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Mediastinal "deep freeze"—transcarinal lymph node cryobiopsy

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Abstract

Background: The diagnostic yield of endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) from mediastinal lymph nodes ranges from 66%–89%. However, in many cases cytologic material is not sufficient for full molecular evaluation. A novel method of transcarinal cryobiopsy aims to provide bronchoscopically obtained, larger specimen samples from mediastinal lymph nodes. We aimed to assess the efficacy and safety of transcarinal EBUS-guided lymph node cryobiopsy.

Methods: Patients referred for EBUS-TBNA, based on abnormal mediastinal clinical and radiographic findings, were enrolled into this prospective interventional study between July 2020 and August 2021. All EBUS-TBNA procedures were performed using ProCore 22G needle (Cook Medical) to create, both a transcarinal tract for the cryoprobe and to obtain TBNA samples. For EBUS guided transcarinal cryobiopsy, we used flexible 1.1 mm or 1.7 mm cryoprobe inserted into the working channel of the EBUS scope and into the target subcarinal lymph node.

Results: Twenty-four patients with male predominance 2:1 and mean age of 60.12 ± 10.16 years were enrolled. All target lymph nodes had hypoechoic, homogenic consistency with demarcated borders, without central structures. Cryobiopsy provided pathological diagnosis in 20 cases (83.33%), with 1.1 mm cryoprobe in 14 and with 1.7 mm cryoprobe in 6 cases. In one case each, pathology was provided by TBNA or by cryoprobe alone. No immediate or late complications were encountered during the procedures.

Conclusion: Transcarinal EBUS guided lymph node cryobiopsy following EBUS-TBNA proved to be efficient with a high diagnostic yield and can be considered safe, because no immediate or late complications occurred.

KEYWORDS
cryoprobe, endobronchial ultrasound, lymph node, transcarinal

INTRODUCTION

As lung cancer is one of the most common and deadliest cancers in the world, early diagnosis is crucial to improve patient survival.[1,2] Mediastinal lymph node sampling is a key component in the diagnosis of thoracic malignancies, infections, and inflammatory diseases. For the last two decades, endobronchial ultrasound (EBUS) has revolutionized the field of mediastinal diagnosis, because surgical mediastinoscopy are seldom needed.[3,4]

EBUS is often used for transbronchial needle aspiration (TBNA) guidance. TBNA is routinely performed by using fine needle aspiration (FNA) needles and core needles of 25G–19G diameter. The diagnostic yield of EBUS-TBNA differs between series ranging from 66% to 89%,[5,6] however, in many cases cytologic material is not sufficient for full molecular evaluation.

In transcarinal cryobiopsy, a cryoprobe is introduced through the working channel of the EBUS scope, which allows sampling mediastinal lymph nodes under real-time sonographic visualization.

A small number of case reports described a novel method of transcarinal cryobiopsy from mediastinal lymph nodes,[7,8] and recently a randomized clinical trial was published with impressive diagnostic results.[9]

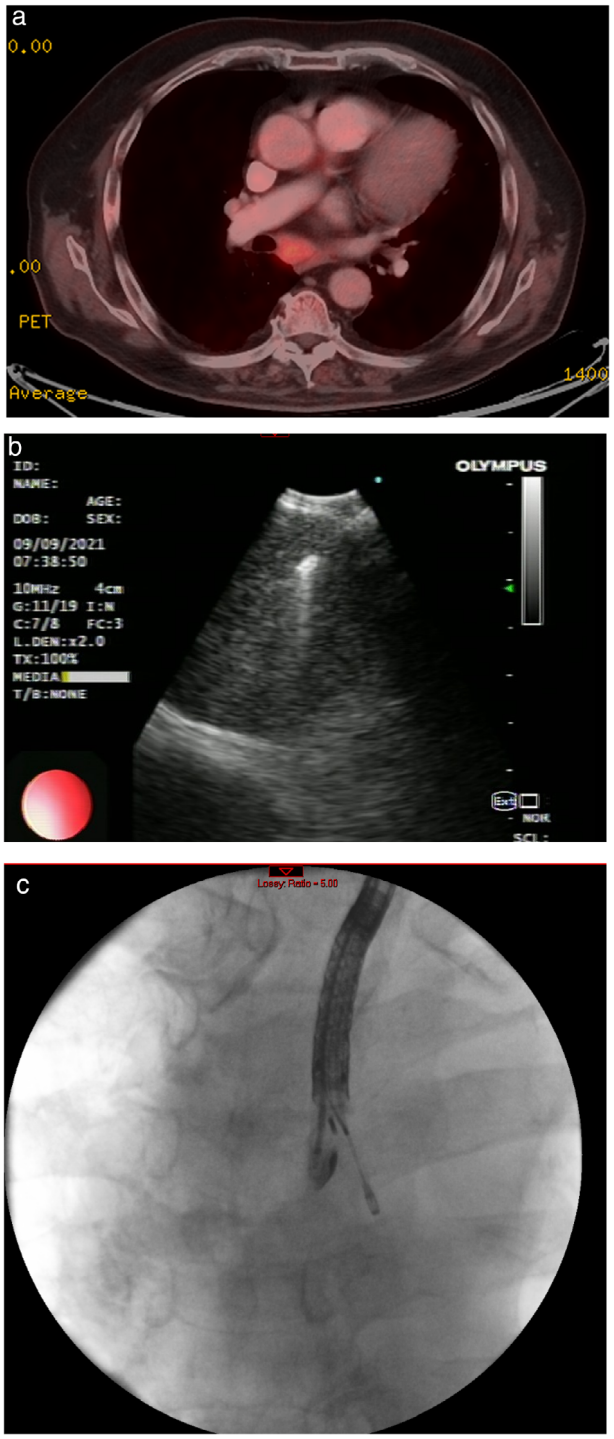

FIGURE 1 Sixty-year-old male with abnormal chest findings on imaging. (a) Positron emission tomography-computed tomography scan with fluorodeoxyglucose avid subcarinal lymph node. (b) Endobronchial sonography of 1.1 mm cryoprobe inside the subcarinal lymph node. (c) Fluoroscopy image of EBUS with cryoprobe in subcarinal lymph node

In this prospective pilot trial, we assessed the efficacy and safety of transcarinal EBUS-guided lymph node cryobiopsy, following EBUS-TBNA in 24 patients.

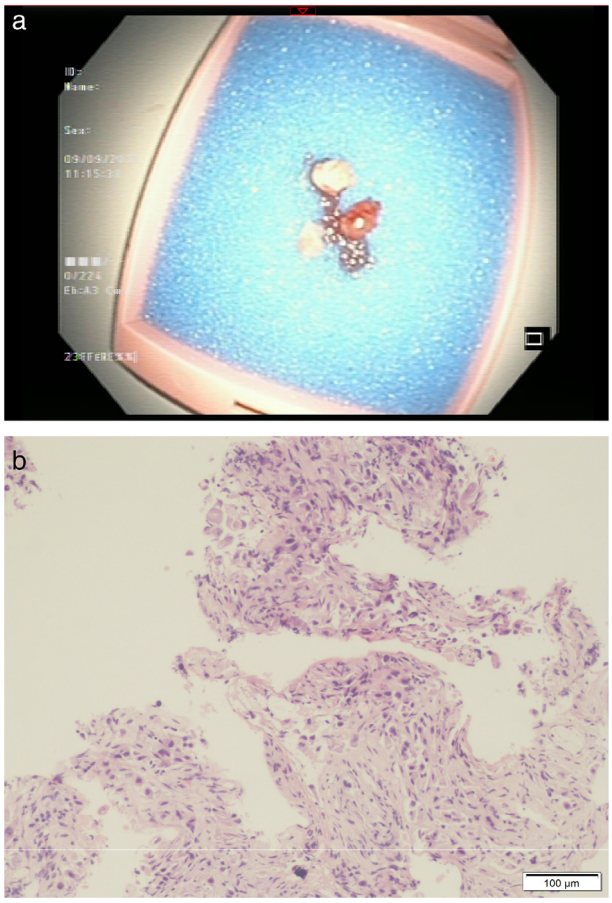

FIGURE 2 Specimen of cryobiopsy and corresponding histopathology. (a) Cryobiopsy specimen from the lymph node. (b) Hematoxylin and eosin ×20 stain of the specimen showing squamous cell carcinoma

METHODS

This prospective interventional pilot trial was conducted between July 2020 and August 2021 at a university affiliated tertiary medical center. The study was approved by institutional ethics committee of Rabin Medical Center (IRB 0752–21).

Patient selection

Patients were eligible for inclusion if they were 18 years or older and presented with mediastinal abnormalities on clinical and radiographic findings requiring pathological examination.

Patients referred for EBUS-TBNA were enrolled on basis of abnormal mediastinal radiographic findings: with lymph nodes >1 cm in diameter, having a positive positron emission tomography (PET) signal or for staging and diagnosis of lung cancer (shown in Figure 1(a)). All procedures in this cohort were performed by experienced interventional pulmonologists (E.G. and M.R.K.) on an ambulatory basis.

TABLE 1 Demographic, clinical, and pathological characteristics of the cohort

No.	Patient age (y)/sex (M/F)	Cryoprobe (1.7 mm/ 1.1 mm)	LN station sampled	LN diameter (mm)	No. of TBNA passes	Diagnosis by TBNA	No. of cryobiopsy samples	Diagnosis by cryobiopsy
1	68/M	1.7 mm	7	14	2	Sarcoidosis	2	Sarcoidosis
2	72/M	1.7 mm	7	10	3	Adenocarcinoma	3	Non-diagnostic
3	49/M	1.7 mm	7	31	3	Small–cell lung cancer	2	Small–cell lung cancer
4	57/F	1.7 mm	7	27	3	Non-diagnostic	3	Non-diagnostic
5	64/M	1.7 mm	7	15	4	Squamous cell carcinoma	3	Squamous cell carcinoma
6	63/F	1.7 mm	7	25		Sarcoidosis	3	Sarcoidosis
7	64/F	1.7 mm	7	20	3	Sarcoidosis	2	Sarcoidosis
8	48/M	1.1 Mm	7	20		Sarcoidosis	4	Sarcoidosis
9	60/F	1.1 mm	7	20	2	Sarcoidosis	3	Sarcoidosis
10	67/F	1.1 mm	7	10	3	Sarcoidosis	3	Sarcoidosis
11	66/M	1.7 mm	7	17	2	Small–cell lung cancer	3	Small–cell lung cancer
12	44/M	1.1 mm	7	20	4	Non-diagnostic	4	Non-diagnostic
13	56/M	1.1 mm	7	15	2	Sarcoidosis	2	Sarcoidosis
14	72/M	1.1 mm	7	20	3	Metastatic salivary gland carcinoma	4	Metastatic salivary gland carcinoma
15	65/F	1.1 mm	7	20	3	Sarcoidosis	2	Sarcoidosis
16	69/M	1.1 mm	7	22	3	Squamous cell carcinoma	2	Squamous cell carcinoma
17	62/M	1.1 mm	7	17	4	Sarcoidosis	3	Sarcoidosis
18	53/F	1.7 mm	7	25	3	Metastatic cholangiocarcinoma	4	Metastatic cholangiocarcinoma
19	56/F	1.1 mm	7	13	3	Sarcoidosis	2	Sarcoidosis
20	74/M	1.1 mm	7	20	2	Sarcoidosis		Sarcoidosis
21	35/M	1.1 mm	7	13	3	Non-diagnostic	3	Non-diagnostic
22	52/M	1.1 mm	7	17	2	Adenocarcinoma	3	Adenocarcinoma
23	52/M	1.1 mm	4 L	10	2	Adenocarcinoma		Adenocarcinoma
24	75/M	1.1 mm	7	11	3	Non-diagnostic	2	Adenocarcinoma
25	60/M	1.1 mm	7	13	3	Squamous cell carcinoma	4	Squamous cell carcinoma
26	49/M	1.1 mm	7	10	3	Metastatic thyroid	3	Metastatic thyroid
27	71/M	1.1 mm	7	25	2	Squamous cell carcinoma	2	Squamous cell carcinoma

Abbreviations: LN, lymph node; TBNA, transbronchial needle aspiration.

Procedural sedation

Once selected, all patients underwent bronchoscopy under moderate-deep sedation using midazolam, fentanyl, and propofol. Informed consent was obtained before all procedures. We used iGel laryngeal mask for airway management and EBUS insertion in all procedures. In all patients, topical anesthesia with lidocaine 1% was applied on the vocal cords (3 cc) and main carina (3 cc) before introduction of TBNA.

During the procedure all patients were monitored for respiratory distress (transcutaneous O_2 saturation), non-invasive blood pressure, and airway bleeding.

After procedure completion all patients were transferred to recovery, post procedure included a chest X-ray and a 7-day course of prophylactic antibiotics.

EBUS-TBNA and EBUS guided transcarinal cryobiopsy

All procedures were performed with the use of EBUS BF-UC180F (Olympus Medical Systems). We used a TBNA ProCore 22G needle (Cook Medical) to create a transcarinal tract for the cryoprobe and to obtain TBNA samples. The TBNA orifice in the airway wall was enlarged by advancing the sheath on top of the needle. In cases in which the cryoprobe could not be introduced through the created orifice, it was enlarged using N YAG Laser (Medialis Fiberton 8100 Dormier Medtech).

Transcarinal cryoprobe biopsy was first attempted in subcarinal and paratracheal lymph nodes, as presented in the results, although in some patients additional mediastinal or hilar lymph nodes were sampled by TBNA alone.

For EBUS guided transcarinal cryobiopsy we used either a flexible 1.1 mm or 1.7 mm cryoprobe (Erbecryo 20 402–401), which was inserted into the working channel of the EBUS scope and through it into the target subcarinal lymph node (shown in Figure 1(b)). When positioned and sonographically visualized inside the lymph node, we activated the cryoprobe for 3 to 4 seconds and retrieved the probe with the EBUS scope en bloc. The specimen was thawed in warm saline and fixed in formalin. We performed 2 to 4 such biopsy passes in every procedure, pending on macroscopic size adequacy. In certain cases, we used fluoroscopy, as additional guidance into the lymph node (shown in Figure 1(c)).

All samples were sent in formalin, for further pathological analysis and staining (shown in Figure 2(a),(b)). Patients received diagnostic results at the 2-week post-procedure follow-up.

RESULTS

Twenty-four patients were enrolled in this prospective interventional pilot trial. Table 1 presents the demographic and clinical characteristics of our cohort. There was a male predominance 2:1 with mean age of 60.12 ± 10.16 years. In all 24 patients, the target lymph nodes had hypoechoic, homogenic consistency with demarcated borders and without central structures.

We used the 1.1 mm cryoprobe in 16 (inserted through the TBNA orifice), and in 8 cases we used 1.7 mm cryoprobe (inserted through the laser dilated transcarinal orifice). Pathological diagnosis was provided by cryoprobe in a total of 20 cases (83.33%), by 1.1 mm in 14 and by 1.7 mm cryoprobe in 6 cases. Pathological diagnosis was provided by TBNA alone in a total of 21 patients (87.5%). In one case each, pathology was provided by TBNA or cryoprobe alone. Sarcoidosis was the diagnosis in 11/20 cases (55%) and malignancy in 9/20 cases (55%).

In 4 patients, (16.67%) specimens were regarded non diagnostic.

Complications

No immediate complications, including respiratory or hemodynamic distress or visible bleeding, were encountered during the procedure. No new procedural related abnormalities were observed on post procedural chest X-ray and all 24 patients were discharged home. Nor were there any late complications as fever, cough, chest pain, or mediastinitis, at the follow up visits.

DISCUSSION

In this prospective interventional pilot study, we present our experience with transcarinal EBUS-guided lymph node biopsy in 24 patients referred to our medical center for EBUS-TBNA for mediastinal lymph node investigation. Transcarinal EBUS-guided lymph node cryobiopsy following EBUS-TBNA proved to be efficient with a high diagnostic yield and can be considered safe, because no immediate or late complications occurred.

The diagnostic yield of bronchoscopic mediastinal lymph node sampling has increased in the last decades to beyond 90%.[6] Nonetheless, in some situations surgical mediastinoscopy will be considered as a first-line procedure, (e.g., in cases of high suspicion for hematological malignancy or failure to provide definite or adequate samples using bronchoscopy). Notwithstanding, mediastinoscopy's very high diagnostic yield, its complication rate is substantial compared to EBUS-TBNA. Transcarinal cryobiopsy aims to provide bronchoscopically obtained larger specimen samples from mediastinal and hilar lymph nodes, while avoiding the need for surgery.

Previous case reports performed in similar conditions, (i.e., in bronchoscopy suit on an ambulatory basis) provided preliminary feasibility and safety estimates of this method. In one such report, Zhang et al.[8] presents a case of mediastinal lymph node sampling in a male with a diagnosis of germinal cell tumor. Another short series, by Gonuguntla et al.,[7] with 4 patients who underwent this procedure showed definite diagnosis in all cases. In their report, Gonuguntla et al.,[7] performed cryobiopsy from both mediastinal and hilar lymph nodes. In all of these five cases, there was no report of any evident complications related to the cryobiopsy procedure.[7,8]

In the first prospective randomized study, Zhang et al.[9] presented their experience in 197 cases comparing transcarinal cryobiopsy versus TBNA with EBUS visualization. The overall diagnostic yield was 79.9% and 91.8% for TBNA and transbronchial mediastinal cryobiopsy, respectively ($p = 0.001$). Diagnostic yields were similar for metastatic lymphadenopathy (94.1% vs. 95.6%, $p = 0.58$), whereas cryobiopsy was more sensitive than TBNA in uncommon tumors (91.7% vs. 25.0%, $p = 0.001$) and benign disorders (80.9% vs. 53.2%, $p = 0.004$).[9] Our cohort of patients showed higher diagnostic yield for TBNA, but lower for cryobiopsy. Because there were only two cases diagnosed in our cohort with one modality alone, we found the TBNA and cryobiopsy methods to be complementary. Moreover, in their study Zhang et al.[9] encountered two cases of pneumothorax and one case of pneumomediastinum (1.5%). In our study, transcarinal cryobiopsy had the diagnostic yield of 83.3% (20/24) with no cases of pneumothorax, pneumomediastinum, bleeding, or thoracic infection.

Our study has several limitations. First, this is a rather small cohort of patients with no randomization for biopsies taken with 1.1 mm versus 1.7 mm cryoprobes, because the former was used in cases the dilation of the orifice could be achieved with TBNA. Second, the procedures were performed by expert interventional pulmonologists and the technical aspects of this procedure are not intuitive and have a learning curve. Third, when using this method, additional procedural time needs to be taken into account because of the sequential use of cryobiopsy following EBUS-TBNA.

Finally, because we performed cryobiopsy following conventional EBUS-TBNA the comparison between these two methods is lacking.

In conclusion, this prospective interventional pilot study demonstrated our early experience with transcarinal cryoprobe. There were no immediate or late complications related to the EBUS or cryobiopsy procedure, and therefore, this method can be considered safe, according to our findings. We achieved a high diagnostic yield with transcarinal cryoprobe and would recommend the sequential use of this method of transcarinal cryobiopsy following EBUS-TBNA, possibly becoming its alternative in the future. This trial represents the experience of a single academic tertiary center, to improve assessment of the efficacy and safety of this method warrants large randomized, multicenter trials.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest, nor any relevant financial interests or relationships or affiliations.

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