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Guide sheath versus non-guide sheath method for endobronchial ultrasound-guided biopsy of peripheral pulmonary lesions: A multicenter randomized trial

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Summary "take home" message: Use of a guide sheath during endobronchial ultrasound-guided transbronchial biopsy enhances the diagnostic yield for small peripheral pulmonary lesions.

ABSTRACT

Introduction: Guide sheaths (GSs) have been widely used during radial probe endobronchial ultrasound-guided transbronchial biopsy (rEBUS-TBB) of peripheral pulmonary lesions. However, it remains unknown whether a GS enhances the diagnostic yield. We compared the diagnostic yields of small peripheral pulmonary lesions between rEBUS-TBB with and without a GS.

Methods: In eight institutions, patients with peripheral pulmonary lesions $\leq$ 30 mm in diameter were enrolled and randomized to undergo rEBUS-TBB with a GS (GS group) or without a GS (non-GS group) using a 4.0-mm thin bronchoscope, virtual bronchoscopic navigation, and fluoroscopy. The primary endpoint was the diagnostic yield of the histology specimens.

Results: A total of 605 patients were enrolled; ultimately, data on 596 (300 in the GS group and 296 in the non-GS group) with peripheral pulmonary lesions having a longest median diameter of 19.6 mm were analyzed. The diagnostic yield of histological specimens from the GS group was significantly higher than that from the non-GS group (55.3% vs. 46.6%, respectively; P = 0.033). Interactions were evident between the diagnostic yields, procedures, lobar locations (upper lobe vs. other regions, P = 0.003), and lesion texture (solid vs. part-solid nodules, P = 0.072).

Conclusions: The diagnostic yield for small peripheral pulmonary lesions afforded by rEBUS-TBB using a GS was higher than that without a GS.

Clinical trial registered with www.umin.ac.jp/ctr/ (UMIN 000024305).

Introduction

The use of radial probe endobronchial ultrasound (rEBUS) is recommended during bronchoscopic transbronchial biopsy (TBB) for the diagnosis of peripheral pulmonary lesions [1–3]. rEBUS can localize the lesions and bronchi leading to them; however, a major limitation is that the views are not obtained in real-time. When the target lesion is located by rEBUS, it is necessary to remove the rEBUS probe from the working channel of the bronchoscope and then insert the biopsy instrument through that channel. In other words, TBB and rEBUS scanning cannot be performed simultaneously, and it is thus impossible to confirm that the biopsy instrument has been advanced through the bronchial route taken by the rEBUS probe to the target lesion. To overcome this issue, Kurimoto *et al*. developed a guide sheath (GS) that bridges the tip of the bronchoscope to the pulmonary lesion, thus serving as an extended working channel [4]. The bronchial route established by the GS facilitates repeat biopsy from the same region. Since the first report by Kurimoto *et al*., many investigators have found rEBUS-guided TBB (rEBUS-TBB) using a GS (the GS method) useful [5–17]; the procedure is now used as standard. In a recent meta-analysis of rEBUS-TBB including 7,601 cases in 51 studies, the GS method was used in 3,837 (50%) [18]. In a Japanese survey including 55,335 cases of TBB for peripheral pulmonary lesions, the GS method was used in 23,916 (43%) [19]. Thus, many bronchoscopists have employed the GS method in clinical and study settings. However, the GS imposes a size limitation on the sampling instruments; in other words, rEBUS-TBB without a GS (the non-GS method) allows the use of larger biopsy forceps that may improve the diagnostic yield. In addition, it has been hypothesized that collecting multiple biopsies from various locations using the non-GS method increases the chance of obtaining at least one diagnostic sample compared to use of the GS method in a fixed location [20]. Disadvantages of the GS method include technical complexity and problems (e.g., displacement of the GS by coughing or deep respiration), and instrumental issues (e.g., kinking or bending of the GS, and

resistance when advancing biopsy instruments through the GS) [21]. To date, only a few small comparative studies on the diagnostic yield of rEBUS-TBB with and without a GS have been conducted [15, 22], and whether use of a GS during rEBUS-TBB enhances the diagnostic yield remains controversial. We performed a randomized study comparing the two major rEBUS-TBB techniques, i.e., the GS and non-GS methods, in terms of the diagnostic yield of peripheral pulmonary lesions.

Methods

Patients

We performed a randomized study comparing the GS and the non-GS methods during rEBUS-TBB for the diagnosis of peripheral pulmonary lesions at eight Japanese institutions. From February 2017 to November 2019, patients with localized peripheral pulmonary lesions ≤ 30 mm in diameter were recruited and randomly assigned to undergo rEBUS-TBB with a GS (GS group) or without a GS (non-GS group). In both groups, a 4.0-mm thin bronchoscope, virtual bronchoscopic navigation (VBN) and fluoroscopy were used; many investigators have demonstrated the effectiveness of this combination [6–12, 14–17]. Randomization was stratified by lesion size (largest diameter of ≤ 20 or > 20 mm on computed tomography [CT] scans), distance from the hilum (in the peripheral, intermediate, or central one-third of the CT lung field, as classified by Baaklini *et al.* [23]), presence or absence of a bronchus sign, operator experience (> 5 or ≤ 5 years after obtaining a medical degree); and lesion texture on CT (solid or part-solid). Allocations (1:1 ratios) were performed electronically. The principal inclusion criterion was a peripheral pulmonary lesion ≤ 30 mm in diameter that required diagnosis. The principal exclusion criteria were central pulmonary lesions, pure ground-glass nodules evident on CT, and the need for a bronchoscopic procedure for a non-target lesion in the same setting. The study was approved by the Institutional Review Board of each institution (e-Table 1) and

registered with the University Hospital Medical Information Network-Clinical Trials Registry (identifier: UMIN000024305). Written informed consent was obtained from all participants.

Procedures

Bronchoscopic procedures were performed with patients under local anesthesia and conscious sedation. A commercial 4.0-mm-thin bronchoscope with a 2.0-mm working channel (BF-P260F; Olympus, Tokyo, Japan) was advanced toward the target lesion through the bronchus. During the approach, pre-prepared virtual bronchoscopic views (from the trachea to the target lesion) were displayed as guides. When the bronchoscope reached the vicinity of the lesion and could not be advanced further, a 1.4-mm-diameter rEBUS probe (UM-S20-17S; Olympus) was advanced toward the lesion (through the working channel) under fluoroscopic guidance. In the GS group, a 1.95-mm-diameter GS (SG-200C; Olympus) was inserted together with the rEBUS probe, as previously described [24]. During the GS method, the use of a curette (CC-6DR-1; Olympus) to guide the GS was permitted [4, 5]. When the target lesion was visualized by rEBUS, the rEBUS probe was withdrawn and biopsies were performed using 1.5-mm-diameter biopsy forceps (FB-32D or FB-233D; Olympus) through a GS in the GS group, and 1.8 or 1.9-mm-diameter biopsy forceps (Radial Jaw 4; Boston Scientific, Marlborough, MA, USA, or FB-231D; Olympus) in the non-GS group. Biopsies were performed where possible until at least six visible specimens were obtained. Additional sampling procedures, including crossover procedures, brushing, and the procedures used in an ancillary study, were permitted. Rapid on-site cytological evaluation was not performed. Bronchial washing was performed after sampling.

Diagnosis

Histological specimens were assessed at each institution. Histological findings of malignant and benign neoplasms, epithelioid cell granulomas, organizing pneumonia, and fungal infections were considered diagnostic. Inconclusive histological findings, such as nonspecific fibrosis and inflammation, were considered non-diagnostic [13, 24]. The final diagnoses were established based on the pathological evidence, microbiological analyses, or clinical follow-up. Benign diagnoses, which could not be diagnosed pathologically or microbiologically, were confirmed radiologically and clinically. Except for patients whose lesions decreased or disappeared, all patients with non-diagnostic lesions were followed-up for at least 1 year after bronchoscopy.

Endpoints

The primary endpoint was the histological diagnostic yield of the allocated procedure, and the secondary endpoints were the diagnostic yields according to the nature of the lesion (benign or malignant), lesion size, lesion location (lobar, or distant from the hilum or visceral pleura) and lesion texture. Other secondary endpoints were the overall diagnostic yield, frequency of complications, probe location on the rEBUS image ("within," "adjacent to," or "invisible," as classified by Kurimoto *et al*. [4]) and the duration of the procedure.

Data analyses

We compared the histological diagnostic yields of the GS and non-GS methods. Based on expected yields of 70% using the GS method and 60% using the non-GS method [25–27], demonstration of the superiority of one of the two modalities with a statistical power of 80% and one-sided significance level of 0.05 would require at least 281 patients in each group (562

patients in total). We enrolled 600 patients to allow for dropouts. Means and percentages are presented as appropriate. Categorical variables were compared using the Pearson chi-squared test, and continuous variables using the Mann–Whitney *U* test. Logistic regression analyses were performed to determine predictors of a higher diagnostic yield for either method. Statistical analyses were performed using PASW Statistics (ver. 18.0; SPSS Inc., Chicago, IL, USA). Except for the regression analyses, in which $P < 0.1$ was taken to indicate statistical significance, $P < 0.05$ was considered to indicate a statistically significant difference.

Results

A total of 605 patients were allocated to the GS and non-GS groups, and 596 (300 in the GS group, 296 in the non-GS group) with peripheral pulmonary lesions with a longest median diameter on CT of 19.6 mm were finally analyzed (Figure 1). The baseline characteristics of the patients and lesions are listed in Table 1. There was no significant difference between the groups in any characteristic. The bronchoscopic findings and final diagnoses are listed in Table 2. The diagnostic yields of the two procedures are listed in Table 3. The diagnostic yield afforded by the GS method was significantly higher than that of the non-GS method (55.3% [166 of 300] vs. 46.6% [139 of 296], P = 0.033). In univariate analysis, the diagnostic yield of the GS method was significantly higher for upper lobe lesions, solid lesions, lesions > 20 to 30 mm in size, lesions abutting the pleura, and malignant and peripheral lesions. The GS method afforded a 20.2% higher diagnostic yield than the non-GS method for upper lobe lesions, whereas the non-GS method afforded a 3.9% higher diagnostic yield for lesions other than upper lobe lesions. Logistic regression analysis demonstrated an interaction between the bronchoscopic diagnostic yield and lobar location (P = 0.003). Similarly, the diagnostic yield of the GS method was 11.6% higher for solid lesions. Conversely, the yield of the non-GS method was 10% higher for part-solid lesions. An interaction was evident between the

bronchoscopic method used and lesion texture (P = 0.072 in logistic regression analysis).

The procedural details and complications of each group are listed in Table 4. The bronchus level (second- [segmental], third- [subsegmental], or fourth- [subsubsegmental] generation) reached was calculated by adding the number of branchings [28], as revealed by the thin bronchoscope; the median level reached was the fourth generation in both groups (P = 0.660). The rEBUS probe could be inserted into the lesions of 71.0% of the GS group and 63.9% of the non-GS group, but there was no significant difference in rEBUS visibility (P = 0.151). In the GS group, a curette guiding the GS to the lesion was used in 20% of cases (60 of 300). Forceps biopsy was feasible in 89.7% of GS group patients (median of nine biopsies) and in 85.8% of non-GS group patients (median of seven biopsies). The overall diagnostic yields of bronchoscopy (combined with the allocated and additional procedures) in the GS and non-GS group were 67.7% (203 of 300) and 60.8% (180 of 296), respectively (P = 0.081). The bronchoscopy time did not differ significantly between the groups (median of 30.0 min in the GS group and 29.0 min in the non-GS group; P = 0.183). Complications such as pneumothorax and pneumonia (which required oral or intravenous antibiotics), as well as bleeding, occurred in 3.7% (11 of 300) of the GS group and 4.1% (12 of 296) of the non-GS group (P = 0.806). One patient in the non-GS group required temporary mechanical ventilation and underwent bronchial artery embolization because of significant bleeding after forceps biopsy. No mortality was observed.

Discussion

To the best of our knowledge, this is the first large randomized study to compare the diagnostic yields of the GS and non-GS methods during rEBUS-TBB of small, peripheral pulmonary lesions. We found that the diagnostic yield of rEBUS-TBB with a GS was significantly higher than that without a GS.

Although many investigators have demonstrated the diagnostic utility of the GS method during rEBUS-TBB, only a few small comparative studies (with controversial results) on the diagnostic performances of the GS and non-GS methods have appeared [15, 22]. In a retrospective study on 110 patients, Minami *et al*. reported that the diagnostic sensitivity of rEBUS-TBB for peripheral lung cancer was significantly higher when using a GS than non-GS method (63.3% vs. 44%, P = 0.043) [15]. On the other hand, a retrospective study by Ito *et al*. reported the opposite results [22]. They evaluated the diagnostic yields of a GS and non-GS method in 80 patients with pulmonary lesions < 20 mm in diameter; the respective yields were 71.7% and 82.9% (P = 0.233). Although the difference for lesions < 20 mm in diameter was not significant, the diagnostic yield of the non-GS method for lesions < 15 mm in diameter was significantly higher than that of the GS method (80.7% vs. 50%. P = 0.036). A few prospective crossover studies have compared the diagnostic yields of the two methods, to approach the same target lesions in the same settings; the yields were similar [29, 30]. In prospective studies that left the use of a GS or non-GS method to the discretion of the bronchoscopist, no differences in diagnostic yield were evident [31, 32]. Some reviews found that the diagnostic yield of the GS method was up to 4% greater than that of the non-GS method [18, 33, 34], but none showed that use of a GS increased the diagnostic yield of rEBUS-TBB. Thus, whether the GS method has a diagnostic advantage has not yet been established.

We found that use of a GS during rEBUS-TBB enhanced the diagnostic yield. The GS and non-GS methods have their own advantages and disadvantages. The principal advantage of the GS method (in terms of increasing the diagnostic yield) is that it enables simple and accurate repeat sampling of a lesion located by rEBUS; the GS serves as the route to the lesion. It is well-known that the positional relationship between the rEBUS probe and target lesion affects the

diagnostic yield; the "within" sign on the rEBUS image is a strong predictor of good diagnostic samples [15, 25]. However, even if the rEBUS shows the "within" sign, the biopsy instrument cannot always be advanced to the same location without a GS [30]. Among the cases with the "within" sign in this study, the diagnostic yield of the GS method was 7.6% higher than that of the non-GS method. Moreover, the proportion of cases with the "within" sign in the GS group was 7.1% higher than in the non-GS group. This may reflect the use of a guiding curette in 20% of the GS group. A guiding curette is usually employed when the rEBUS probe within a GS cannot approach the lesion [5]. rEBUS with a GS and guiding curette yielded the "within" sign in 65% treated in that manner.

A distinct advantage of the non-GS method is the possibility of using larger instruments to obtain larger specimens. Thus, some investigators have advocated that the GS and non-GS methods are complementary for rEBUS-TBB diagnosis of peripheral pulmonary lesions [30, 35, 36]. Kunimasa *et al*. retrospectively investigated 88 patients who had undergone rEBUS-TBB using a GS method followed by a non-GS method in a single session [35]. The diagnostic yields of the GS method, non-GS method, and their combination were 65% (57 of 88), 59% (52 of 88), and 82% (72 of 88) respectively. It was suggested that the addition of forceps biopsy without a GS to the GS method was beneficial, especially for ground-glass nodules and lesions with edges located a short distance from the rEBUS probes. Boonsarngsuk *et al*. also evaluated the utility of adding a non-GS method to a GS method, and recommended additional forceps biopsy (without a GS) for part-solid nodules [30]. In the current study, the diagnostic superiority of the GS method was especially evident for upper lobe lesions; we found a significant interaction between the bronchoscopic method used and lobar lesion location. The GS method afforded a 20.2% higher diagnostic yield for upper lobe lesions. On the other hand, the non-GS method afforded a 3.9% higher diagnostic yield for non-upper lobe lesions, although the latter

difference was not statistically significant. When a bronchoscope is advanced though an upper lobe bronchus, the pushing force is not directly transmitted to the tip because the upper lobe bronchial route curves sharply. Therefore, a thin bronchoscope is seldom advanced close to upper lobe lesions, and repeat biopsy without a GS is often difficult. On the other hand, using the GS method, once the target lesion is located by rEBUS with or without a guiding curette, it is easy to perform repeat biopsies. In addition, the upper lobe is less affected by respiratory motion than are lower lobes [37], which aids accurate sampling by fixing the GS position. For lesions located in areas other than the upper lobe, a thin bronchoscope can be forcefully pushed and is often advanced very close to the lesions. The diagnostic superiority of the GS method was also evident for solid lesions; we found an interaction between the bronchoscopic method used and lesion texture. The GS method afforded an 11.6% higher diagnostic yield for solid lesions, and the non-GS method had a 10% higher diagnostic yield for part-solid nodules, although the latter difference was not statistically significant. Ground-glass nodules seldom invade the bronchus; thus, the use of sampling devices that can obtain large amounts of tissue by penetrating the peripheral bronchial wall seems reasonable [38]. As previously demonstrated [30, 35, 36], larger samples obtained using large forceps may be preferable when diagnosing ground-glass nodules.

In the current study, we performed bronchoscopy under virtual bronchoscopic navigation and fluoroscopic guidance in all cases. Although controversial [10, 39], this ancillary imaging enhanced the diagnostic yield for small peripheral pulmonary lesions [9, 40]. However, equipment availability differs among institutions, and rEBUS-TBB is widely used without ancillary imaging. The GS creates a direct bronchial route to the target lesions, enabling repeat biopsy of the same location without imaging guidance. When the GS method is used, biopsy is effective even without fluoroscopy or navigation devices [39, 41]. Thus, we expect that the

better diagnostic yield of the GS compared to non-GS method that we achieved would also be seen when using rEBUS-TBB procedures without ancillary imaging guidance. Although the diagnostic yield of bronchoscopy increased dramatically after the development of rEBUS and navigational devices, it remains lower than that of image-guided transthoracic needle aspiration [34, 42–44]. However, the latter technique is associated with a higher risk of complications, including pneumothorax and hemorrhage [42–44]. The diagnostic procedure should be chosen with consideration of operator preference, the availability of resources, safety and accuracy.

Our study had certain limitations. First, the final diagnoses were not surgically confirmed in some cases. We thus cannot completely exclude false-positives, although these are extremely rare. In some cases, the final diagnoses were based on clinical follow-up. As in other large studies [45, 46], lesions that did not grow for at least 1 year were considered benign; however, slow-growing malignancies might have been miscategorized as benign. This should not affect the primary endpoint, but might affect the secondary ones. Second, we compared the histological diagnostic yields, but not the molecular diagnostic yields. Although several investigators have reported that molecular testing of specimens obtained by a small forceps is possible [47–50], larger specimens with higher proportions of tumor cells are usually preferable. Molecular testing accuracy is important when selecting the diagnostic procedure. Any procedure should be chosen after comprehensive consideration of diagnostic yield, molecular testing accuracy, safety, invasiveness, procedural time, cost, availability, and operator preference. Third, we allowed (and did not regulate) additional sampling procedures after the GS and non-GS methods, so could evaluate the combined effects of the methods, unlike other studies. Also, it was difficult to determine whether some complications (including pneumonia and pneumothorax) were caused by the assigned or additional sampling procedures. However, the complication rates of both groups were acceptable, even when additional sampling

procedures were employed. Finally, the current study was performed in centers of expertise. Bronchoscopic procedures have learning curves; therefore, the results may not be generalizable to other institutions with less experienced operators.

In conclusion, the diagnostic yield of rEBUS-TBB with a GS was higher than that without a GS for small, peripheral pulmonary lesions. The diagnostic yields of the GS and non-GS methods differed significantly by lesion lobar location and texture.

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Figure Legends

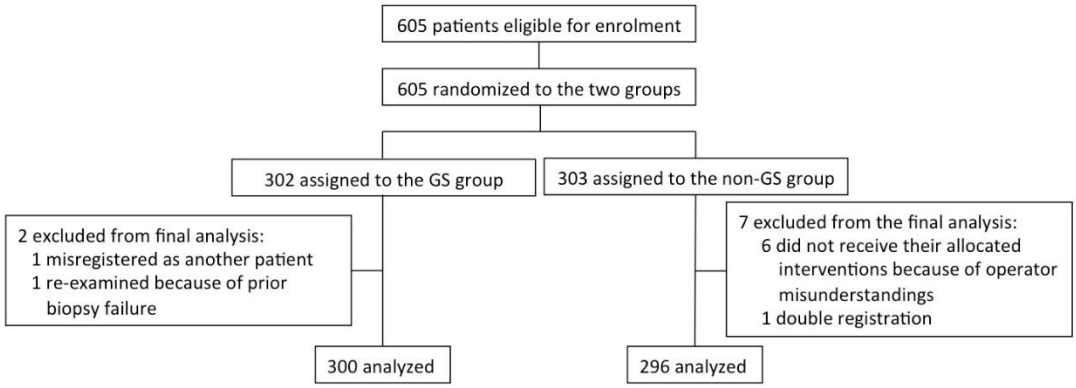

FIGURE 1.

FIGURE 1. Flow chart of patient recruitment.

GS: guide sheath.

TABLE 1 Characteristics of the patients and lesions.

Characteristics	Guide sheath group (n = 300)		Non-guide sheath group (n = 296)		P-value[#]
Sex					
Male	184	(61.3)	169	(57.1)	0.292
Female	116	(38.7)	127	(42.9)	
Age, median, years (range)	72	(24–89)	72	(44–90)	0.396
Smoking history					
Never	95	(31.7)	115	(38.9)	
Former	156	(52.0)	127	(42.9)	0.078
Current	49	(16.3)	54	(18.2)	
Lesion size (longest diameter on CT)					
Median, mm (range)	20.0	(6.7–30.0)	19.0	(6.9–30.0)	0.251
$\leq$ 20	159	(53.0)	163	(55.1)	0.613
> 20 to 30	141	(47.0)	133	(44.9)	
Lesion location					
Right upper lobe	81	(27.0)	90	(30.4)	
Right middle lobe	15	(5.0)	21	(7.1)	
Right lower lobe	63	(21.0)	71	(24.0)	0.183
Left upper lobe	79	(26.3)	57	(19.3)	
Lingula	10	(3.3)	15	(5.1)	
Left lower lobe	52	(17.3)	42	(14.2)	
Lesion location with respect to the hilum					

Intermediate	47	(15.7)	45	(15.2)		0.875
Peripheral	253	(84.3)	251	(84.8)		
Positional relationship with the pleura						
Distant from the pleura	184	(61.3)	167	(56.4)		0.223
Abutting the pleura	116	(38.7)	129	(43.6)		
Bronchus sign						
Present	240	(80.0)	234	(79.1)		0.775
Absent	60	(20.0)	62	(20.9)		
Texture on CT						
Solid	260	(86.7)	256	(86.5)		0.949
Part-solid	40	(13.3)	40	(13.5)		
Final diagnosis						
Malignant	237	(79.0)	231	(78.0)		
Benign	61	(20.3)	60	(20.3)		0.511
Unknown	2	(0.7)	5	(1.7)		
Examiner						
Staff pulmonologist	258	(86.0)	253	(85.5)		0.854
Resident	42	(14.0)	43	(14.5)		

Data are presented as n (%) unless otherwise stated. CT: computed tomography.

[#]: Pearson chi-squared test or Mann-Whitney *U* test.

TABLE 2 Bronchoscopic findings and final diagnoses.

	Numbers of patients and final outcomes			
	Guide sheath group (n = 300)		Non-guide sheath group (n = 296)	
Bronchoscopic findings	**n**	**Final diagnoses and outcomes**	**n**	**Final diagnoses and outcomes**
Diagnostic				
Malignant				
Lung cancer				
Adenocarcinoma	118 (103)		103 (84)	
Squamous cell carcinoma	31 (28)		31 (25)	
Non-small cell carcinoma	8 (7)		4 (4)	
Adenosquamous carcinoma			1 (1)	
Large cell neuroendocrine carcinoma			1 (1)	
Small cell carcinoma	7 (6)		3 (3)	
Cytology positive for malignancy	8 (0)		8 (0)	
Metastatic carcinoma	12 (10)	3 colon, 2 liver, 2 thyroid, 1 rectum, 1 breast, 1 stomach, 1 esophagus, 1 uterus	10 (10)	2 rectum, 2 kidney, 1 larynx, 1 colon, 1 ovary, 1 uterus, 1 prostate, 1 tongue
Cytology positive for malignancy	1 (0)	1 urothelium	2 (0)	2 breast
Lymphoma	1 (1)			
Benign				
Nontuberculous mycobacteriosis	6 (3)		6 (3)	
Tuberculosis	4 (2)		1 (1)	
Granuloma	4 (3)		3 (2)	

Organizing pneumonia	1	(1)			4	(3)	
Bacterial pneumonia	1	(1)			1	(0)	
Aspergillosis	1	(1)			1	(0)	
Fungal infection					1	(1)	
Nondiagnostic							
	97		51 Malignant		116		68 Malignant
			46 Pathologically proven lung cancer				59 Pathologically proven lung cancer
			4 Metastatic carcinoma				3 Metastatic carcinoma
			1 Suspected malignancy				2 Lymphoma
			44 Benign				4 Suspected malignancy
			1 Nontuberculous mycobacteriosis				43 Benign
			1 Organizing pneumonia				1 Granuloma
			1 Cryptococcosis				1 Bronchiolitis with organizing pneumonia
			1 Granuloma				1 Infectious bulla
			1 Squamous cell papilloma				1 Collapsed lung
			1 Pulmonary abscess				20 Improved
			1 Ciliated muconodular papillary tumor				19 Unchanged on ≥ 12-month follow-up
			1 Pleuroparenchymal fibroelastosis				5 No follow-up
			19 Improved				
			17 Unchanged on ≥ 12-month follow-up				
			2 No follow-up				

Numbers of diagnostic results for the allocated interventions are shown in parentheses.

TABLE 3 Histopathological diagnostic yields of the allocated procedures.

	Guide sheath group (n = 300)				Non-guide sheath group (n = 296)					
Variables	**N/Total**	**(%)**	**95% CI**	**P-value**	**N/Total**	**(%)**	**95% CI**	**P-value**	**P-value[#]**	**P-value for interaction[¶]**
Total	166/300	(55.3)	49.5–61.1		138/296	(46.6)	50.8–52.5		0.033	
Lesion size, mm										
≤ 20	79/159	(49.7)	41.7–57.7	0.037	76/163	(46.6)	38.8–54.6	0.999	0.583	0.140
> 20 to 30	87/141	(61.7)	53.2–69.8		62/133	(46.6)	37.9–55.5		0.012	
Lesion type										
Malignant	155/237	(65.4)	59.0–71.4	< 0.001	128/231	(55.4)	46.6–59.8	< 0.001	0.027	0.531
Benign	11/61	(18.0)	9.4–30.0		10/60	(16.7)	8.3–28.5		0.843	
Unknown	0/2	(0)			0/5	(0)			–	
Lobar location										
Upper lobe	101/160	(63.1)	55.2–70.6	0.004	63/147	(42.9)	34.7–51.3	0.197	< 0.001	0.003
Other lobes	65/140	(46.4)	38.0–55.1		75/149	(50.3)	42.0–58.6		0.507	
Lesion location with respect to the hilum										
Intermediate	31/47	(66.0)	50.7–79.1	0.111	28/45	(62.2)	46.5–76.2	0.023	0.709	0.639
Peripheral	135/253	(53.4)	47.0–59.6		110/251	(43.8)	37.6–50.2		0.032	
Positional relationship with the pleura										
Distant from the pleura	106/184	(57.6)	50.1–64.9	0.318	90/167	(53.9)	46.0–61.6	0.004	0.484	0.191
Abutting the pleura	60/116	(51.7)	42.3–61.1		48/129	(37.2)	28.9–46.2		0.022	

Bronchus sign											
Present	142/240	(59.2)	52.7–65.5	0.008	115/234	(49.1)	42.6–55.7	0.091	0.029		0.497
Absent	24/60	(40.0)	27.6–53.5		23/62	(37.1)	25.2–60.3		0.742		
Lesion texture on CT											
Solid	148/260	(56.9)	50.7–63.0	0.158	116/256	(45.3)	39.1–51.6	0.253	0.008		0.072
Part-solid	18/40	(45.0)	29.3–61.5		22/40	(55.0)	38.5–70.7		0.371		

CI: confidence interval; CT: computed tomography; [#]: Pearson chi-squared test; [¶]: logistic regression analysis.

TABLE 4 Procedural details and complications.

Variables	Guide sheath group (n = 300)		Non-guide sheath group (n = 296)		P-value[#]
Bronchus level reached by the bronchoscope					
Median (range), generation	4	(2–8)	4	(2–8)	0.660
Mean ± SD, generation	4.5±1.1		4.5±1.1		
Location of probe in relation to the lesion, confirmed by rEBUS					
Within the lesion	213	(71.0)	189	(63.9)	
Adjacent to the lesion	45	(15.0)	51	(17.2)	0.151
Invisible with rEBUS	42	(14.0)	56	(18.9)	
Forceps biopsy using the assigned procedure					
Performed	269	(89.7)	254	(85.8)	0.151
Median (range), number of biopsies	9	(2–13)	7	(1–16)	0.001
Mean ± SD, number of biopsies	8.3±2.1		7.6±2.3		
Not performed	31	(10.3)	42	(14.2)	
Use of a guiding curette	60	(20.0)	–	–	
Additional procedures in the same setting					
Forceps biopsy					
Crossover procedure[¶]	11/19	(57.9)	19/34	(55.9)	
Ultrathin bronchoscopy	21/38	(55.3)	19/54	(35.2)	
Washing	75/296	(25.3)	52/280	(18.6)	
Brushing	48/92	(52.2)	40/77	(51.9)	
Needle aspiration	3/10	(30.0)	3/4	(75.0)	
Cytological specimens from forceps biopsy	2/2	(100)	3/4	(75.0)	

Cryobiopsy	–	–	1/1	(100)	
Total diagnostic yield of bronchoscopy	203/300	(67.7)	180/296	(60.8)	0.081
Bronchoscopy time, median (range), min	30.0	(11.9–89.8)	29.0	(8.6–100.0)	0.183
Complications, all	11	(3.7)	12	(4.1)	0.806
Pneumothorax (no. requiring drainage)	3	(2)	5	(2)	
Pneumonia	4		3		
Bleeding > 50 mL	1		3	(1 significant)	
Arrythmia	1		–		
Transient hypoxemia	1		1		
Broken guide sheath	1		–		

Data are presented as number (%) or number with diagnostic results/number examined (%) unless otherwise stated. rEBUS: radial probe endobronchial ultrasound; SD: standard deviation.

[#]: Pearson chi-squared test or the Mann-Whitney *U* test; [¶]: Non-guide sheath method for patients in the guide sheath group, and vice versa.

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e-Table 1

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