CHEST

Use of an Ultrathin vs Thin Bronchoscope for Peripheral Pulmonary Lesions

A Randomized Trial

Masahide Oki, MD; Hideo Saka, MD; Fumihiro Asano, MD; Chiyoe Kitagawa, MD; Yoshihito Kogure, MD; Akifumi Tsuzuku, MD; and Masahiko Ando, MD

BACKGROUND: When evaluating peripheral pulmonary lesions, a 3.0-mm ultrathin bronchoscope (UTB) with a 1.7-mm working channel is advantageous regarding good access to the peripheral airway, whereas a 4.0-mm thin bronchoscope provides a larger 2.0-mm working channel, which allows the use of various instruments including a guide sheath (GS), larger forceps, and an aspiration needle. This study compared multimodal bronchoscopy using a UTB and a thin bronchoscope with multiple sampling methods for the diagnosis of peripheral pulmonary lesions.

METHODS: Patients with peripheral pulmonary lesions ≤ 30 mm in diameter were recruited and randomized to undergo endobronchial ultrasonography, virtual bronchoscopy, and fluoroscopy-guided bronchoscopy using a 3.0-mm UTB (UTB group) or a 4.0-mm thin bronchoscope (thin bronchoscope group). In the thin bronchoscope group, the use of small forceps with a GS or standard forceps without the GS was permitted. In addition, needle aspiration was performed for lesions into which an ultrasound probe could not be inserted.

RESULTS: A total of 360 patients were enrolled, and 356 were included in the analyses (median largest lesional diameter, 19 mm). The overall diagnostic yield was significantly higher in the UTB group than in the thin bronchoscope group (70.1% vs 58.7%, respectively; $P = .027$). The procedure duration was significantly shorter in the UTB group (median, 24.8 vs 26.8 min, respectively; $P = .008$). The complication rates were 2.8% and 4.5%, respectively ($P = .574$).

CONCLUSIONS: Multimodal bronchoscopy using a UTB afforded a higher diagnostic yield than that using a thin bronchoscope in the diagnosis of small peripheral pulmonary lesions.

TRIAL REGISTRY: UMIN Clinical Trials Registry; No.: UMIN000010133; URL: https://www.umin.ac.jp/ctr/

CHEST 2019; 156(5):954-964

KEY WORDS: bronchoscopy; endobronchial ultrasound; lung cancer; navigation; solitary pulmonary nodule

ABBREVIATIONS: EBUS = endobronchial ultrasound; GS = guide sheath; rEBUS = radial probe endobronchial ultrasound; TBNA = transbronchial needle aspiration; UTB = ultrathin bronchoscope; VBN = virtual bronchoscopic navigation

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Oki, Saka, Kitagawa, and Kogure), National Hospital Organization Nagoya Medical Center, Nagoya; the Department of Pulmonary Medicine (Drs Asano and Tsuzuku), Gifu Prefectural General Medical Center, Gifu; and the Center for Advanced Medicine and Clinical Research (Dr Ando), Nagoya University Hospital, Nagoya, Japan.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Masahide Oki, MD, Department of Respiratory Medicine, National Hospital Organization Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan; e-mail: masahideo@aol.com

DOI: https://doi.org/10.1016/j.chest.2019.06.038

Modifications of bronchoscopic techniques, such as the use of radial probe endobronchial ultrasound (rEBUS),[1-4] navigation devices,[5-7] and ultrathin bronchoscopes (UTBs) (bronchoscopes with an outer diameter ≤ 3.5 mm),[8-13] have markedly improved the diagnostic yield of bronchoscopy for peripheral pulmonary lesions. Particularly, multimodal bronchoscopy combining these ancillary techniques provides higher diagnostic yield than bronchoscopy using each ancillary technique alone.[13-16]

In a previous randomized study,[13] we showed that the diagnostic performance of bronchoscopy using a 3.0-mm UTB with rEBUS was superior to that using a 4.0-mm thin bronchoscope with rEBUS and a guide sheath (GS), which is effective for diagnosing peripheral pulmonary lesions.[15-23] In that study, we used biopsy instruments of the same size (1.5-mm biopsy forceps) during both procedures. However, the 4.0-mm thin bronchoscope has a larger working channel (2.0 mm in diameter) than the 3.0-mm UTB (1.7-mm working channel). Therefore, if the GS is not used, the working channel of the thin bronchoscope allows the use of standard-sized biopsy forceps measuring 1.8 or 1.9 mm in diameter or performance of transbronchial needle aspiration (TBNA). In fact, adding TBNA to rEBUS-guided transbronchial biopsy reportedly provides additional diagnostic benefit,[24] and adding transbronchial biopsy using standard-sized forceps to rEBUS-GS provides higher diagnostic yield than rEBUS-GS alone.[25] Therefore, the diagnostic performance of bronchoscopy using a thin bronchoscope may have been underestimated in our previous study. In this study, we compared the diagnostic yield of bronchoscopy using a UTB with that using a thin bronchoscope and multiple sampling devices for the diagnosis of small peripheral pulmonary lesions.

Materials and Methods

Patients

We performed a randomized study comparing bronchoscopy using a UTB and a thin bronchoscope for the diagnosis of peripheral pulmonary lesions at National Hospital Organization Nagoya Medical Center and Gifu Prefectural General Medical Center. From February 2013 to August 2016, patients with localized peripheral pulmonary lesions ≤ 30 mm were recruited and randomly assigned to undergo rEBUS, virtual bronchoscopic navigation (VBN), and fluoroscopy-guided bronchoscopy using a UTB (UTB group) or using a thin bronchoscope (thin bronchoscope group). Randomization was stratified according to lesion size (≤ 20 or > 20 mm in the largest diameter on CT scans), lesion location from the hilum (peripheral one-third, intermediate one-third, or central one-third in the lung field on CT scan, as classified by Baaklini et al[26]), presence or absence of a bronchus sign, and operator experience (> 5 or ≤ 5 years after receiving their medical degree) and was performed electronically. The main inclusion criterion was having a peripheral pulmonary lesion ≤ 30 mm in diameter requiring diagnosis. The main exclusion criteria were central pulmonary lesions, diffuse pulmonary lesions, or pure ground-glass nodules on CT scans, or requiring bronchoscopic procedures other than those being used for this study. The study was approved by the institutional review board of each institution (identifier No. 2012-591, Nagoya Medical Center; identifier No. 173, Gifu Prefectural General Medical Center) and registered with the UMIN Clinical Trials Registry (identifier No. UMIN000010133). Written informed consent was obtained from all participants.

Procedures

Before bronchoscopy, a virtual bronchoscopic pathway indicating the bronchial route to the target lesion was made using the VBN system (Bf-NAVI or DirectPath; Cybernet Systems) from helical CT data with a 0.5-mm slice. All bronchoscopic procedures were performed after local anesthesia with lidocaine and conscious sedation using IV midazolam with or without fentanyl. As previously described,[13] a tracheal tube 5.0 mm in inner diameter was inserted transnasally into the trachea under bronchoscopic guidance in most cases.

UTB Method: A prototype 3.0-mm UTB (Y-0025 or Y-0058; Olympus) (Fig 1, marker A) with a 1.7-mm working channel was advanced toward the target lesion through the bronchus. During the approach, preprepared virtual bronchoscopic views from the trachea to the target lesion, created using the VBN system, were displayed and synchronized with the actual bronchoscopic images, to serve as a guide. Once the bronchoscope had reached the vicinity of the lesion and could not be advanced further, a 1.4-mm rEBUS probe (UM-S20–17S; Olympus) (Fig 1, marker C) was advanced toward the lesion through the working channel under C-arm fluoroscopic guidance. Once the target lesion was visualized by rEBUS, the endobronchial ultrasound (EBUS) probe was withdrawn and 1.5-mm biopsy forceps (FB-32D or FB-233D; Olympus) (Fig 1, marker E) were advanced through the same route to the target lesion. Then biopsies were performed under fluoroscopic guidance until 10 visible specimens were obtained. After forceps biopsies, washing was

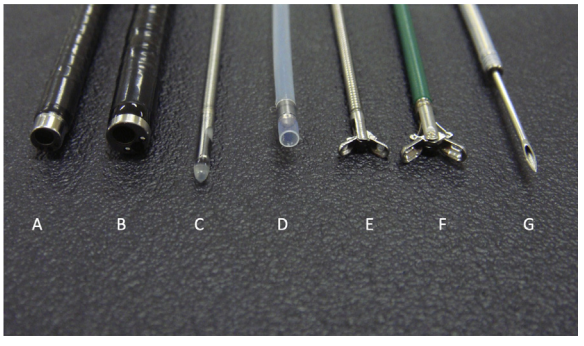

Figure 1 – *Bronchoscopes and sampling instruments: a 3.0-mm ultra-thin bronchoscope with a 1.7-mm working channel (marker A); a 4.0-mm thin bronchoscope with a 2.0-mm working channel (marker B); the 1.4-mm-diameter, radial, endobronchial ultrasound probe (marker C); the guide sheath (marker D); the 1.5-mm biopsy forceps (marker E); the 1.9-mm standard-sized biopsy forceps (marker F); and the 21-gauge needle (marker G).*

performed with 5 to 20 mL saline solution for cytologic and microbiological examination.

Thin Bronchoscope Method: A commercially available 4.0-mm thin bronchoscope (BF-P260F; Olympus) (Fig 1, marker B) with a 2.0-mm working channel was used. The basic technique was similar to the UTB method. In the thin bronchoscope group, the GS method using a 1.95-mm GS (SG-200C; Olympus) (Fig 1, marker D) and 1.5-mm biopsy forceps, and/or the non-GS method using 1.8 or 1.9-mm biopsy forceps (Radial Jaw 4; Boston Scientific; and FB-231D; Olympus) (Fig 1, marker F), was available; selection was left to the operator's discretion. When performing the GS method, using a curette (CC-6-DR-1; Olympus) as a guiding device for the GS was also permitted. Ten visible specimens were obtained when the small forceps were used. When standard forceps or both standard and small forceps were used, at least seven specimens were obtained. In addition, TBNA using a 21-gauge needle (NA-401D-1521; Olympus) (Fig 1, marker G) was performed when the EBUS probe could not be inserted within the lesion (ie, invisible or adjacent to cases, as classified by Kurimoto et al[3]). TBNA was performed for at least two passes under fluoroscopic guidance. Rapid on-site cytologic evaluation was not performed. Bronchial washing was performed after the procedures.

Measurement During the Procedure: In each group, the bronchus level (ie, segmental bronchi, second generation; subsegmental bronchi, third generation; subsubsegmental bronchi, fourth generation bronchi; bronchial generation was calculated by adding the number of further branchings) reached with the bronchoscope, the procedure duration from insertion of the bronchoscope into the trachea to removal from the trachea, and the locational relationship between the EBUS probe and target lesion (within, adjacent to, or invisible on the rEBUS image, as classified by Kurimoto et al[3]) were recorded.

Diagnosis

Each histologic and cytologic specimen was interpreted separately at each institution. Suspicious findings were considered nondiagnostic in this study. Inconclusive histologic findings, such as nonspecific fibrosis and inflammation, were considered nondiagnostic. The final diagnoses were established based on pathologic evidence, microbiological analyses, or clinical follow-up. Benign diagnoses, which could not be diagnosed pathologically or microbiologically, were confirmed by radiologic and clinical compatibility (eg, unchanged or decreased lesion size on CT scans) during the follow-up period for at least 1 year after bronchoscopy.

End Points

The primary end point was the overall diagnostic yield, whereas secondary end points were histologic diagnostic yield, diagnostic yield according to the nature of the lesion (benign or malignant), lesion size, lesion location, sampling procedures, frequency of complications, ultrasonic probe location on the rEBUS image, level of bronchus reached with bronchoscopes, and duration of the procedure.

Data Analyses

This study was designed to compare the diagnostic yields of the UTB and thin bronchoscope methods. If noninferiority was demonstrated, then its superiority was analyzed. Based on the expected diagnostic yield of 65% using the thin bronchoscope method and 70% using the UTB method, demonstration of noninferiority with a statistical power of 90% at a one-sided significance level of 0.05 would require 167 patients in each group. We arranged to enroll a total of 360 patients with 180 patients in each group to account for dropouts. Noninferiority of the UTB method was to be concluded if the lower bound of the 90% CI for the difference in diagnostic yields exceeded the predetermined noninferiority bound of −10%. The means and percentages are presented as appropriate. With the exception of the noninferiority analyses of the primary end point, categorical variables were analyzed using the Pearson χ^2 test or Fisher exact test. Continuous variables were analyzed using the Mann-Whitney U test. Logistic regression analyses were performed to analyze interactions between categories as predictors of higher diagnostic yield of either method compared with the other. Statistical analyses were performed using PASW Statistics 18 (SPSS Inc). In all of the analyses, $P < .05$ was taken to indicate statistical significance.

Results

Patients and Lesions

As shown in Figure 2, the 360 patients were assigned to either the UTB group or the thin bronchoscope group, and 177 patients in the UTB group and 179 patients in the thin bronchoscope group were ultimately analyzed. The median lesion size defined according to the largest diameter on CT scans was 19.0 mm (range, 7.4-30.0 mm). Baseline demographics and lesion characteristics were well balanced between the two groups (Table 1). Bronchoscopic findings and final diagnoses are shown in Table 2.

Procedures

The UTB could be advanced into more distal bronchi than the thin bronchoscope (median, fifth generation vs fourth generation bronchi, respectively; $P < .001$) (Table 3). In the thin bronchoscope group, forceps biopsies using small forceps through the GS (GS method), standard forceps without the GS (non-GS method), and a combination of both were performed in 43.6% (78 of 179), 38.5% (69 of 179), and 15.6% (28 of 179) of cases, respectively. Forceps biopsies were not performed for four lesions (2.2%), which could not be identified by rEBUS. Therefore, the GS method was performed in 106 patients and the non-GS method was performed in 97 patients, including 28 patients with both GS and non-GS methods. During the GS method, a guiding curette was used in 41 patients (38.7%). The GS method was frequently used to evaluate lesions in the upper lobe and peripheral one-third of the lung, and lesions abutting the pleura (Table 4). As shown in Table 3, the rEBUS probe could not be inserted into the lesion in 54 patients in the thin bronchoscope group. Therefore, the 54 patients had indications for additional TBNA according to our study protocol. TBNA with sampling was performed in 50 of these 54 patients. In

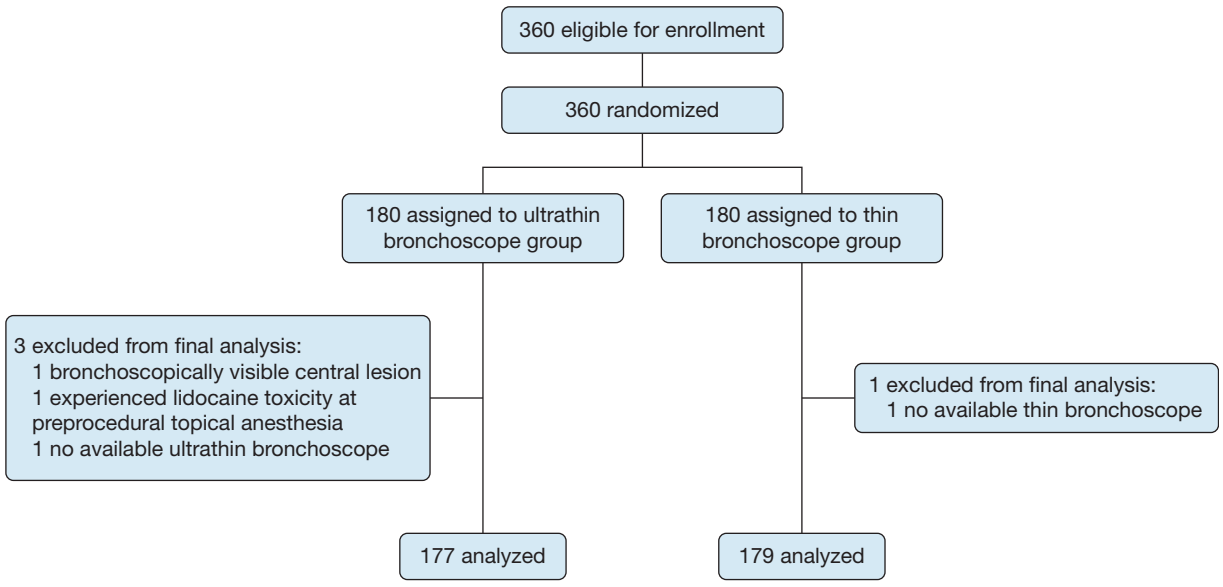

Figure 2 – *Flow of patients enrolled in the study.*

the remaining four patients, the operators attempted to perform TBNA, but sampling could not be performed for technical reasons in two patients, and the operators did not try to perform TBNA in the remaining two patients. Median procedure duration was significantly shorter in the UTB group than in the thin bronchoscope group (24.8 vs 26.8 min, respectively; $P = .008$).

Diagnostic Yields

As shown in Table 5, the diagnostic yields in the UTB group and thin bronchoscope group were 70.1% (124 of 177 patients; 95% CI, 62.7-76.7) and 58.7% (105 of 179 patients; 95% CI, 51.1-66.0), respectively. The difference in diagnostic yield was 11.4% (90% CI, 3.1-19.7). Because the lower limit of the CI was greater than the predetermined margin of −10%, noninferiority of the UTB method was confirmed. In terms of superiority, the overall diagnostic yield was significantly higher in the UTB group than in the thin bronchoscope group ($P = .027$ using the Fisher exact test). In each group, larger lesion size, malignant nature, and the presence of a bronchus sign were associated with a higher diagnostic yield. The diagnostic yields of the UTB method were significantly higher for lesions in the nonupper lobe location, lesions in the peripheral one-third of the lung, benign lesions, lesions > 20 mm, and lesions abutting the pleura compared with those of the thin bronchoscope method in univariate analyses, but these were not factors of higher diagnostic yield of the UTB method, as determined by analyzing the interaction using logistic regression analyses. In patients with nondiagnostic results of forceps biopsy, bronchial washing was diagnostic in six patients (malignancies in three patients, non-TB mycobacteriosis in two patients, and TB in one patient) in the UTB group and three patients (malignancy in one patient and non-TB mycobacteriosis in two patients) in the thin bronchoscope group. Therefore, 118 of 177 patients (66.7%; 95% CI, 59.2-73.6) in the UTB group were given a diagnosis with histologic specimens obtained by forceps biopsy compared with 102 of 179 patients (57.0%; 95% CI, 49.4-64.4) in the thin bronchoscope group ($P = .064$). In the thin bronchoscope group, specimens were sampled by TBNA in 50 patients. TBNA for cytologic analyses provided positive for malignancy results in three patients, suspicious for malignancy results in eight patients, and negative results in 39 patients. One additional diagnosis of non-TB mycobacteriosis was made based on washing fluid of the needle. No additional diagnostic gain was observed by adding TBNA to forceps biopsy and washings. Forceps biopsies using the GS method, non-GS method, and a combination of both methods provided diagnostic histologic specimens in 56.4% (44 of 78), 62.3% (43 of 69), and 53.6% (15 of 28) of cases, respectively. In patients undergoing forceps biopsies using both the GS and non-GS methods, histologic specimens containing diagnostic materials were provided only by the GS method in two patients and by the non-GS method in three patients.

Safety

In the UTB group, two cases of pneumothorax (one of which required chest tube insertion), two cases of

TABLE 1] Demographic and Lesion Characteristics of the Patients

Characteristic	UTB Group (n = 177)	Thin Bronchoscope Group (n = 179)	*P* Value
Sex			
Male	107 (60.5)	111 (62.0)	.763
Female	70 (39.5)	68 (38.0)	
Median age (range), y	71 (34-92)	72 (37-87)	.895
Tobacco-use history			
Never	59 (33.3)	55 (30.7)	
Previous	66 (37.3)	76 (42.5)	.609
Current	52 (29.4)	48 (26.8)	
Lesion size in the largest diameter on CT scan			
Median, mm (range)	18.9 (7.7-30.0)	19.1 (7.4-29.9)	.666
≤ 20 mm	102 (57.6)	101 (56.4)	.819
> 20 to ≤ 30 mm	75 (42.4)	78 (43.6)	
Lobar location			
Upper lobe	85 (48.0)	97 (54.2)	.244
Other	92 (52.0)	82 (45.8)	
Lesion location from the hilum			
Intermediate	40 (22.6)	37 (20.7)	.659
Peripheral	137 (77.4)	142 (79.3)	
Locational relationship with pleura			
Apart from the pleura	102 (57.6)	105 (58.7)	.844
Abutting on the pleura	75 (42.4)	74 (41.3)	
Bronchus sign			
Present	130 (73.4)	133 (74.3)	.854
Absent	47 (26.6)	46 (25.7)	
Appearance on CT scan			
Solid	148 (83.6)	153 (85.5)	.628
Part-solid nodule	29 (16.4)	26 (14.5)	
Final diagnosis			
Malignant	142 (80.2)	140 (78.2)	.754
Benign	32 (18.1)	37 (20.7)	
Unknown	3 (1.7)	2 (1.1)	
Examiner experience			
> 5 y after receiving medical license	166 (93.8)	171 (95.5)	.464
≤ 5 y after receiving medical license	11 (6.2)	8 (4.5)	

Data are presented as No. (%) or as otherwise noted. UTB = ultrathin bronchoscope.

pneumonia (with new pulmonary infiltrates as revealed by chest radiographs, accompanied by symptoms of respiratory infection and requiring antibiotic therapy), and one case of bleeding occurred. In the thin bronchoscope group, two cases of pneumothorax (neither required chest tube insertion), two cases of bleeding, one case of pneumonia, one case of vomiting, one case of nausea, and one case of myocardial infarction were observed. There were no statistically significant differences in the complication rate between the UTB and thin bronchoscope groups (5 of 177 [2.8%] vs 8 of 179 [4.5%], respectively; $P = .574$).

Discussion

The diagnostic yield of multimodal bronchoscopy using a UTB was significantly higher than that using a thin bronchoscope, even using TBNA, larger biopsy forceps, and the GS method during the thin

TABLE 2] Bronchoscopic Findings and Final Diagnosis

Bronchoscopic Findings	No. of Patients and Final Outcomes			
	UTB Group (n = 177)		Thin Bronchoscope Group (n = 179)	
	Total	Final Diagnoses and Outcomes	Total	Final Diagnoses and Outcomes
Diagnostic				
Malignant				
Lung cancer				
Adenocarcinoma	73	…	59	…
Squamous cell carcinoma	22	…	23	…
Non-small cell carcinoma	3	…	4	…
Poorly differentiated carcinoma	1	…	1	…
Carcinoid	1	…	0	…
Adenocarcinoma + pleomorphic carcinoma	0	…	1	…
Small cell carcinoma	2	…	4	…
Cytology positive for malignancy	3	…	1	…
Metastatic carcinoma				
Adenocarcinoma	5	4 colon, 1 rectum	5	1 colon, 1 rectum, 2 breast, 1 endometrium
Squamous cell carcinoma	1	1 larynx	0	…
Transitional cell carcinoma	0	…	1	1 bladder
Benign				
TB	3		0	…
Non-TB mycobacteriosis	4	…	3	…
Aspergillosis	1	…	0	…
Organizing pneumonia	1	…	1	…
Granuloma	4	…	1	…
Amyloidosis	0	…	1	…
Nondiagnostic				
	53	31 malignant	74	41 malignant
		30 pathologically proven malignancy		36 pathologically proven malignancy
		26 lung cancer		31 lung cancer
		4 metastatic carcinoma		3 metastatic carcinoma
		1 suspected malignant		2 malignant lymphoma
		19 benign		5 suspected malignant
		2 pathologically and/or biologically proven benign		31 benign
		17 suspected benign		5 pathologically and/or biologically proven benign
		3 no follow-up		26 suspected benign
				2 no follow-up

See Table 1 legend for expansion of abbreviation.

bronchoscope procedure. Our study demonstrated the high diagnostic performance of navigational endobronchial ultrasonographic bronchoscopy using a UTB.

TBNA has reportedly been a useful method for diagnosing peripheral pulmonary lesions,[1,27,28] but to our knowledge, there has been only one previous randomized study comparing rEBUS-guided

TABLE 3] Procedural Details

Variables	UTB Group (n = 177)	Thin Bronchoscope Group (n = 179)	*P* Value
Bronchus level reached with the bronchoscope			
Median (range), generation	5 (3-11)	4 (2-8)	< .001
Mean ± SD, generation	5.5 ± 1.4	4.4 ± 1.1	
Location of probe in relation to lesion confirmed by rEBUS			
Within the lesion	139 (78.5)	125 (70.6)	
Adjacent to the lesion	20 (11.3)	32 (17.9)	.142
Invisible with rEBUS	18 (10.2)	22 (12.3)	
Sampling procedures			
Forceps biopsy			
Small forceps biopsy[a]	176 (99.4)	78 (43.6)	
Standard forceps biopsy	…	69 (38.5)	
Both small[a] and standard forceps biopsy	…	28 (15.6)	
Not performed	1 (0.6)	4 (2.2)	
TBNA	…	52[b] (29.1)	
Washing	177 (100)	179 (100)	
Procedural duration, median (range), min	24.8 (11-86)	26.8 (10-90)	.008

Data are No. (%) unless otherwise stated. rEBUS = radial probe endobronchial ultrasound; TBNA = transbronchial needle aspiration. See Table 1 legend for expansion of other abbreviation.
[a]Performed through a guide sheath in the thin bronchoscope group.
[b]Includes two patients who were not sampled because of technical difficulty.

TABLE 4] Types of Biopsy Forceps Used in the Thin Bronchoscope Group

Variable	No.	Small Forceps	Standard Forceps	*P* Value
Total	179[a]	106[b] (59.2)	97[b] (54.2)	
Lesion size in the largest diameter on CT scan				
≤ 20 mm	101	65 (64.4)	50 (49.5)	.160
> 20 to ≤ 30 mm	78	41 (52.6)	47 (60.3)	
Lobar location				
Upper lobe	97	68 (70.1)	42 (43.3)	.003
Others	82	38 (46.3)	55 (67.1)	
Lesional location from the hilum				
Intermediate	37	13 (35.1)	28 (75.7)	.003
Peripheral	142	93 (65.5)	69 (48.6)	
Locational relationship with the pleura				
Distant from the pleura	105	55 (52.4)	66 (62.9)	.019
Abutting on the pleura	74	51 (68.9)	31 (41.9)	
Bronchus sign				
Present	133	74 (55.6)	78 (58.6)	.082
Absent	46	32 (69.6)	19 (41.3)	
Appearance on CT scan				
Solid	153	94 (61.4)	82 (53.6)	.385
Part-solid nodule	26	12 (46.2)	15 (57.7)	

Data are No. (%) unless otherwise stated.
[a]Includes four patients for whom forceps biopsy was not performed.
[b]Includes 28 patients biopsied using both small and standard forceps.

TABLE 5] Diagnostic Yield

Variables	UTB Group (n = 177)		Thin Bronchoscope Group (n = 179)		*P* Value	*P* Value for Interaction[a]
Total	124/177 (70.1)		105/179 (58.7)		.027	
Lesion size in the largest diameter on CT scan						
≤ 20 mm	64/102 (62.7)	*P* = .004	52/101 (51.5)	*P* = .027	.120	*P* = .664
> 20 to ≤ 30 mm	62/75 (82.7)		53/78 (67.9)		.041	
Lesion nature						
Malignant	111/142 (78.2)	*P* < .001	99/140 (70.7)	*P* < .001	.173	*P* = .172
Benign	13/32 (40.6)		6/37 (16.2)		.032	
Unknown	0/3 (0)		0/2 (0)		…	
Lobar location						
Upper lobe	56/85 (65.9)	*P* = .244	61/97 (62.9)	*P* = .212	.757	*P* = .089
Other	68/92 (73.9)		44/82 (53.7)		.007	
Lesion location from the hilum						
Intermediate	29/40 (72.5)	*P* = .701	26/37 (70.3)	*P* = .107	> .999	*P* = .163
Peripheral	95/137 (69.3)		79/142 (55.6)		.019	
Locational relationship with pleura						
Apart from the pleura	73/102 (71.6)	*P* = .608	67/105 (63.8)	*P* = .096	.368	*P* = .448
Abutting on the pleura	51/75 (68.0)		38/74 (51.4)		.046	
Bronchus sign						
Present	97/130 (74.6)	*P* = .028	87/133 (65.4)	*P* = .002	.109	*P* = .549
Absent	27/47 (57.4)		18/46 (39.1)		.098	
Appearance on CT scan						
Solid	107/148 (72.3)	*P* = .141	94/153 (61.4)	*P* = .067	.051	*P* = .784
Part-solid nodule	17/29 (58.6)		11/26 (42.3)		.285	

Data are presented as No. with positive result/No. examined (%). See Table 1 legend for expansion of abbreviation.
[a]Logistic regression analysis.

bronchoscopy with TBNA with that without TBNA.[24] In the study by Chao et al,[24] the diagnostic yield of rEBUS-guided forceps biopsy, TBNA, and bronchial washings was higher than that without TBNA (78.4% vs 60.6%, respectively; $P = .015$). Unlike their results, we found no additional gain by adding TBNA to forceps biopsy in this study. This may be explained by the large differences in baseline target lesions and techniques between this study and the Chao et al[24] study. In the study by Chao et al,[24] the mean target lesion diameter was 34.9 mm. In addition, fluoroscopy, VBN, and GS were not used in their study. We encountered some technical problems using TBNA for small peripheral lesions even though we are familiar with this procedure.[29] The needle was too stiff to advance through the bent working channel or curved bronchial branch, particularly for the upper lobe bronchus.[30] The steerability of the stiff needle in the peripheral lung through the thin bronchoscope with weak bending force was quite limited. We think that TBNA would provide little additional gain in challenging cases, for which the approach is difficult even using multimodal bronchoscopy with a thin bronchoscope.

Although controversial,[30,31] rEBUS-GS is a promising bronchoscopic method for diagnosing peripheral pulmonary lesions.[32] The GS works as an extended working channel, so once the target lesion is identified with rEBUS, we can perform biopsy repeatedly from the same location through the GS. In addition, the GS can be directed toward the target lesion with a guiding curette, even through the angulated bronchial branch.[3] Conversely, the GS method has some limitations, the most obvious of which is the small size of compatible biopsy instruments.[25] When we use the GS through a

2.0-mm working channel, we have to use forceps smaller than the inner diameter of the GS of 1.7 mm. However, if we do not use the GS, we can use standard-sized forceps, which provide a larger amount of tissue. This may be advantageous for diagnosis in certain cases, such as cases with a ground-glass nodule and adjacent to or nearly adjacent to cases in rEBUS images.[25] In addition, it is hypothesized that taking multiple biopsies with the non-GS method from various locations increases the chance of sampling at least one diagnostic material compared with biopsies with the GS method from a fixed location.[30] Moreover, the GS method has some technical and instrumental disadvantages such as technical complexity, displacement of the GS by coughing or deep respiration, and kinking or bending of the GS.[33-36] Because the GS and non-GS methods each have advantages and disadvantages, they may play complementary roles. Even with allowing both the GS and non-GS methods during the thin bronchoscope procedure, the present trial demonstrated the diagnostic superiority of bronchoscopy using a UTB over a thin bronchoscope.

The higher diagnostic yield of the UTB method is achieved by the good accessibility, bronchial selectivity, and maneuverability in the peripheral small bronchi. In our study, the mean bronchial generations reached with the UTB, thin bronchoscope, and VBN were 5.5, 4.4, and 5.1, respectively. These observations suggest that the UTB can be advanced beyond the bronchial route indicated by VBN under direct visualization, whereas the thin bronchoscope cannot. Therefore, the UTB can maximize the ability of VBN, and they are well suited to each other. In fact, the diagnostic yield of bronchoscopy in cases where the bronchoscope was able to reach the peripheral end of the bronchial route indicated by VBN was significantly higher than that in cases where the bronchoscope was unable to reach the end (reached bronchus level with bronchoscope $\geq$ VBN, 71% [177 of 250]; VBN $>$ bronchoscope, 49% [52 of 106]; $P < .001$). When the advanced multimodality approach was used by experienced professionals, the diagnostic yield of flexible bronchoscopy used to evaluate peripheral lesions $\leq$ 30 mm in diameter was 58.7% for the thin bronchoscope method and 70.1% for the UTB method. Therefore, further technical modifications are necessary to improve the diagnostic yield of the bronchoscopy. For example, TBNA during the procedure using a UTB was not available in this study. However, promising results obtained with the novel flexible 21-gauge TBNA needle during the UTB procedure have been reported.[37]

This study had some limitations. First, the study was performed only at centers of expertise. We are familiar with the use of multimodal bronchoscopy; however, certain experience and skills are necessary to achieve a good diagnostic yield. Therefore, the results of this study may not be generalizable to other institutions with less experienced staff. Second, the UTB used here was a prototype; therefore, the results of this study should be considered experimental. The UTB has now been released commercially but is still available only in a limited number of countries. Third, the final diagnoses were not pathologically confirmed in all patients. We carefully reviewed and analyzed clinical data, but the final classification as malignant or benign may not be completely accurate in patients with diagnoses obtained from clinical follow-up. Finally, examinations after procedures were performed in accordance with current clinical practice. Therefore, the infectious complications may have been underestimated.[38] For example, oligosymptomatic self-limiting pneumonia might have been missed.

In conclusion, in patients with small peripheral pulmonary lesions, the use of a 3.0-mm UTB during multimodal bronchoscopy resulted in significantly higher diagnostic yield and shorter procedure duration without affecting safety compared with that using a 4.0-mm thin bronchoscope with multiple sampling methods, including TBNA and GS and/or non-GS methods.

Acknowledgments

Author contributions: M. O. is the guarantor of the content of this manuscript, including the data and analysis. M. O. contributed to the study design, data collection, analysis, and interpretation; wrote the initial draft of the manuscript; and performed further editing. H. S. and M. A. contributed to the study design, data collection, analysis, and interpretation; and edited the manuscript. F. A. contributed to the data collection, analysis, and interpretation; and edited the manuscript. C. K., Y. K., and A. T. contributed to the editing of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: M. O. has received speaker fees from Olympus Corporation as an invited guest speaker at academic medical meetings. None declared (H. S., F. A., C. K., Y. K., A. T., M. A.).

Other contributions: The prototype ultrathin bronchoscopes were lent to the authors by Olympus, Tokyo, Japan.

References

1. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 suppl): e142S-e165S.
2. Herth FJ, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. *Eur Respir J*. 2002;20(4):972-974.
3. Kurimoto N, Miyazawa T, Okimasa S, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. *Chest*. 2004;126(3):959-965.
4. Paone G, Nicastri E, Lucantoni G, et al. Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. *Chest*. 2005;128(5):3551-3557.
5. Gildea TR, Mazzone PJ, Karnak D, Meziane M, Mehta AC. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. *Am J Respir Crit Care Med*. 2006;174(9):982-989.
6. Mehta AC, Hood KL, Schwarz Y, Solomon SB. The evolutional history of electromagnetic navigation bronchoscopy: state of the art. *Chest*. 2018;154(4):935-947.
7. Asano F, Matsuno Y, Shinagawa N, et al. A virtual bronchoscopic navigation system for pulmonary peripheral lesions. *Chest*. 2006;130(2):559-566.
8. Dhillon SS, Harris K. Bronchoscopy for the diagnosis of peripheral lung lesions. *J Thorac Dis*. 2017;9(suppl 10):S1047-S1058.
9. Oki M, Saka H, Kitagawa C, et al. Novel thin bronchoscope with a 1.7 mm working channel for peripheral pulmonary lesions. *Eur Respir J*. 2008;32(2):465-471.
10. Oki M, Saka H, Kitagawa C, Kogure Y, Mori K, Kajikawa S. Endobronchial ultrasound-guided transbronchial biopsy using novel thin bronchoscope for diagnosis of peripheral pulmonary lesions. *J Thorac Oncol*. 2009;4(10):1274-1277.
11. Oki M, Saka H, Kitagawa C, et al. Randomized study of endobronchial ultrasound-guided transbronchial biopsy: thin bronchoscopic method versus guide sheath method. *J Thorac Oncol*. 2012;7(3): 535-541.
12. Asano F, Shinagawa N, Ishida T, et al. Virtual bronchoscopic navigation combined with ultrathin bronchoscopy. A randomized clinical trial. *Am J Respir Crit Care Med*. 2013;188(3):327-333.
13. Oki M, Saka H, Ando M, et al. Ultrathin bronchoscopy with multimodal devices for peripheral pulmonary lesions. A randomized trial. *Am J Respir Crit Care Med*. 2015;192(4):468-476.
14. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;176(1):36-41.
15. Ishida T, Asano F, Yamazaki K, et al. Virtual Navigation in Japan Trial Group. Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial. *Thorax*. 2011;66(12):1072-1077.
16. Steinfort DP, Bonney A, See K, Irving LB. Sequential multimodality bronchoscopic investigation of peripheral pulmonary lesions. *Eur Respir J*. 2016;47(2):607-614.
17. Asahina H, Yamazaki K, Onodera Y, et al. Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. *Chest*. 2005;128(3):1761-1765.
18. Asano F, Matsuno Y, Tsuzuku A, et al. Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. *Lung Cancer*. 2008;60(3):366-373.
19. Omiya H, Kikuyama A, Kubo A, et al. A feasibility and efficacy study on bronchoscopy with a virtual navigation system. *J Bronchology Interv Pulmonol*. 2010;17(1):11-18.
20. Oshige M, Shirakawa T, Nakamura M, et al. Clinical application of virtual bronchoscopic navigation system for peripheral lung lesions. *J Bronchology Interv Pulmonol*. 2011;18(2):196-202.
21. Tamiya M, Okamoto N, Sasada S, et al. Diagnostic yield of combined bronchoscopy and endobronchial ultrasonography, under LungPoint guidance for small peripheral pulmonary lesions. *Respirology*. 2013;18(5):834-839.
22. Ikezawa Y, Shinagawa N, Sukoh N, et al. Usefulness of endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation for ground-glass opacity lesions. *Ann Thorac Surg*. 2017;103(2):470-475.
23. Asano F, Ishida T, Shinagawa N, et al. Virtual bronchoscopic navigation without X-ray fluoroscopy to diagnose peripheral pulmonary lesions: a randomized trial. *BMC Pulm Med*. 2017;17(1):184.
24. Chao TY, Chien MT, Lie CH, Chung YH, Wang JL, Lin MC. Endobronchial ultrasonography-guided transbronchial needle aspiration increases the diagnostic yield of peripheral pulmonary lesions: a randomized trial. *Chest*. 2009;136(1):229-236.
25. Kunimasa K, Tachihara M, Tamura D, et al. Diagnostic utility of additional conventional techniques after endobronchial ultrasonography guidance during transbronchial biopsy. *Respirology*. 2016;21(6):1100-1105.
26. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest*. 2000;117(4):1049-1054.
27. Mondoni M, Sotgiu G, Bonifazi M, et al. Transbronchial needle aspiration in peripheral pulmonary lesions: a systematic review and meta-analysis. *Eur Respir J*. 2016;48(1):196-204.
28. Chen AC, Loiselle A, Zhou L, Baty J, Misselhorn D. Localization of peripheral pulmonary lesions using a method of computed tomography-anatomic correlation and radial probe endobronchial ultrasound confirmation. *Ann Am Thorac Soc*. 2016;13(9):1586-1592.
29. Oki M, Saka H, Kumazawa A, Sako C, Ando M, Watanabe A. The role of transcarinal needle aspiration in the diagnosis and staging of lung cancer: computed tomographic correlates of a positive result. *Respiration*. 2004;71(5): 523-527.
30. Ost DE, Ernst A, Lei X, et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions: results of the AQuIRE Registry. *Am J Respir Crit Care Med*. 2016;193(1):68-77.
31. Tanner NT, Yarmus L, Chen A, et al. Standard bronchoscopy with fluoroscopy vs thin bronchoscopy and radial

endobronchial ultrasound for biopsy of pulmonary lesions: a multicenter, prospective, randomized trial. *Chest*. 2018;154(5):1035-1043.

32. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. *Chest*. 2012;142(2):385-393.

33. Roth K, Eagan TM, Andreassen AH, Leh F, Hardie JA. A randomised trial of endobronchial ultrasound guided sampling in peripheral lung lesions. *Lung Cancer*. 2011;74(2):219-225.

34. Dooms CA, Verbeken EK, Becker HD, Demedts MG, Vansteenkiste JF. Endobronchial ultrasonography in bronchoscopic occult pulmonary lesions. *J Thorac Oncol*. 2007;2(2):121-124.

35. Casutt A, Prella M, Beigelman-Aubry C, et al. Fluoroscopic-guided radial endobronchial ultrasound without guide sheath for peripheral pulmonary lesions: a safe and efficient combination. *Arch Bronconeumol*. 2015;51(7):338-343.

36. Schuhmann M, Eberhardt R, Herth FJ. Endobronchial ultrasound for peripheral lesions: a review. *Endosc Ultrasound*. 2013;2(1):3-6.

37. Sczaniecka A, Casal RF, Chen AC, Gonzalez HX. First combined use of a novel flexible 21G peripheral TBNA needle and ultrathin bronchoscope in patients with peripheral lung lesions [abstract]. *Am J Respir Crit Care Med*. 2018;197:A7321.

38. Mehta AC, Gildea T. Burying our heads in the sand: cross-contamination during bronchoscopy. *Chest*. 2018;154(5):1001-1003.