First Evaluation of the New Thin Convex Probe Endobronchial Ultrasound Scope: A Human Ex Vivo Lung Study

Priya Patel, MD, Hironobu Wada, MD, PhD, Hsin-Pei Hu, BSc, Kentaro Hirohashi, MD, PhD, Tatsuya Kato, MD, PhD, Hideki Ujiie, MD, PhD, Jin Young Ahn, MD, Daiyoon Lee, BSc, William Geddie, MD, and Kazuhiro Yasufuku, MD, PhD

Division of Thoracic Surgery and Department of Pathology, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; and Department of General Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

Background. **Endobronchial ultrasonography (EBUS)-guided transbronchial needle aspiration allows for sampling of mediastinal lymph nodes. The external diameter, rigidity, and angulation of the convex probe EBUS renders limited accessibility. This study compares the accessibility and transbronchial needle aspiration capability of the prototype thin convex probe EBUS against the convex probe EBUS in human ex vivo lungs rejected for transplant.**

Methods. **The prototype thin convex probe EBUS (BF-Y0055; Olympus, Tokyo, Japan) with a thinner tip (5.9 mm), greater upward angle (170 degrees), and decreased forward oblique direction of view (20 degrees) was compared with the current convex probe EBUS (6.9-mm tip, 120 degrees, and 35 degrees, respectively). Accessibility and transbronchial needle aspiration capability was assessed in ex vivo human lungs declined for lung transplant. The distance of maximum reach and sustainable endoscopic limit were measured. Transbronchial needle aspiration capability was assessed using the prototype 25G aspiration needle in segmental lymph nodes.**

Results. **In all evaluated lungs (n = 5), the thin convex probe EBUS demonstrated greater reach and a higher success rate, averaging 22.1 mm greater maximum reach and 10.3 mm further endoscopic visibility range than convex probe EBUS, and could assess selectively almost all segmental bronchi (98% right, 91% left), demonstrating nearly twice the accessibility as the convex probe EBUS (48% right, 47% left). The prototype successfully enabled cytologic assessment of subsegmental lymph nodes with adequate quality using the dedicated 25G aspiration needle.**

Conclusions. **Thin convex probe EBUS has greater accessibility to peripheral airways in human lungs and is capable of sampling segmental lymph nodes using the aspiration needle. That will allow for more precise assessment of N1 nodes and, possibly, intrapulmonary lesions normally inaccessible to the conventional convex probe EBUS.**

(Ann Thorac Surg 2017;103:1158–64)

Endobronchial ultrasonography (EBUS) with transbronchial needle aspiration (TBNA) is often recommended as a first line diagnostic modality for lymph nodal staging in lung cancer patients and its application in practice has significantly increased in the last decade [1, 2]. According to a recent survey in 2013 about the availability of EBUS in training programs for pulmonary and critical care in the United States, 98% were found to have EBUS-TBNA equipment available, thus illustrating its increasing prevalence and widespread availability [3].

The currently available convex probe (CP) EBUS introduced in 2002 with the ability to image airway structures parallel to the insertion direction of the bronchoscope has wide-ranging functions, including nodal staging for lung cancer and pathologic diagnosis of lung lesions located adjacent to central airways [4, 5]. EBUS-TBNA allows for sampling of visible lymph nodes (mediastinal and hilar) in real-time for histologic and cytologic analysis with a sensitivity of 89% and a specificity of 100%, as stated in the third edition of the American College of Chest Physicians lung cancer guidelines from 2013 [6]. This recent iteration of the American College of Chest Physician guidelines also suggests EBUS-TBNA is preferable over surgical staging, such as mediastinoscopy, as a best first test in patients with intermediate suspicion of N2 and N3 lymph node involvement as well as N1 node enlargement [6]. In addition, pulmonary lesions adjacent to the central airway are assessable by EBUS-TBNA with 94.1% sensitivity, whereas standard bronchoscopy demonstrates lower diagnostic yields [7].

Despite remarkable advancements in bronchoscopy, the current CP-EBUS has limited accessibility to more distal

Accepted for publication Sept 7, 2016.

Presented at the Annual Meeting of CHEST, Montreal, QC, Canada, Oct 25–28, 2015.

Address correspondence to Dr Yasufuku, Toronto General Hospital, 200 Elizabeth St, 9N-957, Toronto, ON M5G2C4, Canada; email: kazuhiro.yasufuku@uhn.ca.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.09.023

nodal stations [8]. More specifically, it is unable to assess certain N1 lymph nodes distal to interlobar lymph nodes, such as the segmental and subsegmental lymph nodes owing to its external diameter of 6.9 mm, a longer rigid portion, the 35-degree oblique viewing field, and limited flexion at 120 degrees. To overcome this limitation, a new prototype—thin CP-EBUS (TCP-EBUS [BF-Y0055; Olympus, Tokyo, Japan)]—featuring a thinner diameter (5.9 mm), a shorter rigid portion, and a higher degree of flexion (170 degrees), was recently tested by our team using porcine lungs [9]. Our results demonstrated that the prototype TCP-EBUS scope visualized 1 to 3 distal bifurcations further, reached 16 mm farther than the current CP-EBUS, and obtained adequate lymph node samples from segmental lymph nodes using a dedicated 25G needle. Despite these constructive results, the exact range of the TCP-EBUS in human lungs cannot be concluded from that study owing to the difference in size and divergence of the bronchial tree between humans and pigs [9].

The objective of this study is to assess the accessibility, ultrasound image quality, and TBNA capability of the prototype TCP-EBUS in ex vivo human lungs in comparison with the currently used CP-EBUS. Because the TCP-EBUS is able to gain more accessibility to certain areas, we expect that it will contribute to improving the diagnostic yield and accuracy of N1 nodal staging for lung cancer and more distal lesions in the settings of both malignant and benign thoracic diseases.

Material and Methods

Thin Convex Probe Endobronchial Ultrasonography

All experiments and data analysis was conducted at University Health Network. The prototype TCP-EBUS bronchoscope was used in this study for comparison (Fig 1) with the current CP-EBUS bronchoscope (BF-UC180F; Olympus). Many mechanical differences exist between the CP-EBUS and TCP-EBUS. The direction of view of the TCP-EBUS has improved from 35 to 20 degrees, which enhances the endoscopic visibility and makes the manipulation of the scope less difficult. The tip diameter of the TCP-EBUS is 5.9 mm, which is 1 mm smaller than the 6.9-mm tip of the CP-EBUS. The length of the rigid portion is shorter by approximately 8 mm. The upward angle has increased from 120 to 170 degrees whereas the downward angle is slightly compromised. The convex transducer on the TCP-EBUS scans parallel to the direction of the inserted bronchoscope like the probe on the CP-EBUS. The scanning range of ultrasound images is the same as the CP-EBUS; however, the TCP-EBUS does not use a balloon. The obtained images are processed by an ultrasound scanner (EU-Y0009; Olympus) and are transmitted along with the endoscopic view on the dual monitor. A dedicated 25G needle (Olympus) was used for EBUS-TBNA.

Ex Vivo Human Lungs

This study was approved by University Health Network, Research Ethics Board, Toronto, Ontario (REB#06-0283).

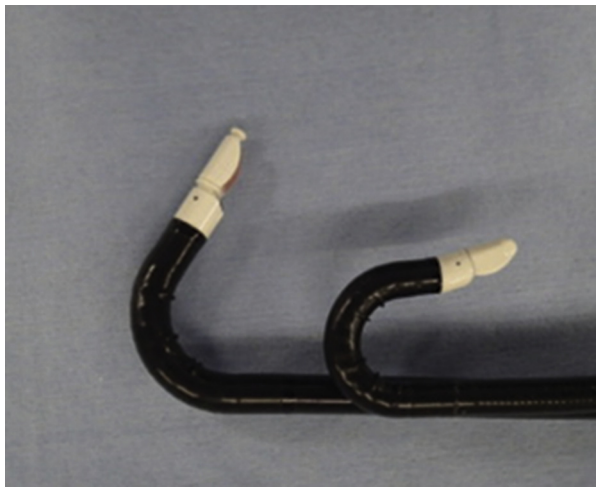

Fig 1. Thin convex probe endobronchial ultrasonography (BF-Y0055; Olympus Medical Systems, Tokyo, Japan), with a thinner tip (5.9 mm), greater upward angle (170 degrees), decreased forward oblique direction of view (20 degrees), seen on the right, compared with current convex probe endobronchial ultrasonography (6.9 mm tip, 120 202 degrees, and 35 degrees respectively), seen on the left.

Retrieved human lungs from five different donors determined to be unsuitable for lung transplantation on the basis of standard clinical criteria were used in this experiment. In all cases, research consent provided by the donor or the donor's proxy was obtained. Lungs without confluent bifurcation at the carina were excluded owing to foreseen instability during the procedure. Lungs were transferred and kept on ice before experimentation. To mimic an in vivo bronchoscopic examination, the lungs were placed in the supine position on the surgical table with the trachea fixed to the table. An endotracheal tube with a diameter of 8.0 mm was inserted into the trachea to allow for mechanical ventilation. Tidal volume was set at 8 mL to 10 mL per ideal body weight, and 5 cmH_2O of positive end-expiratory pressure was applied. A standard bronchoscope was then used for a baseline bronchoscopic examination, and suctioning secretion from the airways. The TCP-EBUS bronchoscope was initially inserted through the endotracheal tube for assessment of lobar, segmental, and subsegmental bronchi. That was again repeated with CP-EBUS for comparison with TCP-EBUS. All assessments were performed with fluoroscopic guidance.

Assessment of TCP-EBUS and CP-EBUS

All bronchoscopic procedures were performed by a board-certified thoracic surgeon (H.W.). Using five human lungs, two endpoints were evaluated: accessibility, and TBNA capability using the TCP-EBUS. The first endpoint, accessibility, was determined by maximum reach (insertion capability from the standard point) and endoscopic visibility (how far the bronchoscope can maintain a clear endoscopic image). Maximum reach was measured by establishing a standard point for each bronchus so that the length of scope inserted could be

Table 1. Characteristics of Subject Human Donor Lungs Rejected for Transplant

Case No.	Height (cm)	Weight (kg)	Age (years)	Sex	Ischemic Time (hours)	Reason for Rejection
1	165	85	69	Male	27	Bilateral lower lobe consolidation
2	197	110	39	Male	97	Right lower lobe consolidation
3	175	84	27	Male	134	Pneumonia/aspiration
4	160	66	56	Female	82	Pneumonia/aspiration
5	198	78	52	Male	66	Right lower lobe consolidation

calculated. The standard point for the examination of each segmental bronchus was a consistent anatomic point for all donor lungs. For the right lung, the right second carina was set as a standard point for right upper lobe segmental bronchi (B1 to B3), the bifurcation between the middle and lower lobe bronchus for the right middle lobe segmental bronchi (B4 and B5), and the bifurcation between B6 and basal bronchus for the right lower lobe segmental bronchi (B6 to B10). For the left side, both upper and lower lobe segmental bronchi shared the same standard point, the left second carina. Fluoroscopy was used to confirm the location of the scope beyond the endoscopic limit. Endoscopic visibility range was also measured with the same method and standard points as described above. Successful assessed rates of lobar and segmental bronchi were compared between the TCP and CP-EBUS. For a simple comparison, the upper and lower division bronchi in the left upper lobe were considered as lobar bronchi for the calculation.

The second endpoint, TBNA capability, was evaluated by sampling N1 lymph nodes using the dedicated 25G aspiration needle. The EBUS-TBNA method used was the same as the current standard method using the CP-EBUS. The aspirates were air blown onto a glass slide and smeared for cytology examination using Diff-Quik (Siemens B4132-1A, Los Angeles, CA) staining. Adequacy of sampling was defined by five or more low-power fields (×100) with 100 or more lymphocytes in each smear.

Statistical Analysis

Owing to the small number of lung subjects, all statistics are reported as mean with standard deviation. Student's paired *t* test was used to report statistical significance between the numbers of airways successfully assessed by TCP and CP-EBUS. A *p* value less than 0.05 was considered statistically significant.

Table 2. Average Difference of Endoscopic Limit and Maximum Reach Between Thin Convex Probe and Convex Probe Endobronchial Ultrasonography

Lobe	Endoscopic Limit (mm)	Maximum Reach (mm)
Right upper	10.6	22.6
Right middle	14.8	21.2
Right lower	8.2	24.3
Left upper	10.5	21.0
Left lower	7.4	21.6
Mean ± SD	10.3 ± 2.9	22.1 ± 1.4

Results

Declined Human Lungs

Characteristics of the human lungs declined for lung transplantation are described in Table 1. Reason for rejection included lung consolidation or pneumonia/aspiration. All lungs were ventilated without difficulty throughout the experiment. Donor 3 provided the right lung only, with intact confluence of the carina and stapled left main stem bronchus.

Accessibility and Operability Assessment

In all evaluated lungs (n = 5), the TCP-EBUS demonstrated a greater reach and a higher success rate in accessing airways compared with the current CP-EBUS. Our results demonstrated that the TCP-EBUS has a mean endoscopic visibility range 10 mm further, and a mean maximum reach 22 mm greater than the current CP-EBUS (Table 2). In all 5 cases, TCP-EBUS was able to assess lobar bronchi with 100% success bilaterally, whereas the CP-EBUS had a 93% success rate on the right (n = 5) and an 83% success rate on the left (n = 4). The bronchi not accessible by CP-EBUS were the right upper (1 of 5 cases) and left upper division segment (2 of 4 cases), respectively (Table 3). The TCP-EBUS could selectively assess nearly all segmental bronchi (98% in right and 91% in left) demonstrating nearly twice the accessibility to segmental airways than the CP-EBUS (48% in right, 47% in left). The segmental bronchi not assessable by TCP-EBUS were B7 (1 of 5 cases), left B1+2 (2 of 4 cases), and left B4 (1 of 4 cases). Evaluation of the upper lobes was most significant when using the TCP-EBUS; most specifically, B1 on the right and B1+2 on the left. The CP-EBUS was never able to be inserted into these segments whereas TCP-EBUS was successful in 5 of 5 on the right and 2 of 4 cases on the left, respectively. Right middle lobe bronchi (B4 and B5) were accessed by TCP-EBUS in 5 of 5 cases, but with CP-EBUS, it was 0 of 5 for B4 and 1 of 5 for B5. The left upper lobe could not be assessed reliably by CP-EBUS; left B3 could only be accessed in 1 of 4 cases and never for left B1+2. However, TCP-EBUS was successful in assessing the left B1+2 segment in 2 of 4 cases. Figure 2 illustrates an example of the ability of the TCP-EBUS to access upper lobe airways in comparison with CP-EBUS. Assessment of the lower segmental airways was most significant with regard to right B10 only. When comparing overall segmental airway assessability, TCP-EBUS was found to be statistically significantly better than CP-EBUS ($p = 0.00056$ on

Table 3. Airway Assessment Capability Comparison Between Thin Convex Probe and Convex Probe Endobronchial Ultrasonography: Segmental Bronchi

Right, n = 5 Segmental Bronchus	Number Assessed		Left, n = 4 Segmental Bronchus	Number Assessed	
	TCP-EBUS	CP-EBUS		TCP-EBUS	CP-EBUS
Apical (B^1)	5	0	Apical-posterior (B^{1+2})	2	0
Posterior (B^2)	5	4	Anterior (B^3)	4	1
Anterior (B^3)	5	3	Superior (B^4)	3	0
Lateral (B^4)	5	0	Inferior (B^5)	4	1
Medial (B^5)	5	1	Superior (B^6)	4	2
Superior (B^6)	5	3	Anteromedial basal (B^8)	4	4
Medial basal (B^7)	4	3	Lateral basal (B^9)	4	3
Anterior basal (B^8)	5	4	Posterior basal (B^{10})	4	4
Lateral basal (B^9)	5	4			
Posterior basal (B^{10})	5	2			
Mean ± SD	4.9 ± 0.32	2.4 ± 1.58	Mean ± SD	3.62 ± 0.74	1.87 ± 1.64
p Value	<0.05		*p* Value	<0.05	

CP = convex probe; EBUS = endobronchial ultrasonography; TCP = thin convex probe.

the right, $p = 0.0079$ on the left); however, no significant difference was found when comparing lobar bronchus assessability (Table 4).

TBNA Capability Assessment

The TCP-EBUS was evaluated for visualization in 3 cases, at a total of seven peripheral N1 lymph nodes by having the ultrasound probe make direct contact with the bronchial walls without the aid of a balloon. The peripheral nodes sampled were stations 12 and 13 (lobar bronchial and segmental nodes) with a 25G aspiration needle. Of seven nodes assessed, five were found to be adequate quality, demonstrating lymphocytes on cytologic examination (Fig 3). The other two punctures failed, resulting in

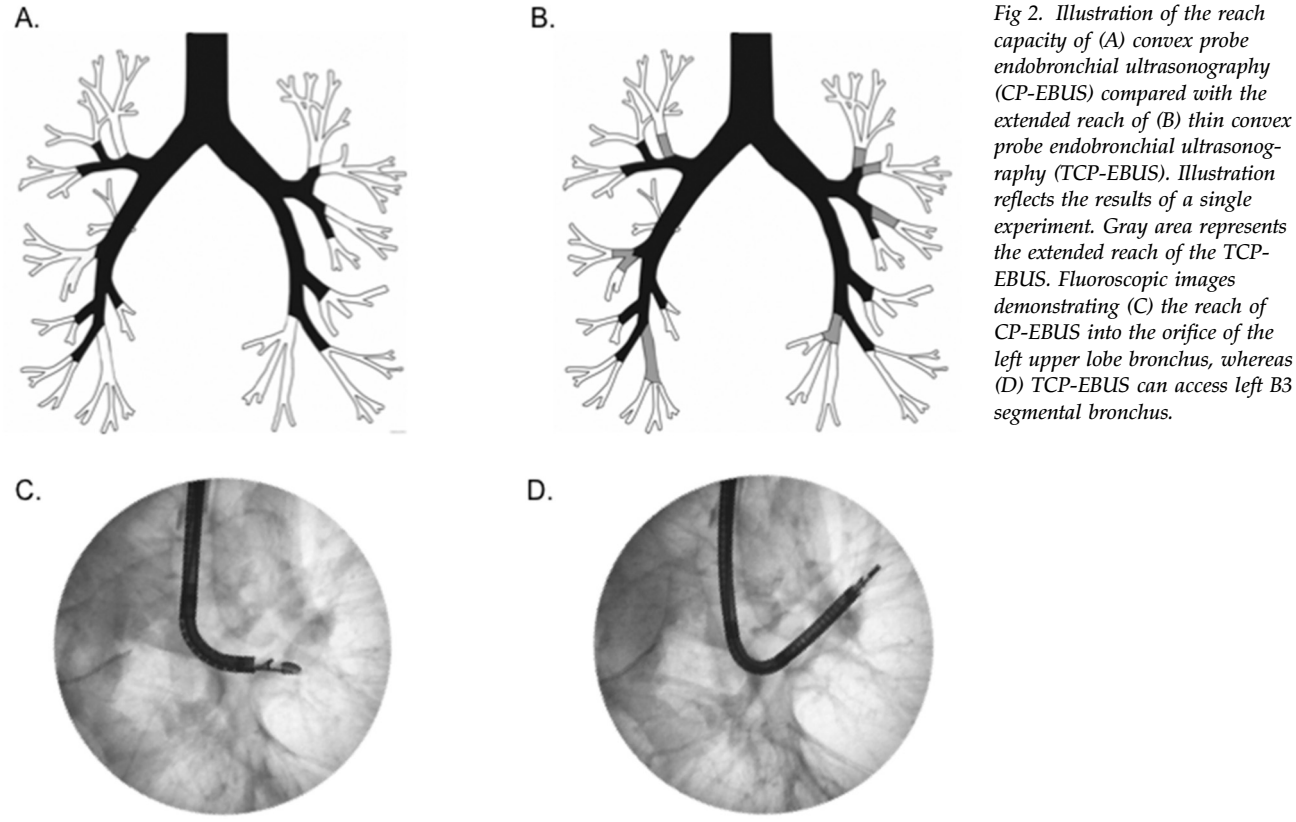

Fig 2. Illustration of the reach capacity of (A) convex probe endobronchial ultrasonography (CP-EBUS) compared with the extended reach of (B) thin convex probe endobronchial ultrasonography (TCP-EBUS). Illustration reflects the results of a single experiment. Gray area represents the extended reach of the TCP-EBUS. Fluoroscopic images demonstrating (C) the reach of CP-EBUS into the orifice of the left upper lobe bronchus, whereas (D) TCP-EBUS can access left B3 segmental bronchus.

Table 4. Airway Assessment Capability Comparison Between Thin Convex Probe and Convex Probe Endobronchial Ultrasonography: Lobar Bronchi

Right, n = 5 Lobar Bronchus	Number Assessed		Left n = 4	Number Assessed	
	TCP-EBUS	CP-EBUS	Lobar Bronchus	TCP-EBUS	CP-EBUS
Right upper	5	4	Left upper	4	1
Right middle	5	5	Left lower	4	4
Right lower	5	5	…		
Mean ± SD	5.0 ± 0	4.76 ± 0.58	Mean ± SD	4.0 ± 0	2.5 ± 2.12
p Value	0.19		*p* Value	0.21	

CP = convex probe; EBUS = endobronchial ultrasonography; TCP = thin convex probe.

insufficient sampling likely due to instability of the lung from case 3, which was the right lung alone.

Comment

The new TCP-EBUS proved to have a significantly improved accessibility to distal airways compared with the CP-EBUS—as the TCP-EBUS demonstrated by the 100% success rate in accessing all lobar bronchi in all 5 cases. Regarding the segmental bronchi, the TCP-EBUS was easily inserted into all 10 segments on the right and all 8 segments on the left selectively (Fig 4, Table 3). Conversely, CP-EBUS showed less than 50% of accessibility in segmental bronchi, significantly lower than that of TCP-EBUS. These findings can be attributed to improvements integrated into the TCP-EBUS. They include a smaller probe size, shorter rigid portion of the tip, greater upward angulation range, and decreased angle of direction of the endoscopic view. Similarly demonstrated by our group with the porcine model [9], these improvements when combined allowed for farther access into the airways with sustained endoscopic view. These

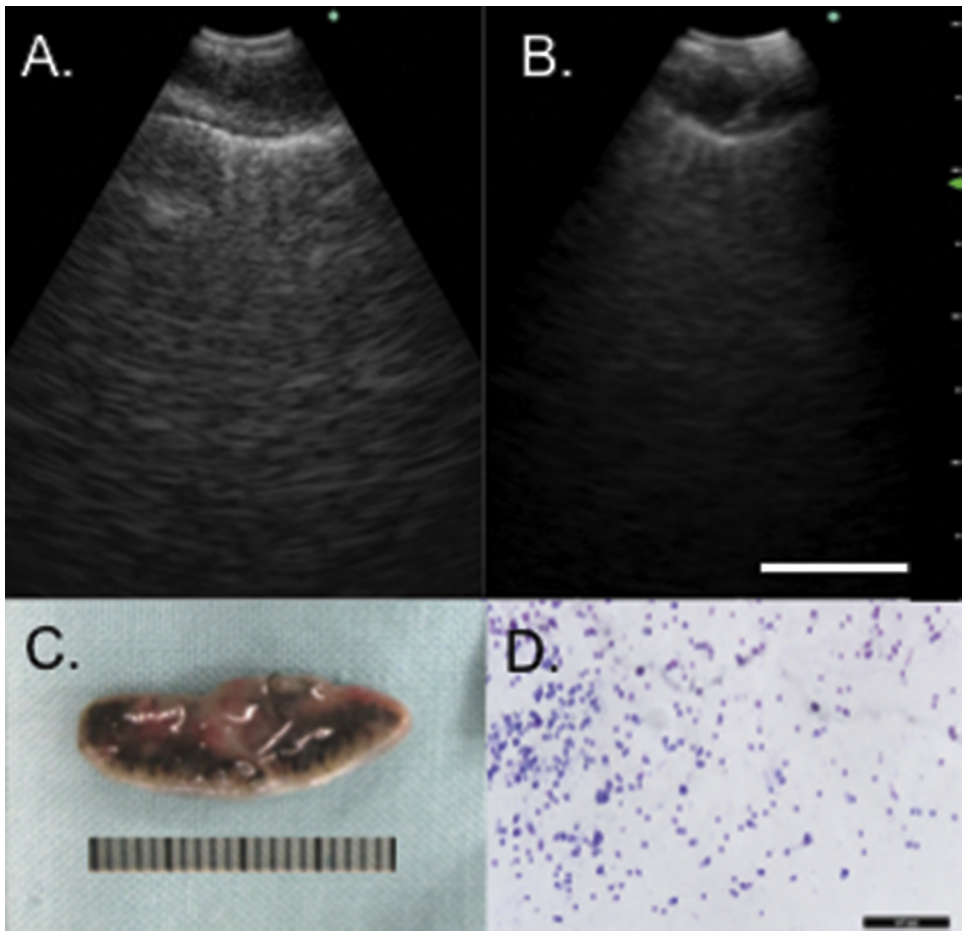

Fig 3. Thin convex probe endobronchial ultrasonography presents adequate lymphoid sampling from a segmental lymph node adjacent to the anterior basal bronchus. (A) Endobronchial ultrasonography visualized the segmental lymph node. (B) A 25G needle was successfully inserted into the lymph node. (C) Gross appearance of the lymph node. (D) Diff-Quik staining demonstrated adequate lymphoid sampling. Scale bars are (B) 1 cm and (D) 200 μm.

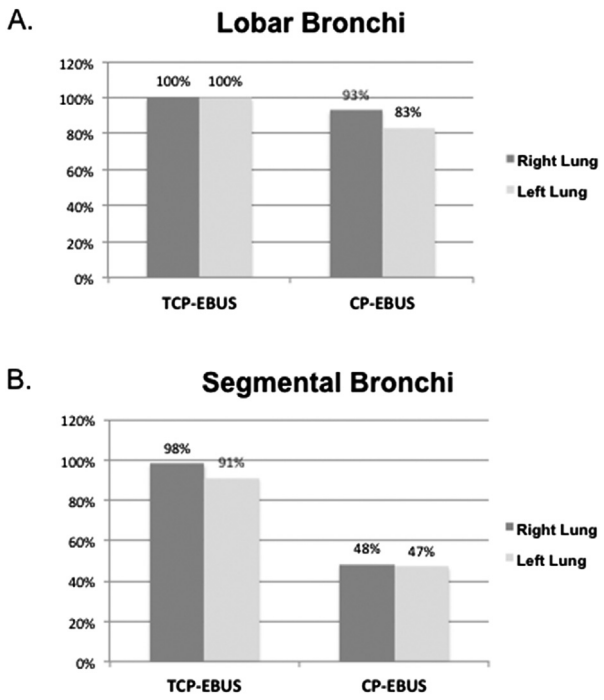

Fig 4. Comparison between thin convex probe endobronchial ultrasonography (TCP-EBUS) and convex probe endobronchial ultrasonography (CP-EBUS) airway assessment. (A) Percent of assessable lobar bronchi. (B) Percent of assessable segmental bronchi. Dark gray bars indicate right lung; light gray bars indicate left lung.

improvements contributed to the TCP-EBUS overcoming the limitations encountered by the CP-EBUS, such as accessing the bilateral upper lobe segmental airways that branch at steeper angles. Of note, accessibility of left B1+2 is a significant improvement given this segment is never assessable with CP-EBUS. It is also plausible that our results may have been negatively affected by factors such as lower lobe edema, consolidation, and pneumonia (reasons for transplant rejection) that caused the airways to be more constricted, preventing access by the larger diameter CP-EBUS scope (Table 1).

The possible limitations encountered when attempting to sample nodes included difficulty with identification of N1 lymph nodes from lack of chronic or malignant pathology, which would normally have caused enlargement or calcification. Also, given there is no blood flow in the ex vivo model, the Doppler function could not be employed to distinguish blood vessels from lymph nodes. Another problem encountered was stability of the specimen given the lung fixation point (fastening the trachea to the table). That rendered the lung somewhat mobile when counterbalance was needed to stabilize the needle for penetration, or for torqueing the scope against the bronchial wall to enable entry into an airway at a steep angle. At these points during the experiment, it would have been useful to have some counterstability from the specimen; however, attempting to affix the parenchyma would have resulted in damage to the tissue, causing air leaks. Nonetheless, the TCP-EBUS demonstrated a far enough reach to be able to sample N1 nodes as far as station 13. In the largest European EBUS trial that reports the results of the technique in 502 patients, the farthest reachable stations were 11R and 11L [10]. Therefore, TCP-EBUS could be a useful tool for systematic evaluation of N1 lymph nodes.

As demonstrated by our results in both the human and porcine models, we predict the TCP-EBUS will permit diagnosis of more distal intrapulmonary lesions. Already it has been shown by Nakajima and colleagues that intrapulmonary lesions located adjacent to the central airway not assessable by conventional bronchoscopy can be easily diagnosed by EBUS-TBNA with 94.1% sensitivity, given it is within the reach of the instrument [7]. Other attempts to diagnose the more peripheral regions have been made using a thin 3.4-mm bronchoscope and radial probe; however, this is a serious limitation because it is not a real-time procedure [11]. TCP-EBUS may be able to expand the diagnostic area in peripheral lung.

The importance of accurately staging N1 nodes in early stage non-small cell lung cancer is especially pressing in this rapidly developing era of minimally invasive surgery. Stage N1 non-small cell lung cancer disease represents a unique group of patients who have various 5-year survival rates between 27% and 67% [12]. Defining the anatomic extent of disease in a nodal station is a requirement for accurately determining nodal status [12]. In a retrospective analysis of 540 patients with N1 non-small cell lung cancer who had at least a lobectomy and mediastinal lymphadenectomy, patients with multiple zone N1 involvement had a poorer 5-year survival rate (39%) than those with single zone N1 involvement (51%, $p = 0.01$) [12]. This discrepancy in 5-year survival among these patients illustrates the possible impact TCP-EBUS could make on the management of these patients.

In conclusion, TCP-EBUS has enhanced accessibility to the peripheral airways compared with CP-EBUS, and it is capable of sampling N1 lymph nodes using the dedicated 25G needle. We believe that the utility of these improvements will allow for better assessment for nodal staging in the setting of lung cancer as well as distal intrapulmonary lesions, thereby enabling more accurate treatment for patients in the future.

The authors acknowledge Mrs Judy McConnell and Mrs Alexandria Grindlay for completing the preparation for this study. This work was supported by Olympus Corporation, who provided the prototype for the thin convex endobronchial ultrasonography probe. Hironobu Wada received a research scholarship from the Honjo International Scholarship Foundation.

References

1. 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.

2. Kingsey M, Arenberg D. Endobronchial ultrasound-guided transbronchial needle aspiration for non-small cell lung cancer staging. Am J Resp Crit Care Med 2014;189:640–9.
3. Tanner NT, Pastis NJ, Silvestri GA. Training for linear endobronchial ultrasound among US pulmonary/critical care fellowships: a survey of fellowship directors. Chest 2013;143:423–8.
4. Nakajima T, Yasufuku K, Yoshino I. Current status and perspective of EBUS-TBNA. Gen Thorac Cardiovasc Surg 2013;61:390–6.
5. Dooms C, Muylle I, Yserbyt J, et al. Endobronchial ultrasound in the management of non small cell lung cancer. Eur Respirol Rev 2013;22:169–77.
6. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: ACCP evidence-based clinical practice guidelines. Chest 2013;143(Suppl): e211–50.
7. Nakajima T, Yasufuku K, Fujiwara T, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of intrapulmonary lesions. J Thorac Oncol 2008;3: 985–8.
8. Gilbert C, Akulian J, Ortiz R, et al. Novel bronchoscopic strategies for the diagnosis of peripheral lung lesions: present techniques and future directions. Respirology 2014;19: 636–44.
9. Wada H, Hirohashi K, Nakajima T, et al. Assessment of the new thin convex probe endobronchial ultrasound bronchoscope and the dedicated aspiration needle: a preliminary study in the porcine lung. J Bronchol Interv Pulmonol 2015;22:20–7.
10. Herth FJF, Eberhardt R. Actual role of endobronchial ultrasound. Eur Radiol 2007;17:1806–12.
11. Oki M, Saka H, Kitagawa C, et al. Endobronchial ultrasound-guided transbronchial biopsy using novel thin bronchoscope for diagnosis of peripheral pulmonary lesions. J Thorac Oncol 2009;4:1274–7.
12. Demir A, Turna A, Kocaturk C, et al. Prognostic significant of surgical pathologic N1 lymph node involvement in non-small cell lung cancer. Ann Thorac Surg 2009;87:1013–22.