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Comments on "Comparative yield of transbronchial cryo-nodal biopsy, transbronchial intra-nodal forceps biopsy, and transbronchial needle aspiration for mediastinal lesions at a tertiary care center in India (COLD-FORCEPS study)"

Vidushi Rathi

Department of Pulmonary Medicine, VPCI, University of Delhi, New Delhi, India

Dear Editor,

The recent study by Madan *et al*. provides valuable information on the utility of intranodal cryobiopsy or forceps to endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) during sampling of mediastinal lymph nodes [1]. It found that intranodal cryoprobe acquires a larger tissue and increases diagnostic yield. However, the increase in the diagnostic yield was statistically not significant. This is an important observation. Often, pilot studies with small sample sizes find significant differences between two procedures that larger studies fail to find. However, finding an insignificant advantage of intranodal cryobiopsy to EBUS-TBNA raises doubt about whether larger studies would change this observation.

The diagnostic utility of cryobiopsy has gained traction over time, with increasing evidence supporting its benefits. A systematic review and meta-analysis of 39 studies published in 2022 on the diagnostic yield of cryobiopsy for peripheral pulmonary lesions, interstitial lung diseases, and lung cancers found a significantly greater yield with a larger tissue size [2]. None of the more than 3500 biopsies included in the meta-analysis included mediastinal lymph node sampling by intranodal cryobiopsy.

A randomized trial of 197 patients has found that cryobiopsy of mediastinal lymph nodes improves the yield of diagnosis of benign lesions and uncommon tumors, whereas, for common lung malignancies and diagnosis of metastatic lymphadenopathy, the yield is similar to EBUS-TBNA [3]. This again emphasizes the fact that the use of cryobiopsy can help us to possibly increase the yield when a benign etiology like tuberculosis or sarcoidosis is suspected. This is of immense importance in developing countries, where the diagnostic dilemma of underlying tuberculosis in any sarcoidosis patient remains unclear. Larger studies for cryobiopsy in mediastinal lymphadenopathy in this subgroup of patients are required to provide more evidence.

A recently published randomized study comparing cryobiopsy and forceps biopsy with EBUS-TBNA also found a similar yield with all three modalities [4]. The observation resonates with that made by Manu *et al*. [1]. However, they found that cryobiopsy yielded larger tissue sizes. This has a particular advantage in conditions like lung cancer. Smaller tissues from EBUS-TBNA with or without intranodal forceps often get consumed during histopathological and/or immunohistochemistry analysis. This leaves no or inadequate tissue for conducting molecular analysis. As the target gene library to which pharmacotherapy is approved increases, so does the size of the tissue required for molecular analysis. In case of inadequate tissue, either a repeat sampling is required, or less reliable methods like blood biopsy are resorted to. Cryobiopsy, by yielding tissue of larger sizes, becomes clearly advantageous in terms of yield and procedure time compared to EBUS-TBNA alone or forceps biopsy.

The work by Manu *et al*. provides evidence that intranodal forceps biopsy at present does not have a statistically significant benefit. Similarly, adding cryobiopsy to EBUS-TBNA may not

Correspondence: Vidushi Rathi, Department of Pulmonary Medicine, VPCI, University of Delhi, Vijay Nagar Marg, New Delhi, 110007, India.
Tel.: +91-0-9971891536.
E-mail: vidushirathi@gmail.com

Key words: EBUS, cryobiopsy, guidelines.

Conflict of interest: the author declares that she has no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: this is a letter where no patient data was recorded. Thus, ethical approval is not applicable/required.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: no new clinical data of patients in this letter.

Funding: none.

Received: 18 January 2024.
Accepted: 9 February 2024.
Early view: 19 February 2024.

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Monaldi Archives for Chest Disease 2025; 95:2918
doi: 10.4081/monaldi.2024.2918

increase the diagnostic yield of mediastinal lymph node sampling compared to EBUS-TBNA alone. However, the addition of cryobiopsy to EBUS-TBNA has an advantage in suspected neoplastic lymphadenopathy. It provides a larger tissue sample that can be subjected to molecular testing for immunotherapy or targeted therapy and avoids the need for a repeat biopsy.

The current national guidelines recommend cryobiopsy for mediastinal lymphadenopathy in patients with negative previous EBUS-TBNA or negative onsite pathological examination [5]. There is no mention of the underlying etiology (benign *vs.* malignant) suspected in the recommendations.

Thus, as the emerging evidence in recent studies is not very robust, the indication of cryobiopsy of mediastinal lymphadenopathy remains unclear and should be individualized.

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