Received: 2 June 2022 | Accepted: 31 October 2022

DOI: 10.1111/resp.14405

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

Virtual bronchoscopic navigation and endobronchial ultrasound with a guide sheath without fluoroscopy for diagnosing peripheral pulmonary lesions with a bronchus leading to or adjacent to the lesion: A randomized non-inferiority trial

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Funding information
National Multi-disciplinary Treatment Project for Major Diseases, Grant/Award Number: 2020NMDTP; Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support, Grant/Award Number: 20181815

Associate Editor: Noriaki Kurimoto;
Senior Editor: Phan Nguyen

Abstract

Background and Objective: Transbronchial sampling of peripheral pulmonary lesions (PPLs) is routinely performed under fluoroscopy. However, advanced ancillary techniques have become available, such as virtual bronchoscopic navigation (VBN) and radial endobronchial ultrasound with a guide sheath (rEBUS-GS). This study was performed to determine whether the diagnostic utility of VBN and rEBUS with a GS is similar with or without fluoroscopy.

Methods: This multicenter non-inferiority trial randomized patients to a VBN-rEBUS-GS with or without fluoroscopy group at three centres. The primary endpoint was the diagnostic yield. The secondary endpoints were the time for rEBUS, GS, and the total operation. Complications were also recorded.

Results: Four hundred and ninety-six subjects were assessed and 426 subjects were included in the analysis (212 in non-fluoroscopy-guided-group and 214 in fluoroscopy-guided-group). The diagnostic yield in the non-fluoroscopy-guided-group (84.0%) was not inferior to that in the fluoroscopy-guided-group (84.6%), with a diagnostic difference of −0.6% (95% CI: −6.4%, 5.2%). Multivariable analysis confirmed that bronchus sign and lesion nature were valuable diagnostic predictors in non-fluoroscopy-guided-group. The non-fluoroscopy-guided-group had shorter rEBUS, GS, and total operation time. No severe complications occurred in either group.

Conclusion: Transbronchial diagnosis of PPLs suspicious of malignancy and presence of a bronchus leading to or adjacent to lesions using VBN-rEBUS-GS without fluoroscopy is a safe and effective method that is non-inferior to VBN-rEBUS-GS with fluoroscopy. Bronchus leading to lesions and malignant nature are associated with high diagnostic yield in VBN-rEBUS-GS without fluoroscopy for the diagnosis of PPLs.

KEYWORDS
endobronchial ultrasound, fluoroscopy, peripheral pulmonary lesions, transbronchial lung biopsy, virtual bronchoscopic navigation

INTRODUCTION

Peripheral pulmonary lesions (PPLs) are defined as focal radiographic opacities located beyond the segmental bronchi and surrounded by normal lung parenchyma, which makes them undetectable using conventional bronchoscopy.[1,2] Traditional transbronchial sampling of PPLs is routinely guided by fluoroscopy, although this strategy does not provide a sufficient diagnostic yield, especially in identifying small lesions or lesions that overlap with other chest structures.[1,3–5] Moreover, fluoroscopy requires radiation exposure and specialized equipment.

Xiaoxuan Zheng and Changhao Zhong contributed equally to the research study.

Multiple attempts have been made to identify modalities that can complement fluoroscopy.[6] For example, radial endobronchial ultrasound (rEBUS) can provide confirmation of a target lesion and use of a guide sheath (GS) creates a pathway that can permit repeated delivery of sampling tools to the lesion.[7,8] Navigation bronchoscopy mainly involves virtual bronchoscopic navigation (VBN) and electromagnetic navigation bronchoscopy, which establish a bronchoscopy route to correspond with the actual bronchoscopic view.[9–12] These advanced ancillary techniques may offer effective alternatives to fluoroscopy for diagnosing PPLs.

A series of single-arm studies have explored the feasibility of guided-bronchoscopy without fluoroscopy, which revealed diagnostic yields of 61.8%–80.0% and low complication rates.[13,14] However, it remains unclear whether the diagnostic utility of advanced bronchoscopy is similar with or without fluoroscopy. Asano et al. performed a randomized trial that failed to confirm the non-inferiority of VBN-assisted bronchoscopy relative to fluoroscopy-guided bronchoscopy.[15] Tachihara et al. reported a noninferior diagnostic yield for VBN-rEBUS-GS without fluoroscopy versus with fluoroscopy, but the finding was not conclusive due to the small sample size.[16] Therefore, we performed a study to compare the diagnostic efficacies and safety profiles of VBN-rEBUS-GS bronchoscopy with or without fluoroscopy in patients with PPLs.

SUMMARY AT A GLANCE

The randomized multicenter clinical trial evaluated that transbronchial diagnosis of PPLs suspicious of malignancy and presence of a bronchus leading to or adjacent to lesions using VBN-rEBUS-GS without fluoroscopy was a safe and effective method and it was non-inferior to VBN-rEBUS-GS with fluoroscopy.

METHODS

Design and randomization

This is a prospective, multicenter, non-inferiority, randomized study. Consecutive patients were recruited at three centres. Subjects were randomly assigned to the non-fluoroscopy-guided and fluoroscopy-guided groups based on central stratified randomization and quorum methods by computer. The stratification factors were lesion size (>30 mm, ≤30 mm), distance to the hilum (central, intermediate, peripheral), and the bronchus sign on the thin-slice CT (leading to, adjacent to). One hundred ninety-eight patients for each group were needed to demonstrate non-inferiority with 80% power at a one-sided significance level of 0.05. However, based on an assumed drop-out rate of 10%, the trial aimed to enrol 436 patients (Appendix S1 in the Supporting Information).

Study participants

The eligibility criteria were: (1) patients ≥18 years old, (2) PPL suspicious of malignancy based on clinical assessment and in need of non-surgical biopsy, (3) the longest PPL diameter (i.e., the long axis diameter) was ≥8 mm. Only one lesion was selected for sampling if the patient had multiple PPLs. The exclusion criteria were: (1) absence of a bronchus leading to or adjacent to the lesion on the thin-slice CT, (2) pure ground glass opacity, (3) severe cardiopulmonary dysfunction and other contraindications for bronchoscopy, and (4) concomitant endobronchial lesions that were visualized using bronchoscopy. All patients provided written informed consent before enrolment.

Procedures

Chest CT (slice thickness: 0.5–1 mm, interval: 0.5–1 mm) was performed before the bronchoscopy. The data were transferred to a VBN system (DirectPath, Olympus, Tokyo, Japan) to construct the virtual bronchoscopic images and pathways. A 2.0-mm working channel bronchoscope was used (BF-P260F or BF-P290, Olympus) with a rEBUS probe (UM-S20-17 S, Olympus) and a GS (K-201, Olympus) under general anaesthesia or local anaesthesia with/without moderate sedation. The other details were shown in Appendix S1 in the Supporting Information.

VBN-rEBUS-GS (non-fluoroscopy-guided-group)

The procedure did not involve fluoroscopy. When the lesion was visualized via rEBUS, the variation of lesion image from the proximal to the distal end of the lesion on rEBUS was used to measure the target lesion length and guide the insertion depth of sampling instruments. The GS provided a stable pathway for repeated sampling.

VBN-rEBUS-GS-fluoroscopy (fluoroscopy-guided-group)

Fluoroscopy was used to adjust and confirm the rEBUS position and monitor the sampling process. For lesions directly visualized by rEBUS, the fluoroscopy was used to confirm probe position and monitor sampling process. If the radial probe did not locate at the target lesions, we would adjust the radial probe under fluoroscopic guidance to find a better position. If the lesion was undetectable even after the adjustment, the probe was withdrawn and sampling was performed under fluoroscopic guidance.

Sampling procedures

The rEBUS was withdrawn after lesion localization and the GS was left in position. The sampling steps involved brushing, forceps biopsy, brushing, and GS flushing with saline to collect liquid specimens. At least five biopsy specimens were recommended.[17] If the lesion could not be verified using all ancillary instruments, we washed the targeted bronchus with 20 ml of saline as a remedy. Microbiological examinations were based on the bronchoscopist's personal experience.

Interpreting the findings

The bronchoscopic diagnosis was determined based on the pathological and microbiological results. Diagnostic yield was defined as all instances in which the results of bronchoscopy matched the final diagnoses.[9] A lesion was considered malignant if tumour cells were identified from the histological or cytological specimens. A lesion was considered benign if the pathological evaluation revealed specific benign characteristics and/or positive microbiological results. All lesions with non-diagnostic results or benign pathology were monitored until a definitive diagnosis was made by an additional procedure (e.g., transthoracic needle aspiration, surgery) and/or at least 1 year of follow-up.

Study outcomes

The primary endpoint was the diagnostic yield. The secondary endpoints were the time for rEBUS, GS, and the total operation. The safety endpoints were procedural complications, which were graded according to version 4.0 of the Common Terminology Criteria for Adverse Events.[18]

Definitions

Bronchus leading to the PPL was defined as a positive bronchus sign and bronchus adjacent to the PPL and non-involvement were defined as negative bronchus

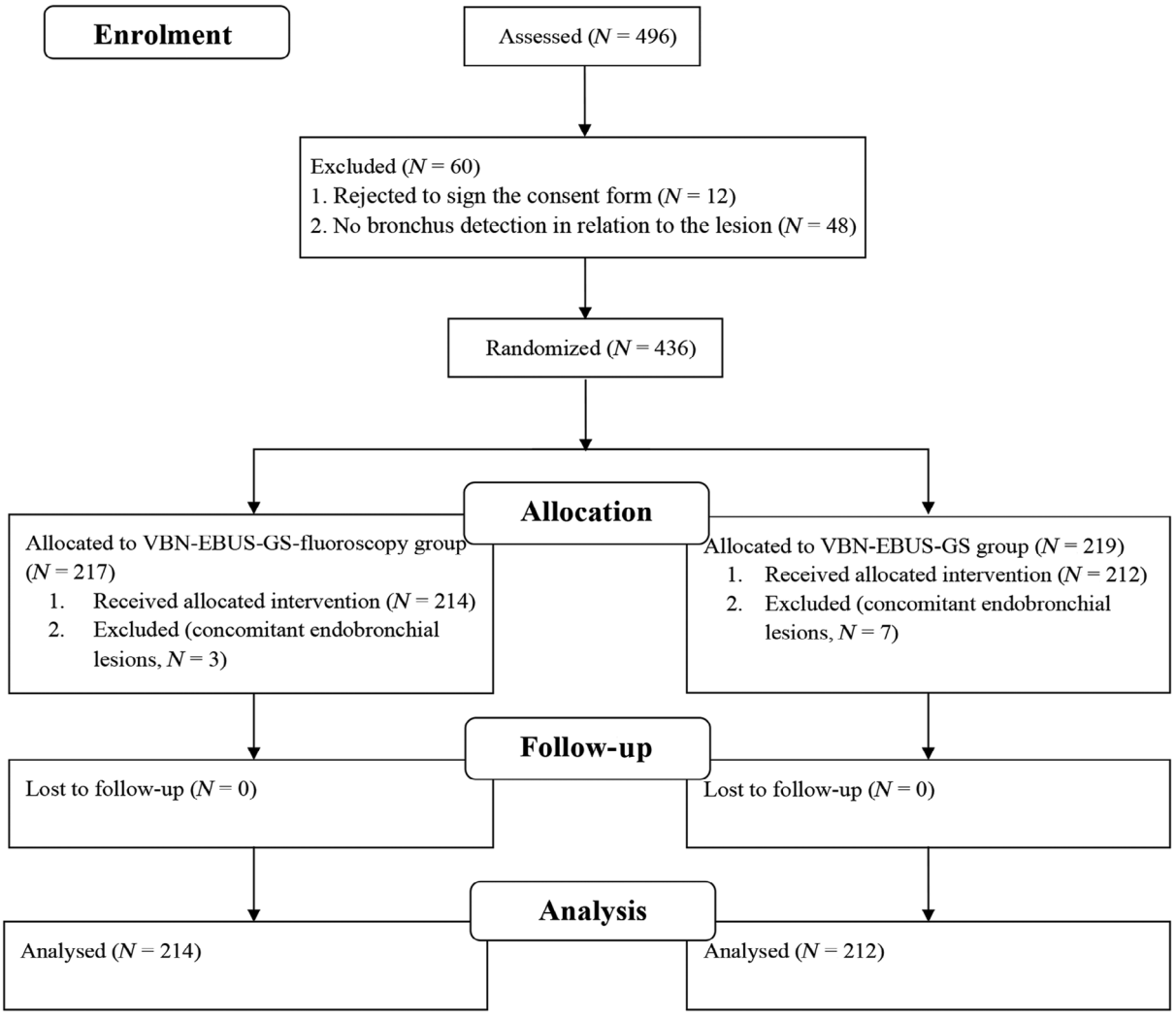

FIGURE 1 Consort flow diagram

sign. The lesion size,[19] the relationship between bronchus or rEBUS and lesions,[17,20,21] the distance from the lesion to the hilum or pleura,[4,22] the navigation distance, the time for rEBUS, GS, the total operation, and radiation exposure etc., were shown in Appendix S1 in the Supporting Information.

Statistical analysis

Variables were expressed as mean ± SD, number (percentage), median interquartile range (IQR). Comparison was performed by *t* test, Mann–Whitney test, Fisher's exact test or the Pearson x^2 test as appropriate. The crude and adjusted difference of diagnostic yield was used to determine whether non-inferiority was present, by comparing the lower 95% CI with the non-inferiority margin (−10%). Significant predictors were determined by multivariate logistic regression. The other detailed statistics were shown in Appendix S1 in the Supporting Information.

RESULTS

Patient characteristics

Totally, 496 consecutive patients were assessed and 436 were eligible and enrolled from September 2018 to July 2019.

TABLE 1 Baseline characteristics

	Non-fluoroscopy-guided ($N = 212$)	Fluoroscopy-guided ($N = 214$)	Total ($N = 426$)
Age, years	59.5 ± 10.6	62.5 ± 10.1	61.0 ± 10.5
Sex, *n* (%)			
Male	127 (59.9)	119 (55.6)	246 (57.7)
Female	85 (40.1)	95 (44.4)	180 (42.3)
Smoking, *n* (%)			
Yes	83 (39.2)	88 (41.1)	171 (40.1)
No	129 (60.8)	126 (58.9)	255 (59.9)
Lesion size, *n* (%)			
Average, mm	32.3 ± 12.2	31.4 ± 11.0	31.8 ± 11.6
Median (IQR), mm	31.0 (23.5–40.2)	30.8 (22.8–38.7)	31.0 (23.1–39.1)
>20 mm	179 (84.4)	173 (80.8)	352 (82.6)
≤20 mm	33 (15.6)	41 (19.2)	74 (17.4)
>30 mm	113 (53.3)	114 (53.3)	227 (53.3)
≤30 mm	99 (46.7)	100 (46.7)	199 (46.7)
Lesion location, *n* (%)			
LUS	37 (17.5)	39 (18.2)	76 (17.8)
LLS	23 (10.8)	14 (6.5)	37 (8.7)
LLL	40 (18.9)	37 (17.3)	77 (18.1)
RUL	51 (24.1)	67 (31.3)	118 (27.7)
RML	21 (10.0)	13 (6.1)	34 (8.0)
RLL	40 (18.9)	44 (20.6)	84 (19.7)
Bronchus sign, *n* (%)			
Leading to	188 (88.7)	191 (89.3)	379 (89.0)
Adjacent to	24 (11.3)	23 (10.7)	47 (11.0)
Distance to the hilum, *n* (%)			
Central	32 (15.1)	28 (13.1)	60 (14.1)
Intermediate	111 (52.4)	114 (53.3)	225 (52.8)
Peripheral	69 (32.5)	72 (33.6)	141 (33.1)
Distance to the pleura (IQR), mm	12.1 (4.5–18.6)	11.4 (4.7–21.9)	11.6 (4.7–19.9)
Navigation distance (IQR), mm	57.1 (45.1–68.1)	58.8 (44.9–70.6)	57.7 (45.0–69.3)
Lesion nature, *n* (%)			
Malignant	171 (80.7)	173 (80.8)	344 (80.8)
Benign	41 (19.3)	41 (19.2)	82 (19.2)

Abbreviations: IQR, interquartile range; LLL, left lower lobe; LLS, left lingular segment; LUS, left upper segment; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

Finally, 426 patients were analysed (Figure 1). The two groups had generally well-balanced characteristics (Table 1).

Both groups had similar proportions of malignant and benign diseases, as well as similar procedural characteristics (Table 2). The average radiation exposure time in the fluoroscopy-guided-group was 54.0 (33.8–78.5)s. The rEBUS time, GS time, and total operation time tended to be shorter in the non-fluoroscopy-guided-group, although the difference was not statistically significant.

Study outcomes

The bronchoscopic outcomes and final diagnoses are shown in Table 3. Bronchoscopic diagnoses were made for 359 patients (84.3%), which included 300 malignant lesions and 59 benign lesions. Overall, the diagnostic yields in non-fluoroscopy-guided and fluoroscopy-guided-group were 84.0% (178 of 212) and 84.6% (181 of 214), respectively, with the difference of −0.6% (95% CI: −6.4%, 5.2%). The adjusted diagnostic yields were 84.2% in the non-fluoroscopy-guided-group and 84.4% in the fluoroscopy-guided-group, with the difference of −0.2% (95% CI: −6.8% to +6.4%), confirming the non-inferiority because the lower bound was not below the pre-determined limit (−10%). In subgroup analysis with PPLs ≤30 mm, the adjusted diagnostic yields were 83.7% in the non-fluoroscopy-guided-group and 80.0% in the fluoroscopy-guided-group. The difference in the diagnostic yield was 3.8% (95% CI: −6.3%, 13.9%). Furthermore, when only cases confirmed by surgery were defined as diagnostic non-specific inflammation, the diagnostic yields in non-fluoroscopy-guided-group (74.1%, 157 of 212; adjusted yield: 74.1%) were also non-inferior to fluoroscopy-guided-group (71.0%, 152 of 214; adjusted yield: 71.0%), with the adjusted difference of 3.1% (95% CI: −3.6%, 9.8%; crude difference: 3.0%).

The bronchoscopic diagnostic yields are shown in Table 4. Lesion nature, bronchus sign, rEBUS positioning, and lesion size (>20 mm vs. ≤20 mm) were valuable diagnostic predictors. In the non-fluoroscopy-guided-group, the univariate analyses revealed that higher diagnostic yield was associated with rEBUS positioning within the PPL, a bronchus leading to the PPL, the lesion being malignant in nature. In the fluoroscopy-guided-group, rEBUS positioning was significantly associated with diagnostic yield, which was also associated with lesions located in the right upper lobe and left upper segment, lesion size (>20 mm), and a bronchus leading to the PPL (Table 4).

The associations of quantitative parameters with diagnostic yield are shown in Table S1 in the Supporting Information. The diagnosed cases had significantly larger average lesion size and shorter rEBUS time when compared to the undiagnosed cases.

The multivariate analysis identified bronchus sign and lesion nature as independent diagnostic predictors in the non-fluoroscopy-guided-group (Table 5). In the fluoroscopy-guided-group, lesion location, and lesion size were independent diagnostic predictors. Among all patients, lesion nature, lesion size, and bronchus sign were independent diagnostic predictors.

Complications

Moderate bleeding was observed for three patients in the fluoroscopy-guided-group and four patients in the

TABLE 2 Procedures details

	Non-fluoroscopy-guided ($N = 212$)	Fluoroscopy-guided ($N = 214$)	*p* value	Total ($N = 426$)
Anaesthesia, *n* (%)				
Local	116 (54.7)	102 (47.7)	0.38	218 (51.2)
Local + sedation	32 (15.1)	32 (15.0)		64 (15.0)
General	64 (30.2)	80 (37.4)		144 (33.8)
Bronchoscopes, *n* (%)				
BF-P260F	135 (63.7)	134 (62.6)	0.84	269 (63.1)
BF-P290	77 (36.3)	80 (37.4)		157 (36.9)
rEBUS position, *n* (%)				
Within	174 (82.1)	178 (83.2)	0.97	352 (82.6)
Adjacent to	35 (16.5)	33 (15.4)		68 (16.0)
Outside	3 (1.4)	3 (1.4)		6 (1.4)
Number of specimens (IQR), *n*	6.0 (5.0–7.0)	6.0 (5.0–7.0)	0.87[a]	6.0 (5.0–7.0)
rEBUS time(IQR), s	130.5 (80.3–223.5)	151.0 (92.0–253.0)	0.052[a]	140.0 (87.0–239.0)
GS time(IQR), s	578.5 (424.3–909.8)	666.0 (455.3–1059.3)	0.06[a]	620.5 (436.8–996.3)
Total operation time (IQR), s	1005.0 (731.8–1514.5)	1061.5 (747.0–1580.3)	0.16[a]	1030.0 (741.0–1552.5)

Abbreviations: GS, guide sheath; IQR, interquartile range; rEBUS, radial endobronchial ultrasound.
[a]Mann–Whitney test.

TABLE 3 Bronchoscopic findings and final diagnoses

	Non-fluoroscopy-guided	Fluoroscopy-guided	Total
Diagnosed by bronchoscopy[a]	178	181	359
Malignant	150	150	300
Lung cancer	150	147	297
Ad	111	125	236
Sq	17	10	27
NSCLC-NOS	8	6	14
SCLC	8	2	10
Undifferentiated	6	4	10
Metastatic carcinoma	0	3	3
Benign	28	31	59
Inflammation	22	29	51
Tuberculosis	5	2	7
Aspergillosis	1	0	1
Undiagnosed by bronchoscopy[b]	34	33	67
Malignant	21	23	44
Lung cancer	20	22	42
Ad	10	15	25
Sq	1	1	2
SCLC	1	1	2
Adenosquamous carcinoma	1	0	1
Undifferentiated	7	5	12
Mesothelioma	1	0	1
Metastatic carcinoma	0	1	1
Benign	13	10	23
Inflammation	10	8	18
Tuberculosis	3	1	4
Aspergillosis	0	1	1
Total	212	214	426

Abbreviations: Ad, adenocarcinoma; NSCLC-NOS, non-small cell lung cancer not otherwise specified; SCLC, small cell lung cancer; Sq, squamous cell carcinoma.
[a]For lesions with non-specific inflammation, only if the lesions were further confirmed by surgery or the lesions demonstrated at least 2 years of stability or resolution on repeat CT imaging, they were considered to be successfully diagnosed by bronchoscopy.
[b]The 67 bronchoscopically undiagnosed lesions were evaluated via surgery (20 lesions), repeat biopsy (22 lesions, bronchoscopy or transthoracic needle aspiration), and clinical follow-up (25 lesions).

non-fluoroscopy-guided-group. No severe bleeding, pneumothorax or other complications were observed.

DISCUSSION

Combining VBN with rEBUS-GS reportedly improves biopsy accuracy and shortens the procedure time.[9,23] This study compared the diagnostic yields of VBN-rEBUS-GS-guided bronchoscopy with VBN-rEBUS-GS-fluoroscopy-guided bronchoscospy (84.0% vs. 84.6%) and confirmed its non-inferiority. In subgroup analysis with PPLs ≤30 mm, the results were also confirmed. These results were comparable or superior to those from previous studies of VBN-rEBUS-GS without fluoroscopy.[14–16] This could be related to the present study including substantial proportions of relatively large lesions (>30 mm, 53.3%), within two-third from hilum (66.9%) and malignant lesions (80.8%).[6,7,24] In addition, the substantial proportions of the bronchus leading to the PPL (89.0%) and rEBUS positioning within the PPL (82.6%) might help explain the diagnostic yields.[7,8,13,20]

Fluoroscopy is helpful throughout the entire transbronchial sampling process, including guiding the bronchoscope, confirming the lesion, and monitoring sample collection. VBN can substitute for fluoroscopic guidance to some extent, especially for fluoroscopically invisible lesions.[9,14,25] It can reconstruct an average of 6 generations of virtual bronchi, and help navigate the bronchoscope along the biopsy route.[26] Thin bronchoscopes are also very important for better lesion access, as these devices can be advanced on average up to the 4th generation of bronchial division.[27] When the targeted bronchus cannot be reached using thin bronchoscopes, the GS can also serve as an extending working channel for reliable delivery of biopsy instruments. In the non-fluoroscopy-guided-group, we observed a bronchus leading to the PPL for 88.7% of cases and a bronchus adjacent to the PPL for 11.3% of cases. During the bronchoscopy, 82.1% of cases had rEBUS positioning within the PPL, 16.5% had probe positioning adjacent to the PPL, and only 1.4% had probe positioning outside the PPL. The good agreement between the presentation of the bronchus sign and the rEBUS positioning indicates that most bronchoscopes were successfully navigated to the target location using VBN non-fluoroscopy-guided-group.

The rEBUS was used to confirm the lesion site, which is particularly useful when the lesion is too small for fluoroscopic visualization.[5] Furthermore, rEBUS positioning is reportedly an important diagnostic predictor.[8] We also observed that bronchus leading to the PPL provided a significantly higher diagnostic yield compared with lesions adjacent to the bronchus. That's probably because the lesions adjacent to the rEBUS were eccentrically attached to the bronchus, and the bronchoscope tip needs to be angled for successful sampling. In cases without fluoroscopic guidance, VBN and pre-reviewed thin-slice CT, which provided positional information between the PPL and the current arrival bronchus, were used to guide the biopsy. The rEBUS was guided with the bronchoscope tip to the point where the lesion appears at its largest and clearest and the sampling was performed at the same point. Our results suggest that VBN and rEBUS-GS can effectively guide transbronchial sampling of PPLs with involved bronchus, and fluoroscopy is not indispensable in these special kinds of lesions.

Although the biopsy instruments can be accurately delivered via the GS, fluoroscopy remains indispensable for monitoring the forceps status, for example, insufficient opening of biopsy forceps may lead to an inadequate specimen.[15] Moreover, small changes in the GS position

TABLE 4 Diagnostic yield of bronchoscopy by categorical parameters

Variable	Non-fluoroscopy guided (%)		Fluoroscopy guided (%)			Adjusted	Total (%)	
	Diagnostic yield	*p* value	Diagnostic yield	*p* value	*p* value	*p* value	Diagnostic yield	*p* value
Lesion size								
>30 mm	85.0 (96/113)	0.67	87.7 (100/114)	0.17	0.54	0.45[a]	86.3 (196/227)	0.21
≤30 mm	82.8 (82/99)		81.0 (81/100)		0.74	0.46[a]	81.9 (163/199)	
Lesion size								
>20 mm	86.0 (154/179)	0.06	87.3 (151/173)	0.02	0.73	0.76[a]	86.6 (305/352)	0.003
≤20 mm	72.7 (24/33)		73.2 (30/41)		0.97	0.91[a]	73.0 (54/74)	
Lesion size								
≤20 mm	72.7 (24/33)	0.54	73.2 (30/41)	0.3	0.97	0.91	73.0 (54/74)	0.10
≤30 >20 mm	87.9 (58/66)		86.4 (51/59)		0.81	0.47	87.2 (109/125)	
≤40 >30 mm	85.0 (51/60)		86.8 (59/68)		0.77	0.59	85.9 (110/128)	
≤50 >40 mm	83.8 (31/37)		86.8 (33/38)		0.71	0.61	85.3 (64/75)	
≤60 >50 mm	88.9 (8/9)		100.0 (5/5)		1 (F)[b]		92.9 (13/14)	
>60 mm	85.7 (6/7)		100.0 (3/3)		1 (F)[b]		90.0 (9/10)	
Lesion nature								
Malignant	87.7 (150/171)	0.002	86.7 (150/173)	0.08	0.78	0.78[c]	87.2 (300/344)	<0.001
Benign	68.3 (28/41)		75.6 (31/41)		0.46	0.74[c]	72.0 (59/82)	
Bronchus sign								
Leading to	87.8 (165/188)	<0.001	86.4 (165/191)	0.03	0.69	0.67[d]	87.1 (330/379)	<0.001
Adjacent to	54.2 (13/24)		69.6 (16/23)		0.28	0.27[d]	61.7 (29/47)	
rEBUS position								
Within	89.1 (155/174)	<0.001	89.9 (160/178)	<0.001	0.80	0.81[c]	89.5 (315/352)	<0.001
Adjacent to	62.9 (22/35)		57.6 (19/33)		0.66	0.99[c]	60.3 (41/68)	
Outside	33.3 (1/3)		66.7 (2/3)		1 (F)[b]		50.0 (3/6)	
Lesion location								
RUL + LUS	81.8 (72/88)	0.47	91.5 (97/106)	0.005	0.04	0.03[c]	87.1 (169/194)	0.14
Others	85.5 (106/124)		77.8 (84/108)		0.13	0.07[c]	81.9 (190/232)	
Lesion location								
LUS + RUL	81.8 (72/88)	0.37	91.5 (97/106)	0.02	0.04	0.03[c]	87.1 (169/194)	0.18
LLS + RML	90.9 (40/44)		77.8 (21/27)		0.12	0.17[c]	85.9 (61/71)	
LLL + RLL	82.5 (66/80)		77.8 (63/81)		0.45	0.28[c]	80.1 (129/161)	
Distance to the hilum								
Central	87.5 (28/32)	0.49	75.0 (21/28)	0.30	0.21	0.17[e]	81.7 (49/60)	0.5
Intermediate	85.6 (95/111)		86.8 (99/114)		0.78	0.85[e]	86.2 (194/225)	
Peripheral	79.7 (55/69)		84.7 (61/72)		0.44	0.45[e]	82.3 (116/141)	
Total	84.0 (178/212)		84.6 (181/214)		0.86	0.95[c]	84.3 (359/426)	

Abbreviations: LLL, left lower lobe; LLS, left lingular segment; LUS, left upper segment; rEBUS, radial endobronchial ultrasound; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

[a]Adjusted for centre, bronchus sign, distance to the hilum.

[b]Fisher exact, unadjusted.

[c]Adjusted for centre, lesion size, bronchus sign, distance to the hilum.

[d]Adjusted for centre, lesion size, distance to the hilum.

[e]Adjusted for centre, lesion size, bronchus sign.

cannot be readily evaluated without fluoroscopy, and small deviations could be relevant when sampling small lesions. Thus, acquisition of adequate specimens was mainly determined by the bronchoscopists' experience and visual evaluation of sample in the non-fluoroscopy-guided-group.[28]

Presence of a bronchus leading to or adjacent to the lesion was enrolled in the study, which was similar to previous studies.[29–32] Studies showed that the diagnostic yield of no bronchus detection in relation to the lesion is low using traditional method of transbronchial lung biopsy, which needs to use transbronchial needle aspiration (TBNA) with

TABLE 5 Multivariate analyses of predictors associated with the diagnostic yield

Variable	Non-fluoroscopy-guided		Fluoroscopy-guided		Total	
	p value	Exp (95% CI)	*p* value	Exp (95% CI)	*p* value	Exp (95% CI)
Group (non-fluoroscopy-guided vs. fluoroscopy-guided)					0.92	0.97 (0.55–1.72)
Center	0.055		0.62		0.07	
Center 1	Ref		Ref		Ref	
Center 2	0.06	0.21 (0.04–1.05)	0.48	0.50 (0.08–3.37)	0.10	0.37 (0.12–1.19)
Center 3	0.37	2.18 (0.39–12.11)	0.63	1.46 (0.31–6.84)	0.29	1.82 (0.60–5.47)
Bronchus sign (leading to vs. adjacent to)	0.003	5.80 (1.83–18.35)	0.72	1.25 (0.37–4.19)	0.02	2.52 (1.16–5.48)
Lesion size (>20 mm vs. ≤20 mm)	0.12	2.50 (0.79–7.98)	0.01	3.71 (1.35–10.22)	0.01	2.53 (1.24–5.19)
Lesion location (RUL + LUS vs. others)	0.07	0.45 (0.19–1.08)	0.001	4.49 (1.78–11.29)	0.23	1.44 (0.80–2.59)
Distance to the hilum	0.23		0.30		0.47	
Central	Ref		Ref		Ref	
Intermediate	0.67	0.76 (0.21–2.75)	0.14	2.29 (0.76–6.90)	0.34	1.48 (0.66–3.31)
Peripheral	0.16	0.37 (0.09–1.46)	0.18	2.32 (0.68–7.97)	0.91	1.05 (0.45–2.48)
Anaesthesia (local ± sedation vs. general)	0.46	1.51 (0.51–4.47)	0.45	1.68 (0.44–6.40)	0.36	1.46 (0.65–3.29)
Bronchoscopes (BF-P260F vs. BF-P290)	0.22	0.49 (0.15–1.55)	0.63	1.38 (0.37–5.14)	0.75	0.88 (0.38–1.99)
Lesion nature (malignant vs. benign)	0.02	3.20 (1.22–8.39)	0.11	2.46 (0.82–7.41)	0.007	2.61 (1.30–5.22)

Abbreviations: LUS, left upper segment; Ref, reference; RUL, right upper lobe.

the guidance of fluoroscopy to improve the diagnostic yield.[33,34] Subjects were randomized into bronchoscopy procedures with or without fluoroscopy, however, it may be unsafe to conduct TBNA without fluoroscopy guidance. Therefore, we did not enrol subjects with no bronchus detection in relation to the lesion. It is true that the diagnostic difference between with and without fluoroscopy groups may be reduced when removing these cases. Moreover, multivariate analysis showed that bronchus sign was the predictive factor of diagnostic yield in the non-fluoroscopy group, which was similar to the meta-analysis,[35] indicating that VBN-EBUS-GS was more suitable for lesions with bronchus leading to in case of diagnosis without fluoroscopy.

The PPL's properties affect diagnostic yield, as benign PPLs usually have lower diagnostic yield than malignant lesions.[11] Benign lesions are typically more scattered and heterogeneous, which makes it difficult to collect specific tissue samples. Another factor is that specific characteristics of benign lesions are rarely identified during cytological evaluations, meanwhile some benign lesions can display atypical cells that may be considered malignant.[36]

This trial has several limitations. First, the procedures were performed by experienced bronchoscopists, and similar results may not be achieved by less experienced staff. Second, although the diagnostic yield of VBN guided bronchoscopy with or without fluoroscopy was comparable, we cannot conclude that fluoroscopy can be omitted for challenging PPLs since lesions enrolled in the study were relatively large (more than half were >30 mm and by size definition not pulmonary nodules), proximal to the hilum, and had a high proportion of positive bronchus sign. All of these factors would account for the high diagnostic yield of both groups and also possibly contribute to the non-inferiority result. Third, we did not use guiding curettes and TBNA, however, fluoroscopy may be necessary when such tools are needed for diagnosis. Fourth, not all nonspecific inflammations were verified by surgery. The diagnostic yield may have been overestimated although these patients were followed-up for at least 2 years. The results of the study may not be generalized to lesions with presumably benign lesions due to the limited sample size. Further randomized trials are necessary to clarify these issues.

In conclusion, VBN and rEBUS-GS combined with a thin bronchoscope but not fluoroscopy was an effective diagnostic method that was non-inferior to fluoroscopy-guided bronchoscopy for the diagnosis of PPLs suspicious of malignancy and presence of a bronchus leading to or adjacent to lesions, especially for bronchus leading to and malignant lesions. Furthermore, this strategy did not prolong the total procedure time or induce more complications.

AUTHOR CONTRIBUTION

Xiaoxuan Zheng: Data curation (equal); formal analysis (equal); investigation (lead); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (supporting). **Changhao Zhong:** Data curation (equal); formal analysis (equal); investigation (equal); project administration (equal); writing – review and editing (equal). **Fangfang Xie:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Shiyue Li:** Conceptualization (equal); project administration (equal); supervision (supporting); writing – review and editing (supporting). **Guiqi Wang:** Conceptualization (equal); supervision (supporting); writing – review and

editing (supporting). **Lei Zhang:** Data curation (equal); formal analysis (equal); investigation (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Jiayuan Sun:** Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (equal); methodology (lead); project administration (lead); resources (lead); supervision (lead); writing – original draft (lead); writing – review and editing (lead).

ACKNOWLEDGEMENTS

We thank all colleagues, research assistants, respiratory physicians involved and those supporting this study.

Research funding: This work was supported by National Multi-disciplinary Treatment Project for Major Diseases (2020NMDTP), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20181815).

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The study protocol is available from ClinicalTrials.gov (NCT02484066). Data are available from the corresponding author upon reasonable request.

HUMAN ETHICS APPROVAL DECLARATION

The clinical trial protocol was approved by the ethics committee of each participating hospital (KS1844). Informed patient consents were obtained from every participant.

Clinical Trial Registration: NCT02484066 at www.clinicaltrials.gov

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zheng X, Zhong C, Xie F, Li S, Wang G, Zhang L, et al. Virtual bronchoscopic navigation and endobronchial ultrasound with a guide sheath without fluoroscopy for diagnosing peripheral pulmonary lesions with a bronchus leading to or adjacent to the lesion: A randomized non-inferiority trial. Respirology. 2022. https://doi.org/10.1111/resp.14405