sup>14</sup>. Soo et al reported a small case series of transoesophageal cryobiopsy diagnoses via endoscopic ultrasound with bronchoscope-guided fine needle aspiration (EUS-B)<sup>15</sup>.

The first randomised comparison between EBUS-MCB and intranodal forceps biopsy (IFB), another histological sampling technique, was reported by Cheng et al<sup>16</sup>. Among 155 patients with undiagnosed mediastinal lymphadenopathy, randomised to EBUS-TBNA followed by IFB then MCB or vice versa, diagnostic yield was 91.6% for

the cryobiopsy first group and 85.7% for those who had IFB first, both superior to EBUS-TBNA (76%). The difference between MCB and IFB was not statistically significant, however cryobiopsy produced larger, less-crushed samples and fewer access failures.

A 2024 meta-analysis by Zhang et al included ten RCT and prospective cohort studies that compared MCB and TBNA samples taken from the same patient, excluding studies that only reported on combined MCB-TBNA findings. The analysis revealed a pooled diagnostic yield of 89.6% for MCB versus 77.1% for EBUS-TBNA ( $n=538$  patients)<sup>7</sup>. A subsequent 2025 systematic review by Kamath et al. (eleven studies,  $n=857$ ) reported pooled diagnostic yields of 91.7% for MCB and 76.6% for EBUS-TBNA, with yield in benign conditions ~94%<sup>17</sup>. It should be noted that this pooled diagnostic yield encompassed studies that reported combined TBNA-MCB results as well those that presented biopsy outcomes for each modality separately.

### Sarcoidosis

The diagnostic yield for sarcoidosis with EBUS-TBNA is reported to be 79-84% in previous meta-analyses<sup>18,19</sup>. In the MCB literature, EBUS-MCB has consistently outperformed EBUS-TBNA for sarcoidosis confirmation, however, overall numbers have been small, with benign diagnoses tending to be aggregated in subgroup analyses<sup>8-10</sup>. A recent prospective multi-centre study by Todisco et al. compared MCB and TBNA in 91 patients with low pre-test probability for primary lung malignancy, allowing for an enrichment of sarcoidosis cases<sup>20</sup>. In this group ( $n=41$ ) the combined yield of TBNA and MCB was 90.2%, with individual yields of 68.3% (TBNA) and 80.5% (MCB); the 12.2% increase in overall yield did not reach statistical significance ( $p=0.206$ ). Given combined results will be used for diagnosis in real-world application of MCB, the evidence supports stepwise addition of this technique if granulomata are not found on TBNA ROSE.

### Lymphoma

Data for lymphoma diagnosis with MCB is comparatively sparse. Romero et al. showed a pooled diagnostic yield of 89.7% in 29 patients across 20 studies, compared with 27.6% for EBUS-TBNA alone, with cryobiopsy samples allowing both histologic diagnosis and adequate subtyping<sup>18</sup>. A separate retrospective analysis of 40 patients with lymphoma (of a total 534 MCB cases performed across twelve European centres) showed diagnostic confirmation with MCB in 38 (95%) patients, compared with TBNA: 6 (15%), and flow cytometry: 8 (20%)<sup>21</sup>. Although signals for utility in lymphoproliferative conditions have emerged in prospective studies, small overall patient numbers limit strength of evidence compared with available TBNA data<sup>8-10,18,22</sup>.

## Non-small cell lung cancer ancillary testing

Molecular and PD-L1 proportion score testing in NSCLC provide further potential indications for EBUS-MCB. Randomised and observational studies suggest improved adequacy when cryobiopsy is added to TBNA, with Fan et al. reporting rates of 97% versus 79% ( $p=0.03$ ) for either molecular or PD-L1 testing<sup>9</sup>, and Zhang et al. showing 93.3% versus 73.5% ( $p<0.001$ ) specimen adequacy for molecular testing<sup>8</sup>. Notably, optimised TBNA alone can achieve highly cellular sampling, considered adequate for further analysis in experienced centres<sup>18,19,22</sup>. Overall, cryobiopsy appears to improve sample integrity and molecular performance, but the magnitude of benefit is unclear. To date, no studies have been designed or sufficiently powered to definitively demonstrate superiority of MCB over TBNA for ancillary testing. As such, some uncertainty remains in optimally selecting the appropriate malignant cases to perform EBUS-MCB.

## Safety data

Across published series, complication rates remain consistently low. Minor bleeding occurs in 10-20% of procedures, pneumomediastinum or pneumothorax in <2%, and serious adverse events or deaths have not been reported<sup>7-18</sup>. No study has demonstrated higher risk than EBUS-TBNA alone when performed by experienced operators. Mediastinal abscess is reported to complicate 0.1-0.5% EBUS-TBNA cases in previous literature, with lymph node necrosis an identified risk factor<sup>23,24</sup>. Although no specific cases are yet described for MCB, heightened caution or avoidance of necrotic nodal sampling is recommended in clinical settings. Recent sentinel case reports of needle tract tumour seeding in two MCB cases signal potential longer-term hazards, highlighting a need for multicentre registry data to quantify risk of this and other rare events and elucidate appropriate MCB indications<sup>25,26</sup>.

## Technical Overview

The mediastinal cryobiopsy workflow builds upon standard linear EBUS-TBNA. Appropriate target lymph node selection(s) depend on procedural factors and biopsy indication. Adherence to principles of systematic nodal examination and “upstaging” should occur when lung malignancy is suspected, with initial sampling of the most suspicious node that would yield the highest cancer stage relative to the parenchymal lesion. Rapid onsite examination (ROSE) of cytology specimens may assist in determining the need for MCB by providing contemporaneous feedback on TBNA cellularity. For patients with lymphadenopathy but no parenchymal lesions, the largest and most technically accessible node is selected. A minimum nodal short axis of 10 mm has been used in most MCB studies<sup>8-12,18</sup>. Vascular and necrotic nodes are avoided to reduce bleeding risk and infection complications, as described above.



**Figure 1:** Endobronchial ultrasound image of cryoprobe in lymph node

Anticoagulation and dual antiplatelet therapy are relative contraindications, along with other uncontrolled bleeding risks<sup>18,27</sup>.

Repeated EBUS-TBNA is performed through the same entry point using a 19–22 G needle. All stations amenable to TBNA have been shown to be accessible by MCB<sup>17,18</sup>. The tract can be widened by advancing the guide-sheath into the puncture site, repeated needle agitations, or by electric needle-knife incision, depending on operator preference. Typically, a 1.1mm diameter cryoprobe (Erbe, Tübingen, Germany) is advanced through the tract under ultrasound guidance (Figure 1), with 1.7mm probe use also reported<sup>10</sup>. Freezing for two to ten seconds achieves firm adhesion, with factors such as tissue fibrosis and water content, ambient conditions of the operating theatre, and probe integrity all contributing to extracted tissue size. Conventionally, the bronchoscope and probe are withdrawn en bloc<sup>8,9</sup>. A more recent practice of tissue extraction through the working channel without en bloc bronchoscope removal, has the advantage of continued biopsy site vision, without apparent compromise of the sample or the bronchoscope working channel<sup>28</sup>. Whether this practice causes long-term damage to the EBUS endoscope is unknown and warrants future study. Following extraction, the sample (typically 2–4 mm in diameter) is thawed in saline and transferred to formalin for fixation and subsequent analysis. Inspection for bleeding after each sample is performed under direct vision.

The ideal number of EBUS-TBNA passes or cryobiopsy samples is not well-defined. Typically, a minimum of three needle passes are performed prior to attempting cryoprobe insertion and more can be attempted if there is difficulty with probe insertion<sup>18</sup>. Between one and four cryobiopsy samples are typically obtained from the lymph node. This combined approach modestly extends procedure time and is readily incorporated into existing EBUS workflows<sup>17,18</sup>.

## Limitations

Current data on EBUS-MCB remain limited by heterogeneity in study design, reported outcomes, operator experience, and procedural technique. The lack of uniformity in technical parameters, (including tract creation method, freeze duration, number of passes, and the sequencing of cryobiopsy relative to TBNA) makes it difficult to define an optimal procedural approach or expected learning curve. Although all large prospective series report low complication rates, long-term safety data from multicentre registries will be important to identify signals such as tract seeding or other unanticipated adverse events once the technique is adopted more widely.

## Practical Implementation

EBUS-MCB may be best viewed as a selective adjunct within the broader diagnostic algorithm of mediastinal sampling. Current evidence suggests that cryobiopsy is most likely to provide additional or confirmatory diagnostic information over EBUS-TBNA alone in selected benign and lymphoid conditions. In such cases, proceeding to EBUS-MCB upfront can reduce the likelihood of non-diagnostic cytology and the need for repeat sampling or more invasive investigation. When malignancy is suspected, especially in lung cancer staging, EBUS-TBNA has been demonstrated to perform reliably in most cases. Here, cryobiopsy may be considered selectively, such as when EBUS-TBNA material appears insufficient for molecular testing or when histologic confirmation is required for treatment planning.

Cost-effectiveness remains an unresolved question. Most published series originate from high-volume interventional pulmonology centres with early access to technology. Broader implementation will depend on structured training, equipment availability, and procedural standardisation to ensure consistency of outcomes across different health systems. Increased procedural time has potential downstream effects on service delivery and logistics. The disposable cryoprobe and associated equipment increase direct procedural costs, though this may be offset by reduced rates of non-diagnostic procedures and avoidance of repeat bronchoscopy or surgical mediastinoscopy. Further economic analyses are needed to compare the additional expenditure against diagnostic yield, NSCLC ancillary testing adequacy, and healthcare savings.

In practice, an adaptive workflow may allow for the best use of resources. EBUS-TBNA should remain the initial step in all cases, with cryobiopsy incorporated upfront in patients with radiologic or clinical features suggestive of benign disease or added selectively in malignancy diagnostics where tissue adequacy is uncertain. ROSE assessment of TBNA material may provide some guidance for gauging adequacy, however inability to quantify cell

block material for ancillary testing during the procedure limits the precision of this approach. Centres without ROSE must also consider other metrics to decide on whether incorporation of MCB is indicated in suspected malignancy cases. Previous inadequate EBUS-TBNA sampling or need to fulfil criteria for therapeutic clinical trial participation, for example, could be reasonable justifications for MCB.

## Conclusion

EBUS-guided mediastinal cryobiopsy provides a safe and effective histologic complement to endoscopic lymph node sampling, particularly for suspected benign conditions and lymphoproliferative disease. Implementation into routine clinical practice will require balancing available resourcing and potential gains in diagnostic information, aligning the technique with highest-yield indications. Collaborative registry data will provide further insights into rarer complications and efficacy in real-world settings, helping to refine patient selection and workflows for optimal use of this technology.

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## Conflicts of interest

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