ORIGINAL ARTICLE

Novel ProCore 25-gauge needle for endobronchial ultrasound-guided transbronchial needle aspiration reduces the puncture time and frequency, with comparable diagnostic rate for mediastinal and hilar lymphadenopathy

Li Yang[1†], Ye Gu[1†], Hai Wang[1], Dongmei Yu[1], Haiping Zhang[2] & Hao Wang[1,3]

1 Endoscopy Center, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
2 Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
3 Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Correspondence
Hao Wang, Endoscopy Center, Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine,
507 Zhengmin Road, Shanghai 200092, China.
Tel: +86 21 6511 5006
Fax: +86 21 6511 3665
Email: shfknj@163.com; and
Haiping Zhang, Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, 507 Zhengmin Road, Shanghai 200092, China.
Tel: +86 137 0192 3690
Fax: +86 21 6511 3665
Email: zhp7341@sina.com

[†]These authors contributed equally to this work.

Abstract

Background: The ProCore 25-gauge needle is a novel specifically designed puncture needle for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), which may improve the puncture efficiency of the procedure while ensuring the diagnostic rate. The aim of the present study was to evaluate the diagnostic accuracy, mRNA yield, and complication rate of 25-gauge needles compared to those of 22-gauge needles in the evaluation of mediastinal and hilar lymphadenopathy.

Methods: A total of 39 patients undergoing EBUS-TBNA at our institution were evaluated. All the procedures were performed by an experienced endoscopist formally trained in interventional pulmonology. Both the traditional 22-gauge and ProCore 25-gauge needles were used at each lymph node station. For all specimens obtained via EBUS-TBNA, 50 μL was used to extract mRNA and detect the RNA concentration, whereas the other part was sent to the pathological evaluation. χ^2 test and t-test were performed to determine the differences between the two types of the needles. A P-value of <0.05 was considered significant.

Results: A total of 88 lymph nodes were punctured by the two needles separately. The diagnostic accuracy for each puncture between the two needles did not show any significant difference ($P > 0.05$). No serious procedure-related complications were reported. In addition, the mRNA concentration did not differ between the two types of needles ($P > 0.05$).

Conclusion: The ProCore 25-gauge needle gained a similar diagnostic yield with less puncture time and frequency compared with the 22-gauge needle.

Introduction

Initially, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed mainly for lung cancer staging, but it is now used as a standard of care for the diagnosis of mediastinal and hilar lymphadenopathy from various causes.[1–3] It is possible to sample multiple mediastinal and hilar lymph nodes (LNs) in the same procedure under moderate sedation in outpatient settings with high accuracy and minimal complications using EBUS-TBNA.[4] It has been reported as a minimally invasive and safe procedure in multiple systematic reviews and meta-analyses.[5,6]

EBUS-TBNA has been used to diagnose lung cancer, sarcoidosis, tuberculosis, and lymphoma, and has a significant impact on their subsequent management.[3] It guides

treatment in patients with lung cancer by diagnosing, subtyping, staging, molecular subtyping, and also restaging when indicated.[4] Although computed tomography (CT) and positron emission tomography (PET) scan can show mediastinal lymphadenopathy, pathological confirmation is still required to complete the staging evaluation. Compared to mediastinoscopy, EBUS-TBNA is a minimally invasive technique with similar diagnostic rate, less postoperative pain and decreased complication rates.[7–9]

The quality of the samples punctured by EBUS-TBNA is very crucial for a precise diagnosis. There may be several potential factors that impact the quality of the samples, such as the size and type of the puncture needle. In order to identify the affect, several studies have been carried out.[10] There are many types of puncture needles for this procedure. Traditionally, the 22-gauge needle (Olympus, Tokyo, Japan) has been the most commonly used needle for EBUS-TBNA due to its ease of use and better sampling. Recently, a new type of 25-gauge puncture needle has been released. Compared with the 22-gauge needle, it is more slender and the unique design of the side-cutting groove allows tissue to enter the needle lumen and aids in procuring a complete tissue specimen. However, it is uncertain if this novel core needle achieves comparable diagnostic accuracy with a shorter puncture time, lesser frequency, and lower complication rate.

The aim of the present study was to evaluate the diagnostic accuracy, mRNA yield, and complication rate of the 25-gauge needle compared to that of the 22-gauge needle in the evaluation of mediastinal and hilar lymphadenopathy.

Methods

Patients

Patients with clinical and radiological features of mediastinal or hilar lymphadenopathy were enrolled in the study. According to their doctor's advice, the patients underwent EBUS-TBNA for tissue confirmation. Chest computed tomography (CT) was performed prior to bronchoscopic examination. Based on CT findings, at least one enlarged mediastinal or hilar lymphadenopathy >10 mm in the short axis was observed in all the patients. Patients were usually given local anesthesia unless they were unable to tolerate local anesthesia or required general anesthesia before surgery. Written informed consent was obtained from all patients included in this study. The study protocol was approved by the Institutional Review Board of Shanghai Pulmonary Hospital.

Procedural technique

The target LNs were determined before the operation based on the chest CT scan. If there were multiple target LNs for the same patient, we followed the order of N3-N2-N1 and puncture from the farthest to the nearest. Each LN was punctured three times with a 22-gauge needle (NA-201SX-4022; Olympus) and once with a 25-gauge needle (ECHO-HD-25-EBUS-O-C; Cook Medical, Bloomington, IN, USA). Under sedation, aspiration of LNs was performed 15 times for each puncture. The order of the puncture needles was randomly arranged to exclude the bias which was caused by the different order of puncture needles. The operation process was carried out according to the standard procedure by the same experienced endoscopist, using an Olympus EBUS-TBNA system (BF-UC260FW endoscope and CV-260SL main engine, Olympus).

Pathological diagnosis and RNA concentration detection

The specimens obtained with each needle pass were extracted to the slides by pushing the stylet and flushing the syringe with air.

For all the specimens obtained via EBUS-TBNA, 50 μL was immediately placed in an RNase-free Eppendorf tube containing 500 μL of RNA later (Cat No.AM 7021, Life Technologies) and stored at −20°C. Once the specimen was confirmed by our pathologists to have more than 50 tumor cells, the RNA later preserved part was removed from storage to extract mRNA. RNeasy Mini Kit (Qiagen, Hilden, Germany) was used to extract the mRNA, which was subsequently quantitated by the NanoDrop 2000 Spectrophotometer (Thermo Scientific, Waltham, MA, USA).

The other specimens were sent for pathological evaluation. If material such as core tissue was found on the slide, it was removed for histological analysis. It was formalin fixed, processed, paraffin embedded, and subsequently stained with hematoxylin and eosin. Immunohistochemical staining was performed only by a pathologist. The remaining slides were smeared and fixed in 100% ethanol for off-site cytological analysis. They were prepared with staining. Cytological and histological evaluations were performed by a single pathologist who was blinded to the types of the needles. The pathologists also assessed the quality of the specimen. The experimental process is shown in Fig 1.

Statistical analysis

Categorical data were analyzed by the χ^2 test as appropriate. Continuous data were analyzed by the t-test. All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and a P-value of <0.05 was considered significant.
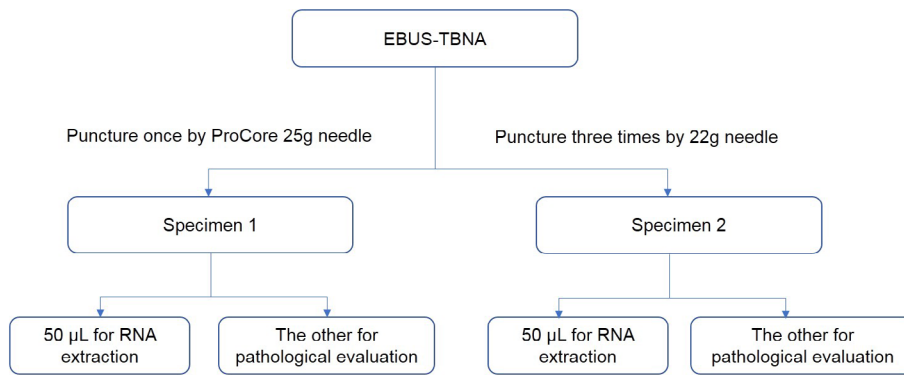
Results

A total of 39 patients were enrolled in the study including 20 men and 19 women. The average age was 63 years (range, 43–73 years). During the EBUS-TBNA procedure, general anesthesia and local anesthesia were given to nine and 30 patients, respectively. Of the 39 patients, 74% underwent puncture of two target LNs and 26% underwent puncture of three target LNs (Table 1).

A total of 88 LNs were punctured separately by the two needles. The images of chest CT and ultrasonography during puncture from one case are shown in Fig 2. There was no significant difference in the pathological diagnosis between the two groups by McNemar's test ($P = 0.21$, Table 2).

The most common complications were bleeding and hypoxia during puncture. There were 12 cases of bleeding at the puncture site by the novel needle, and only one patient was given further treatment. A total of 15 bleeding cases occurred using the 22-gauge needle, and four patients were given further treatment. A few patients developed mild hypoxia during the examination but improved after symptomatic treatment. No serious procedure-related complications were observed. In addition, the mean time cost per puncture was not different between the two needles (five minutes vs. four minutes) (Table 3).

The extracted mRNA underwent quality testing to ensure that it was not degraded during the procedure. The mRNA concentration did not differ between the two types of needles ($P > 0.05$, Fig 3).

Discussion

This study demonstrated that the diagnostic outcomes, including accuracy of diagnosis and adequacy of sample, were comparable between the novel 25-gauge and traditional 22-gauge needles. The ProCore needle reduced the puncture time and frequency while achieving the same diagnostic rate as that of the traditional needle.

EchoTip ProCore is designed to acquire cytological and histological samples (cells) during endobronchial ultrasonography. The Menghini tip was used for the ProCore needles, which is much more safe and sharper than the traditional tip. Further, we observed that the ProCore needle more easily reached the LNs of each station, especially stations 10 LNs. This is probably because the ProCore needle has better elasticity and greater puncture force. In addition, the unique design of the CoreTrap allows tissue to enter the needle lumen and aids in procuring a complete tissue specimen (Fig 4).

Our study showed that the novel 25-gauge needle could obtain enough samples for diagnosis though a single-pass puncture. The mean time of each puncture was similar between the two needles. Therefore, the novel needle could greatly reduce the total puncture time, risk of puncture, and patient's discomfort.

In recent years, progress has been made in the development of molecular targeted drugs and immune therapy for lung cancer.[11–19] Detection of gene mutations is important

Table 1 The demographic and clinical characteristics of the patients

Characteristics	N (%)
Age, years, median (range)	63 (43–73)
Sex	
Male	20 (51%)
Female	19 (49%)
Anesthesia	
General anesthesia	9 (23%)
Local anesthesia	30 (77%)
Number of sampled LNs for each patient	
2	29 (74%)
3	10 (26%)
The stations of sampled LNs	
2	1 (1%)
4	37 (42%)
7	23 (26%)
10	9 (11%)
11	18 (20%)

LNs, lymph nodes.

Figure 2 (**a**) Chest computed tomography scan before bronchoscopic examination (the arrow points to the punctured lymph node). (**b**) The ultrasonogram of the target lymph node punctured by the ProCore needle.
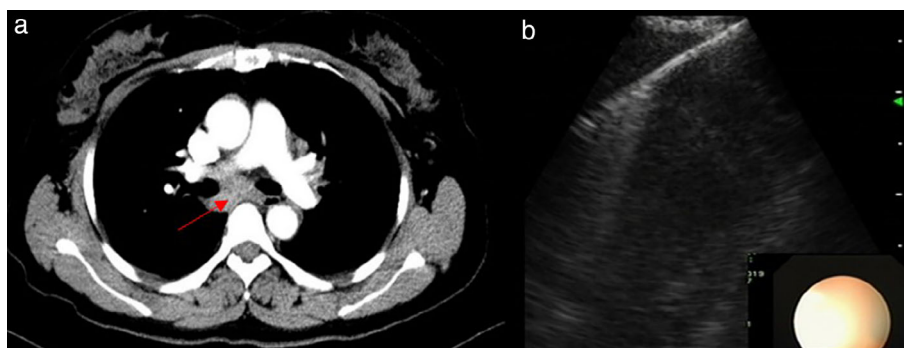

Table 2 Pathological diagnostic results of all sampled lymph nodes by the traditional 22-gauge needle and novel 25-gauge needle

	Traditional 22-gauge needle						
	Adenocarcinoma	Squamous	NSCLC	SCLC	Malignant tumor cells	Negative	Total
Novel 25-gauge needle							
Adenocarcinoma	3	2	3	9	3	2	22
Squamous cells	2	0	0	4	0	0	6
NSCLC	6	1	2	7	0	0	16
SCLC	5	2	7	10	1	5	30
Malignant tumor cells	1	0	0	0	0	2	3
Negative	5	1	4	1	0	0	11
Total	22	6	16	31	4	9	88

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Table 3 Complications and puncture time

	Novel 25-gauge needle	Traditional 22-gauge needle
Complications		
Bleeding	12 (31%)	15 (38%)
No intervention necessary	11 (28%)	11 (28%)
Local hemostasis with thrombin	1 (3%)	4 (10%)
SO$_2$ decrease	2 (5%)	3 (8%)
>80%	2 (5%)	3 (8%)
Mean time per puncture (minutes)	5	4

for lung cancer, especially NSCLC. Identification of the tumor's molecular characteristics is crucial for subsequent management of the disease. Several studies showed that EBUS-TBNA sampling is a feasible approach in detecting EGFR mutations, ALK rearrangements, and other gene alterations due to sequencing, fluorescence in situ hybridization, or polymerase chain reaction analyses.[20–24] Both DNA and RNA can be used to detect mutations by different methods. The detection frequency of mutation is much higher in RNA than in DNA because genes with driver mutations have high transcriptional activity.[17,25] However, RNA is more susceptible to degradation than DNA during sample collection and RNA extraction. Since RNA is more susceptible to degradation and more sensitive to the process of obtaining tissue specimens, we chose to detect the RNA concentration of the tissue in order to indirectly reflect the time of the puncture, and simultaneously prove that the amount of tissue obtained using the new puncture needle is sufficient for pathological examination.

In addition, obtaining specimens with complete organizational structure is very important for pathologists to diagnose diseases such as sarcoidosis. Sarcoidosis is a multisystem disorder of unknown etiology that is characterized by noncaseating epithelioid cell granulomas.[26] In addition to its clinical features, a pathological confirmation is crucial for the diagnosis of sarcoidosis and the exclusion of other possible diseases. It has become possible to diagnose sarcoidosis because EBUS-TBNA allows the collection of adequate morphologically intact specimens. We believe that the improvement in the puncture needle could also benefit sarcoidosis diagnosis.

In conclusion, with less puncture time and frequency, the novel 25-gauge needle exhibited a similar diagnostic yield compared with the traditional 22-gauge needle. This may improve operational efficiency and expand the clinical applications. Further studies need to be carried out to identify the various possible applications of this procedure.
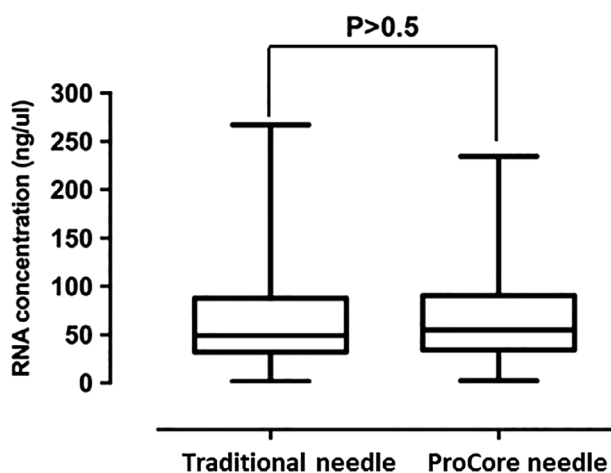
Figure 3 The mRNA concentration between the traditional 22-gauge needle and novel 25-gauge needle.

Figure 4 The unique design of the CoreTrap for the ProCore 25-gauge needle.

Acknowledgments

Disclosure

The authors have no conflicts of interest to declare.

References

1 Okamoto H, Watanabe K, Nagatomo A *et al*. Endobronchial ultrasonography for mediastinal and hilar lymph node metastases of lung cancer. *Chest* 2002; **121**: 1498–506.

2 Yasufuku K, Chiyo M, Sekine Y *et al*. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest* 2004; **126**: 122–8.

3 Vaidya PJ, Kate AH, Chhajed PN. Endobronchial ultrasound-guided transbronchial needle aspiration: The standard of care for evaluation of mediastinal and hilar lymphadenopathy. *J Cancer Res Ther* 2013; **9**: 549–51.

4 Vaidya PJ, Kate AH, Yasufuku K, Chhajed PN. Endobronchial ultrasound-guided transbronchial needle aspiration in lung cancer diagnosis and staging. *Expert Rev Respir Med* 2015; **9**: 45–53.

5 Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: A systematic review and meta-analysis. *Respir Med* 2012; **106**: 883–92.

6 Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: A systematic review. *Eur Respir J* 2009; **33**: 1156–64.

7 Hashimi H, Cooke DT, David EA, Brown LM. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of non-small cell lung cancer. *J Vis Surg* 2018; **4**: 37.

8 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.

9 Marchand C, Medford ARL. Relationship between endobronchial ultrasound-guided (EBUS)-transbronchial needle aspiration utility and computed tomography staging, node size at EBUS, and positron emission tomography scan node standard uptake values: A retrospective analysis. *Thorac Cancer* 2017; **8**: 285–90.

10 McCracken DJ, Bailey M, McDermott MT, McManus TE. A retrospective analysis comparing the use of ProCore® with standard fine needle aspiration in endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). *Ir J Med Sci* 2019; **188** (1): 85–8.

11 Mok TS, Wu YL, Thongprasert S *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.

12 Shaw AT, Yeap BY, Solomon BJ *et al*. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: A retrospective analysis. *Lancet Oncol* 2011; **12**: 1004–12.

13 Zhou C, Wu YL, Chen G *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-

label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.

14 Rosell R, Carcereny E, Gervais R *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; **13**: 239–46.

15 Yang JC, Wu YL, Schuler M *et al.* Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-lung 3 and LUX-lung 6): Analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015; **16**: 141–51.

16 Ou SH, Ahn JS, De Petris L *et al.* Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: A phase II global study. *J Clin Oncol* 2016; **34**: 661–8.

17 Shaw AT, Gandhi L, Gadgeel S *et al.* Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: A single-group, multicentre, phase 2 trial. *Lancet Oncol* 2016; **17**: 234–42.

18 Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015; **33**: 1974–82.

19 Melosky B, Chu Q, Juergens R, Leighl N, McLeod D, Hirsh V. Pointed progress in second-line advanced non-small-cell lung cancer: The rapidly evolving field of checkpoint inhibition. *J Clin Oncol* 2016; **34**: 1676–88.

20 Nakajima T, Yasufuku K, Suzuki M *et al.* Assessment of epidermal growth factor receptor mutation by endobronchial ultrasound-guided transbronchial needle aspiration. *Chest* 2007; **132**: 597–602.

21 Sakairi Y, Nakajima T, Yasufuku K *et al.* EML4-ALK fusion gene assessment using metastatic lymph node samples obtained by endobronchial ultrasound-guided transbronchial needle aspiration. *Clin Cancer Res* 2010; **16**: 4938–45.

22 Jurado J, Saqi A, Maxfield R *et al.* The efficacy of EBUS-guided transbronchial needle aspiration for molecular testing in lung adenocarcinoma. *Ann Thorac Surg* 2013; **96**: 1196–202.

23 Reynolds JP, Tubbs RR, Minca EC *et al.* EGFR mutational genotyping of liquid based cytology samples obtained via fine needle aspiration (FNA) at endobronchial ultrasound of non-small cell lung cancer (NSCLC). *Lung Cancer* 2014; **86**: 158–63.

24 Tanaka H, Tone K, Hayashi A *et al.* Clinical application of immunocytochemical detection of ALK rearrangement on cytology slides for detection or screening of lung adenocarcinoma. *Lung Cancer* 2013; **80**: 289–92.

25 Wilkerson MD, Cabanski CR, Sun W *et al.* Integrated RNA and DNA sequencing improves mutation detection in low purity tumors. *Nucleic Acids Res* 2014; **42**: e107.

26 Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the world Association of Sarcoidosis and other granulomatous disorders (WASOG) adopted by the ATS Board of directors and by the ERS executive committee, February 1999. *Am J Respir Crit Care Med* 1999; **160**: 736–55.