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EDITORIAL

Combination of cryobiopsy with EBUS-TBNA—Might rapid on-site evaluation successfully drive patient selection?

Endosonography, which is a minimally invasive technique adopted for the diagnosis of hilar and mediastinal lymphadenopathies, is the gold standard for mediastinal staging of non-small cell lung cancer (NSCLC).[1,2]

Small cytological samples collected by needle-based endosonography may be inadequate to describe histopathology of lymphoproliferative disorders and to assess molecular patterns in patients with advanced lung cancer.[3-5]

Needles of different size and alternative sampling modalities, such as endobronchial ultrasound-guided intranodal forceps biopsy (EBUS-IFB), have been proposed to overcome this limitation[2,6,7]; however, studies have shown that different needle size[s] do not affect overall diagnostic yield and tissue sampling.[2,6,7] The addition of EBUS-IFB to endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) may increase the diagnostic yield in cases of sarcoidosis and lymphoma.[8] Unfortunately, the complication rate of the combined approach is higher when compared with EBUS-TBNA alone.[8]

Mediastinal cryobiopsy has emerged as a promising technology to improve the diagnostic yield of mediastinal lymphadenopathy.[9-12]

Experimental and observational studies which compared EBUS-cryobiopsy with EBUS-TBNA demonstrated the added diagnostic value of cryobiopsy, without any increased rate of adverse events[9-12]; however, no differences in the accuracy of the diagnosis of lung cancer were detected. Cryobiopsy was associated with a higher sensitivity in the diagnosis of uncommon malignancies, lymphoproliferative disorders, and benign lesions; moreover, the material collected with cryobiopsy in cases of advanced NSCLC was more suitable for molecular analysis.[9-12]

In a recent issue of the Journal, two studies evaluated the utility of EBUS-cryobiopsy in combination with EBUS-TBNA.[13,14]

Cheng et al. found that both cryobiopsy and nodal forceps biopsy can increase the diagnostic yield for mediastinal lesions when added to EBUS-TBNA.[13] No differences were found for lung cancers but the sensitivity was higher in the diagnosis of uncommon tumours.[13] The inclusion of cryobiopsy in the diagnostic process resulted in a higher yield for benign diseases and improved the collection of biological materials for molecular testing in those with NSCLC. Few minor adverse events were recorded.[13]

Poletti et al. retrospectively reviewed 48 patients who underwent EBUS-cryobiopsy after EBUS-TBNA.[14] The Authors described a higher yield of cryobiopsy (95.8 %) but the reported sensitivity of EBUS-TBNA (54 %) was lower than previously described.[9-14] Notably, the diagnosis of hyperplastic lymphadenopathy was considered formally acceptable only when specific morphologic criteria based on the recognition of lymph node architecture were identifiable.

No differences were detected in the diagnosis of lung cancer, but a higher yield of cryobiopsy was demonstrated in sarcoidosis, lymphoproliferative disorders, rare mediastinal disorders and hyperplastic lymphadenopthies. Furthermore, pathologists favoured cryobiopsy samples for molecular analysis in patients with advanced NSCLC. No adverse events were reported.[14]

The studies confirmed previous findings on the safety and accuracy of the technique showing the advantages of cryoprobe in comparison with forceps biopsy: its added value can be proved when needle aspiration fails to provide enough material for molecular analysis of NSCLC and when a definitive diagnosis of benign diseases and less common mediastinal tumours has to be confirmed.[13,14]

However, some critical points need to be clarified, from the procedures to patients who may really benefit.[15,16]

Cheng et al. performed EBUS-TBNA (four passes), then cryobiopsy (one sampling) and forceps biopsy (3 samplings) using a randomized approach.[13] An incision in the tracheobronchial wall was performed with an electrosurgical knife to insert cryoprobe and forceps into the mediastinum during spontaneous breathing, with conscious sedation and without intubation (oral/nasal route).[13] A complicated procedure including the use of an electrosurgical knife, not available in the majority of the centers, was carried out by expert bronchoscopists.[13]

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Poletti et al. described an easier technique passing cryoprobe through the puncture site of EBUS-TBNA. All the procedures were performed using rigid bronchoscopes. The number of samplings was not reported.[14]

No studies have compared diagnostic yield, safety profile, and patient comfort during cryo-EBUS using different sedation protocols and endoscope insertion routes. Different strategies of nodal cryo-sampling have been described in the literature.[11-14,17] However, the best technique in terms of probe insertion, adequate number of biopsies, and cooling time has not been determined yet.

A standardized, easy-to-perform procedure would be needed to achieve a widespread adoption.

In both studies cryobiopsy was added to EBUS-TBNA and the use of rapid on-site evaluation (ROSE)[2,18] was not reported.

The need for an additional sampling tool (i.e., cryo- or forceps biopsy) might be superfluous if ROSE is included in the diagnostic workflow of endosonography: ROSE does not increase the diagnostic yield[2,18,19] but can provide immediate information on the quantity and quality of the material. It can reduce the number of needle passes and can improve sample adequacy for diagnosis and molecular profiling or might guide subsequent sampling with cryoprobe in case of poor collection, suspected uncommon tumours or lymphoproliferative disorders.[2,18,19]

In conclusion, the studies by Cheng et al. and Poletti et al. highlight the potential utility of mediastinal cryobiopsy in comparison with forceps biopsy as a complementary tool to overcome limitations of conventional EBUS-TBNA.[13,14]

Future studies including ROSE could help understand the subgroups of patients with mediastinal lymphadenopathies who can have a diagnostic advantage from cryobiopsy. Larger studies should assess the accuracy of this technique in the diagnosis of lymphomas and benign lesions. The role of mediastinal cryobiopsy to identify genomic background in common epithelial tumours represents another interesting field of investigation.

Standardization of the technique is needed before its wider adoption in daily clinical practice.

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