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Original research

Novel electromagnetic navigation bronchoscopy system for the diagnosis of peripheral pulmonary nodules: a prospective, multicentre study

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ABSTRACT

Background Traditional electromagnetic navigation bronchoscopy (ENB) is a real-time image-guided system and used with thick bronchoscopes for the diagnosis of peripheral pulmonary nodules (PPNs). A novel ENB that could be used with thin bronchoscopes was developed. This study aimed to evaluate the diagnostic yield and the experience of using this ENB system in a real clinical scenario.

Methods This multicentre study enrolled consecutive patients with PPNs adopting ENB from March 2019 to August 2021. ENB was performed with different bronchoscopes, ancillary techniques and sampling instruments according to the characteristics of the nodule and the judgement of the operator. The primary endpoint was the diagnostic yield. The secondary endpoints included the diagnostic yield of subgroups, procedural details and complication rate.

Results In total, 479 patients with 479 nodules were enrolled in this study. The median lesion size was 20.9 (IQR, 15.9–25.9) mm. The overall diagnostic yield was 74.9% (359/479). A thin bronchoscope was used in 96.2% (461/479) nodules. ENB in combination with radial endobronchial ultrasound (rEBUS), a guide sheath (GS) and a thin bronchoscope was the most widely used guided method, producing a diagnostic yield of 74.1% (254/343). The median total procedural time was 1325.0 (IQR, 1014.0–1676.0) s. No severe complications occurred.

Conclusion This novel ENB system can be used in combination with different bronchoscopes, ancillary techniques and sampling instruments with a high diagnostic yield and safety profile for the diagnosis of PPNs, of which the combination of thin bronchoscope, rEBUS and GS was the most common method in clinical practice.

Trial registration number NCT03716284.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Electromagnetic navigation bronchoscopy (ENB) has been shown to improve the diagnostic yield of peripheral bronchoscopy, with yield estimates of 65%–73%. Most data, however, have been collected in well-designed clinical trials.

WHAT THIS STUDY ADDS

⇒ We describe the utility of a novel ENB system in clinical practice, demonstrating comparable results to previous ENB studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The novel ENB system used with a thin bronchoscope can obtain a high diagnostic yield and safety profile in combination with different ancillary techniques and sampling instruments for the diagnosis of peripheral pulmonary nodules.

INTRODUCTION

The evaluation of indeterminate pulmonary nodules remains a difficult problem in clinical practice. Although transthoracic needle aspiration (TTNA) exhibits outstanding sensitivity for peripheral pulmonary lesions (PPLs), it is far from optimal because of its high complication rates, especially when puncturing deep lesions located in proximity to the hilum, lesions for which the needle must traverse fissures or lesions surrounded by emphysema.[1–3] It does not offer any staging and is associated with increased risk of ipsilateral pleural metastasis.[4] Conventional bronchoscopy is a less invasive approach for the diagnosis of PPLs because it accesses the nodules through the natural bronchial lumen, thus inducing fewer complications such as pneumothorax; however, it is limited by its low diagnostic yield.[5] The suboptimal diagnostic performance of conventional bronchoscopy for PPLs has led to the development of advanced techniques, such as radial endobronchial ultrasound (rEBUS), virtual bronchoscopic navigation (VBN) and electromagnetic navigation bronchoscopy (ENB). The diagnostic efficacy of advanced bronchoscopy platforms for PPLs has thus vastly improved, and the operation time has been reduced.[6–9]

ENB has been used to sample PPLs for more than 10 years.[10] A recent meta-analysis of ENB revealed a pooled sensitivity of 0.77 for lung cancer diagnosis.[11] ENB is recommended as an alternative option when lesions are difficult to reach with conventional bronchoscopy.[2] However, most of these data were obtained from well-designed clinical trials involving select patients. The generalisability of these results to clinical practice requires further exploration. Folch *et al* conducted a large-scale real-world study demonstrated that the overall

diagnostic yield was 73% of the superDimension ENB system with 12-month follow-up.[12]

In this study, we introduced a novel ENB system with a 1.45 mm diameter thin locatable wire (LW) that can be used in combination with a thin bronchoscope as well as thick and ultrathin bronchoscopes, providing a variety of nodule sampling approaches.[13] We have conducted a randomised study on the diagnosis of peripheral pulmonary nodules (PPNs) using this ENB system. The diagnostic yields with and without ENB were 82.9% and 73.4%, respectively, demonstrating its diagnostic value.[14] To further evaluate its diagnostic performance in a real clinical scenario, we carried out a multicentre study to assess the diagnostic yield, application strategies, clinicians' operational preferences and other relevant factors of using this ENB system for the diagnosis of PPNs among a Chinese population.

STUDY DESIGN AND METHODS

Participants

Consecutive patients were recruited at six clinical centres throughout China (online supplemental e-Table 1). The inclusion criteria were an age of >18 years; PPNs with suspicion of malignancy, in need of non-surgical biopsy and with a long diameter of >8 to ≤30 mm; no contraindications to bronchoscopy; and provision of written informed consent. A PPN was defined as a lesion with a diameter of ≤30 mm located beyond the segmental bronchus and not visible by standard bronchoscopy.[15] The lesion size was defined as the longest diameter on the largest cross section of the CT lung window.[16] The exclusion criteria were concomitant endobronchial lesions observed during bronchoscopy and severe cardiopulmonary dysfunction and other contraindications for bronchoscopy. For patients with multiple nodules, only one major lesion meeting the criteria was included in the study. The study is registered at ClinicalTrials.gov (NCT03716284), and the protocol has been previously published.[13]

Study design

This was a multicentre study to assess the using of the novel ENB system in a real clinical scenario. There were no restrictions on techniques or instruments during ENB procedure. The ENB system (figure 1) (LungCare navigation system; LungCare Medical Technologies, Suzhou, China) could be combined with a thin (BF-P260F or BF-P290; Olympus, Tokyo, Japan), standard (BF-Q290; Olympus), thick (BF-1T260 or BF-1TQ290; Olympus) or ultrathin (BF-MP290F; Olympus) bronchoscope. Ancillary instruments including rEBUS device (UM-S20-17S or UM-S20-20R; Olympus), guide sheath (GS) (SG-200C or SG-201C; Olympus or LK-NK-YSQG-95; LungCare Medical Technologies), fluoroscopic unit and rapid on-site evaluation (ROSE) system could also be used during ENB procedure. The sampling instruments used to obtain histological specimens included biopsy forceps (FB-233D or FB-231D; Olympus and LK-NK-HJQ-P; LungCare Medical Technologies), cryoprobe (1.9 or 1.1 mm; Erbe, Tübingen, Germany). Brushing (BC-204D-2010 or BC-202D-2010; Olympus and LK-NK-XBS-P; LungCare Medical Technologies), transbronchial needle (NA-1C/2C-1; Olympus) or washing were conducted to obtain cytological samples. Bronchial lavage with 20 mL of saline was performed when the nodule was considered infected and in need of microbiological examination. All operators were experienced in transbronchial lung biopsy (TBLB) (>100 cases) and had performed at least five procedures using this ENB system prior to this study. Lung cancer staging could be performed using linear endobronchial ultrasound for patients with intrathoracic adenopathy after the ENB procedure if needed, but the pathological results were independently evaluated and not counted as the diagnostic results of the ENB procedure.

Endpoints

The primary endpoint was the overall diagnostic yield, defined as all instances in which the diagnostic results of the ENB procedure matched the final diagnosis divided by the total ENB

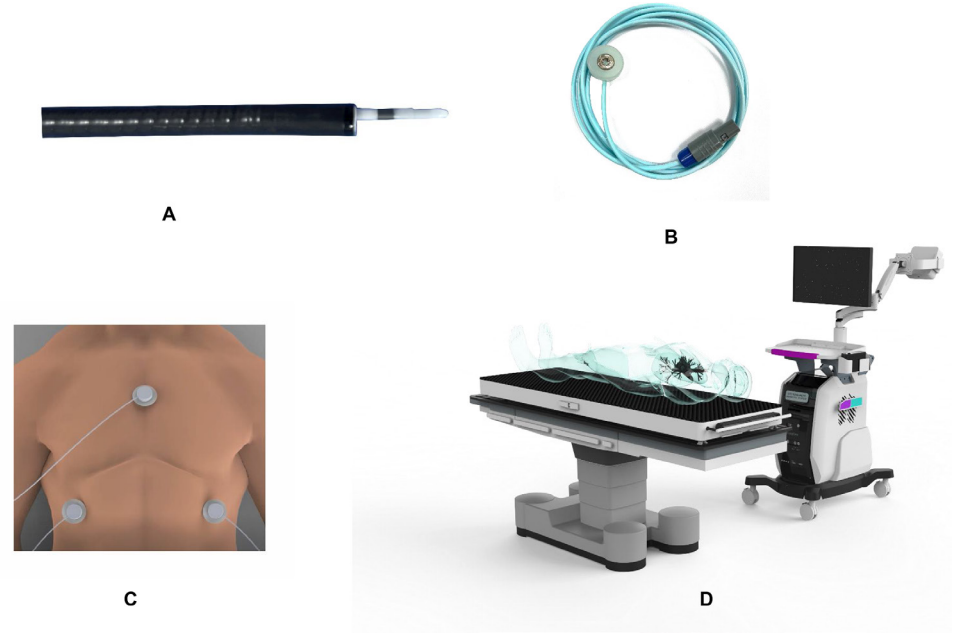

Figure 1 Bronchoscope and ENB system. (A) The position of bronchoscope (outer diameter 4.2 mm with a 2 mm working channel), guide sheath (1.95 mm) and locatable wire (1.45 mm diameter). (B) Body position detector. (C) Respiratory gating sensors. (D) ENB system. ENB, electromagnetic navigation bronchoscopy.

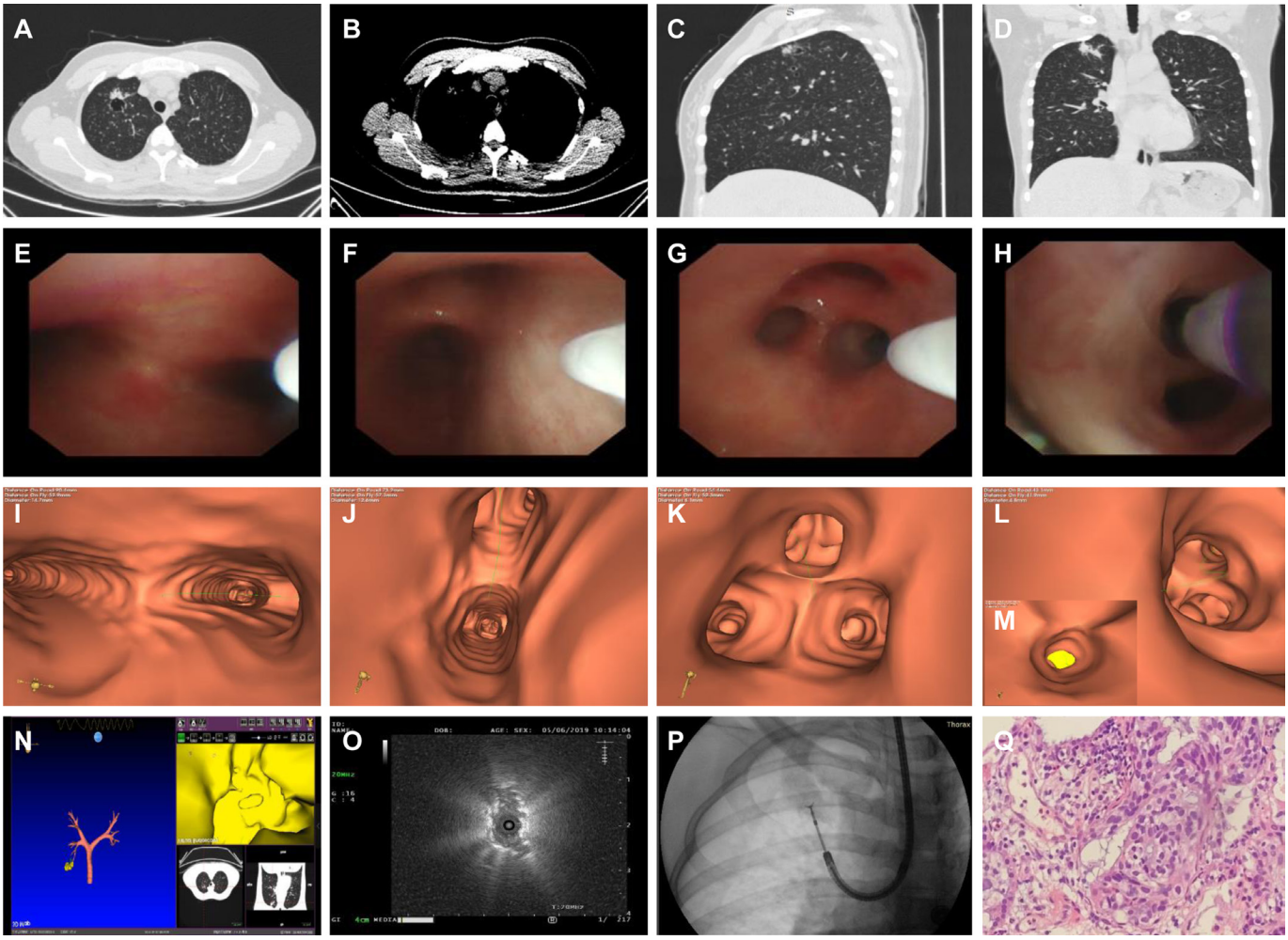

Figure 2 A representative case of ENB in combination with rEBUS and a GS using a thin bronchoscope with fluoroscopy for the diagnosis of a PPN. (A–D) CT scan of the chest showed a PPN in the right upper lobe with a long diameter of 16.6 mm in the axial plane. (E–H) White light bronchoscopy images. (I–L) Corresponding ENB images. (M) Target bronchus leading to the nodule (yellow) as shown by the ENB system. (N) The panel of the ENB system when the locatable wire reached the nodule (yellow). (O) The rEBUS probe confirmed the nodule. (P) Biopsy under fluoroscopy. (Q) The pathological examination revealed adenocarcinoma (200× magnification). ENB, electromagnetic navigation bronchoscopy; GS, guide sheath; PPN, peripheral pulmonary nodule; rEBUS, radial endobronchial ultrasound.

procedures analysed, described as the method 2 by Vachani *et al*.[17] A lesion was considered malignant if tumour cells were identified in the histological and/or cytological specimens. A lesion was considered benign if the pathological evaluation revealed specific benign characteristics and/or positive microbiological results. Lesions with non-specific inflammation were considered successfully diagnosed by bronchoscopy only if they were further confirmed by subsequent surgery or demonstrated at least 1 year of stability or resolution on repeat CT imaging. Non-diagnostic results of bronchoscopy, regardless of whether the follow-up results are benign or malignant, are not included in the numerator of the diagnostic yield calculation. At least 1 year of follow-up, including repeat bronchoscopy, TTNA, surgery, clinical and imaging follow-up or therapeutic response evaluation, was conducted to determine the final diagnosis for lesions with non-diagnostic results or benign pathology.

The secondary endpoints were the diagnostic yields for malignant and benign diseases; the diagnostic yields of different guided bronchoscopy techniques; factors affecting the diagnostic yield; procedural details including the registration time, navigation time, time for finding lesions, total procedural time, visibility rate with rEBUS and usage rate of fluoroscopy; the sensitivity, specificity, positive predictive value and negative predictive value for malignancy; and the complication rate. The definitions of registration time, time for finding lesions, total procedural time, visibility rate with rEBUS and usage rate of fluoroscopy are shown in online supplemental e-Appendix 1. The safety endpoint was procedural complications, such as pneumothorax, bleeding and pneumonia, graded by the Common Terminology Criteria for Adverse Events V.4.0.[18]

Sample size

Sample size was calculated by the primary endpoint. According to the relevant literature and expert experience, the diagnostic yield should not be lower than 73%,[12 19] and the expected diagnostic yield of the test group was 80% for PPNs suspicious of malignancy. Thus, a sample size of 297 cases was needed at 80% power and with a one-sided α of 0.025. A final sample size of no less than 471 cases should be included, considering the estimated malignant proportion of 70% and the drop out of 10%.

ENB procedure

Similar to the principle of traditional ENB, but the novel ENB system can be used with a thin LW and a thin bronchoscope

Table 1 Baseline characteristics

	Total (N=479)
Age, years	65 (57–71)
Sex	
Male	261 (54.5%)
Female	218 (45.5%)
Smoking	
Yes	137 (28.6%)
No	342 (71.4%)
Lesion size	
>8 to ≤20 mm	226 (47.2%)
>20 to ≤30 mm	253 (52.8%)
Lobar location	
Left lower lobe	64 (13.4%)
Left lingular segment	22 (4.6%)
Left upper segment	101 (21.1%)
Right lower lobe	67 (14.0%)
Right middle lobe	50 (10.4%)
Right upper lobe	175 (36.5%)
Lesion density	
Solid	386 (80.6%)
Mixed ground-glass opacity	80 (16.7%)
Pure ground-glass opacity	13 (2.7%)
CT bronchus sign*	
Leading to	394 (82.3%)
Adjacent to	61 (12.7%)
Outside	24 (5.0%)
Distance to the hilum	
Central	71 (14.8%)
Intermediate	236 (49.3%)
Peripheral	172 (35.9%)
Emphysema	
Yes	91† (19.0%)
No	388 (81.0%)
Distance to the costal pleura, mm	13.6 (0–24.0)

Data are presented as median (IQR) or numbers (%).
*Lesions were categorised based on the nearest bronchus using thin-slice CT scans: leading to referred that the bronchus clearly reached the inside of the target nodule, adjacent to referred that the bronchus was adjacent to the target nodule, outside referred that no bronchus could be detected in relation to the nodule.
†18 cases were chronic obstructive pulmonary disease.

Table 2 Procedural details

	Total (N=479)
Anaesthesia type	
General anaesthesia	371 (77.5%)
Local anaesthesia with or without moderate sedation	108* (22.5%)
Bronchoscope	
Thick	6 (1.3%)
Thin	463† (96.7%)
Ultrathin	10 (2.1%)
rEBUS	
UM-S20-17S	476 (99.4%)
UM-S20-20R	3 (0.6%)
Guide sheath	
K201	438‡ (91.4%)
K203	4 (0.8%)
Unemployed	37 (7.7%)
rEBUS position	
Within	359 (74.9%)
Adjacent to	113 (23.6%)
Outside	7 (1.5%)
Fluoroscopy	
Visible	96 (20.0%)
Invisible	30 (6.3%)
Unemployed	353 (73.7%)
Sampling methods	
Brushing	466 (97.3%)
Washing	389 (81.2%)
Forceps biopsy	460 (96.0%)
Bronchial lavage	70 (14.6%)
Cryobiopsy	26 (5.5%)
1.9 mm diameter	8 (1.7%)
1.1 mm diameter	18 (3.8%)
Transbronchial needle aspiration	4 (0.8%)
Rapid on-site evaluation	
Employed	213 (44.5%)
Unemployed	266 (55.5%)
Registration time, s	34.0§ (26.0–47.0)
Navigation time, s	126.0¶ (83.0–194.0)
Time for finding lesions, s	261.0** (187.3–368.0)
Total procedural time, s	1325.0†† (1014.0–1676.0)

Data are presented as median (IQR) or numbers (%).
*Three nodules were performed under local anaesthesia with moderate sedation.
†Two cases used standard bronchoscope (BF-Q290).
‡Including 17 cases using LK20C that had the same specification with K201.
§Missing data in 20 cases.
¶Missing data in 22 cases.
**Missing data in 83 cases.
††Missing data in 83 cases.
rEBUS, radial endobronchial ultrasound.

to reach more distal bronchus. The operator manoeuvres the thin bronchoscope to the target as closer as possible under direct vision, similar to VBN but with real-time guidance. An LW covered with a GS could be manoeuvred further to the target per the direction indicated by the ENB system for invisible distal bronchus.

In the planning phase, thin-slice CT scan data of the chest in standard format was imported into the ENB system to reconstruct a three-dimensional virtual airway roadmap. White light bronchoscopy was conducted before registration to exclude concomitant endobronchial lesions. In the navigation phase, the LW (either covered with the GS or uncovered) was introduced via the bronchoscope's working channel to show the real-time positional information of the LW tip detected within an electromagnetic field. The operator introduced the bronchoscope to the target per the real-time guidance of the airway roadmap. After arriving at the

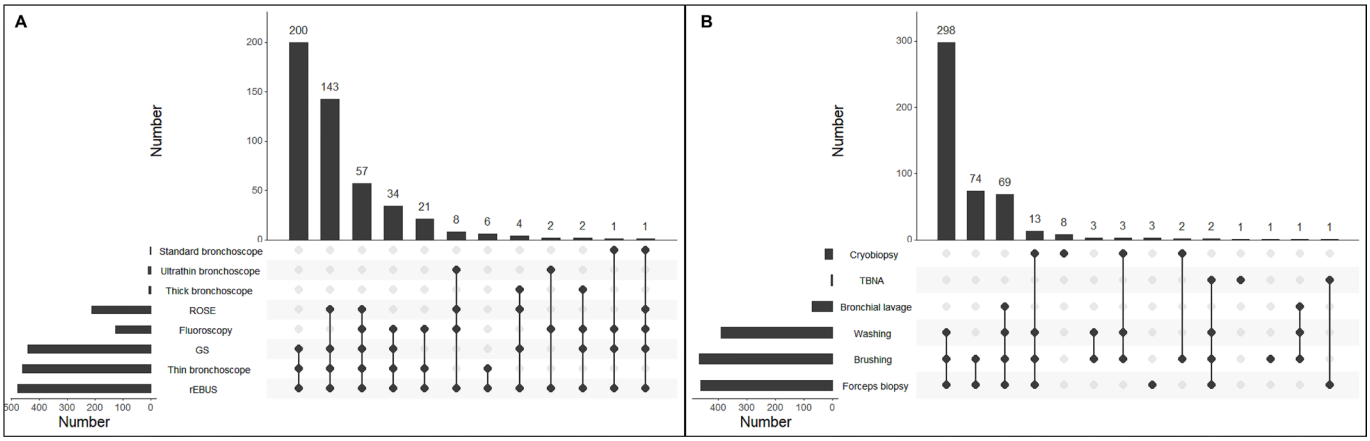

Figure 3 Tools used during the electromagnetic navigation bronchoscopy procedure in the present study. (A) Bronchoscopes and auxiliary tools used. (B) Sampling methods used. Side bar represents the number of patients in whom a certain tool was used. Top bar represents the number of patients in whom the combined tools or a single tool alone was used. GS, guide sheath; rEBUS, radial endobronchial ultrasound; ROSE, rapid on-site evaluation; TBNA, transbronchial needle aspiration.

target, the LW was withdrawn, and the rEBUS probe was inserted into the GS or working channel to confirm the lesion. The location of the probe in relation to the lesion as confirmed by rEBUS was defined as within (concentric view), adjacent to (eccentric view) or outside the lesion (invisible view).[20 21] In the sampling phase, sampling instruments were introduced via the GS or working channel to obtain samples. All tools used and the number of sampled specimens were determined by the operator while considering factors such as the possibility of obtaining a definitive diagnosis, safety, subsequent diagnostic testing and lesion characteristics. Biopsy, brushing and washing were usually performed during the procedure. Auxiliary tools such as fluoroscopy and ROSE and other sampling methods such as transbronchial needle aspiration (TBNA), cryobiopsy and lavage were also used at the operator's discretion and access to the technology. In general, for lesions located in the distal bronchus (ie, fifth generation of bronchus or more distal), a thin bronchoscope in combination with GS or ultrathin bronchoscope was preferred. Fluoroscopy was an effective complement for lesions which were difficult to diagnose, susceptible to procedure-related complications and those underwent TBNA or cryobiopsy. ROSE was proposed if it was available to evaluate the acceptability of specimens.

Statistical analysis

The statistical analyses were performed using SPSS V.25.0. Descriptive variables are presented as number (percentage) as appropriate. The Shapiro-Wilk test was used for normality testing. Normally distributed continuous data are presented as mean±SD. Data with a skewed distribution are reported as median (IQR). Fisher's exact test or Pearson's χ^2 test was used to compare categorical variables. A t-test or Mann-Whitney U test was used to compare continuous variables. All statistically significant variables and variables considered important based on clinical practice were included in the full multivariable logistic regression model. All p values of <0.05 were considered significant.

RESULTS

In total, 483 consecutive participants were enrolled from March 2019 to August 2021, 479 patients with 479 nodules were finally analysed. Figure 2 shows a representative case. Table 1 shows the baseline characteristics of the patients and nodules. The median lesion size was 20.9 (IQR, 15.9–25.9) mm. Most nodules were located in the upper lobe (298 (62.2%)), had a bronchus leading to them (394 (82.3%)) and solid (386 (80.6%)).

Table 2 shows the procedure details. rEBUS was adopted in all cases with a visibility rate of 98.5% (472/479), among which rEBUS in combination with a GS was used in 442 (92.3%) cases. Fluoroscopy was employed in 126 (26.3%) cases; among these, cone-beam CT was used in 5 cases and fluoroscopy provided visibility in 96 (76.2%) cases. ROSE was conducted in 213 (44.5%) cases. A thin bronchoscope was the most widely used bronchoscope (461 (96.2%) cases). Of the 479 nodules, 466 (97.3%) were sampled using at least two sampling methods, and the combination of brushing, forceps biopsy and washing was the most commonly used sampling method (298 (62.2%) nodules) (figure 3). The median registration time, navigation time, time for finding lesions and total procedural time were 34.0 (IQR, 26.0–47.0) s, 126.0 (IQR, 83.0–194.0) s, 261.0 (IQR, 187.3–368.0) s and 1325.0 (IQR, 1014.0–1676.0) s, respectively.

Of the 479 nodules, ENB-aided procedures allowed for diagnosis of malignancy in 278 (58.0%) and revealed negative findings of malignancy in 201 (42.0%) (figure 4). Of these 201 nodules, 26 were specific benign, 92 were non-specific benign and 83 were non-diagnostic; 90 were false negative and 111 were true negative with 81 diagnosed by ENB. As a result, the overall diagnostic yield was 74.9% (359/479). The strict diagnostic yield (method 1) and liberal diagnostic yield (method 3) were 63.3% (303/479) and 81.2% (389/479), respectively, according to the study of Vachani *et al*.[17] The diagnostic yield for malignant and benign diseases was 75.5% (278/368) and 73.0% (81/111), respectively. The sensitivity, specificity, positive predictive value and negative predictive value for malignancy were 75.5% (278/368), 100% (111/111), 100% (278/278) and 55.2% (111/201), respectively.

ENB in combination with rEBUS, a GS and a thin bronchoscope was the most widely used guided method, producing a diagnostic yield of 74.1% (254/343) (table 3). There was a statistical difference among these guidance strategies (p=0.02). There was no statistically significant difference between nodules diagnosed with ENB–rEBUS with versus without fluoroscopy (p=0.54), with versus without GS (p=0.09).

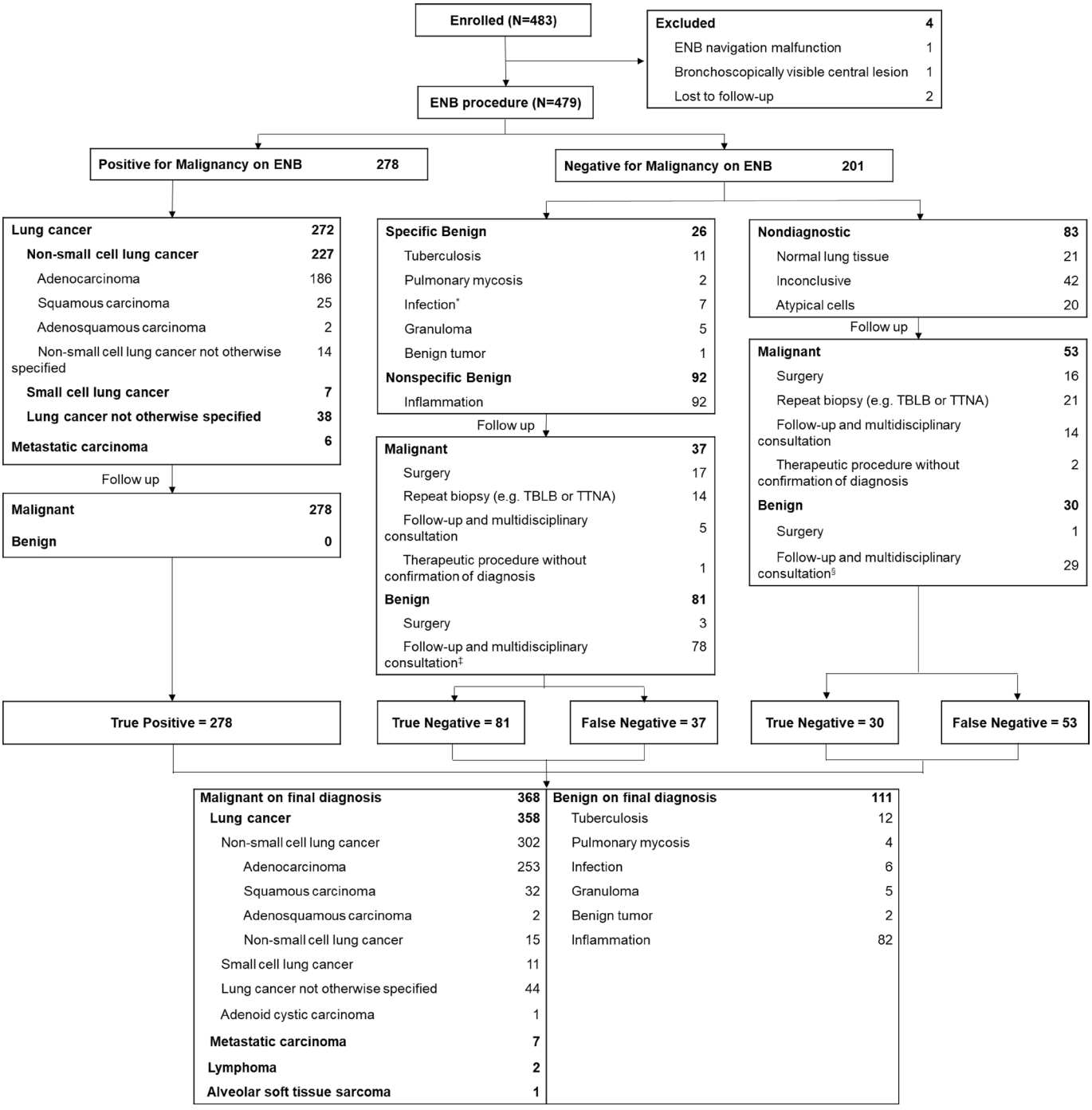

Figure 4 Details of bronchoscopic findings and final diagnosis. *One turned out to be small cell lung cancer. ‡Seven had a repeat biopsy (eg, TBLB or TTNA). §One had a repeat biopsy (eg, TBLB or TTNA). ENB, electromagnetic navigation bronchoscopy; TBLB, transbronchial lung biopsy; TTNA, transthoracic needle aspiration.

The diagnostic yields of brushing, forceps biopsy, washing, bronchial lavage, cryobiopsy and TBNA used alone for the diagnosis of PPNs were 54.5% (254/466), 67.2% (309/460), 36.8% (143/389), 14.3% (10/70), 73.1% (19/26) and 75.0% (3/4), respectively, with significant differences ($p<0.001$). When they added either sampling method separately, the diagnostic yields for PPNs were 74.5% (347/466), 75.2% (346/460), 73.0% (284/389), 68.6% (48/70), 80.8% (21/26) and 75.0% (3/4), respectively. The diagnostic yields of these combination sampling methods showed no significant differences ($p=0.81$), but they were higher than the diagnostic yield of each used alone, except for TBNA. Four patients enrolled in the current study who underwent cryobiopsy were analysed retrospectively in our previous study.[22] The diagnostic yield of the combination of brushing, forceps biopsy and washing was 74.5% (222/298).

The diagnostic yield by each clinical parameter is shown in table 4. Univariable analysis identified lesion size ($p<0.001$), lesion density ($p<0.001$), CT bronchus sign ($p<0.001$), rEBUS position ($p<0.001$) as predictors of diagnostic yield. According to the results of the univariable analysis and clinical factors, we conducted multivariable analysis and found that lesion size (>20 mm), lesion density (solid) and the CT bronchus sign

Table 3 Diagnostic yield of different guided strategy

Guided strategy	Diagnostic yield (%)	P value
ENB+rEBUS+GS+thin bronchoscope	254/343 (74.1%)	0.02
ENB+rEBUS+GS+fluoroscopy+ thin bronchoscope	70/93* (75.3%)	
ENB+rEBUS+fluoroscopy+thin bronchoscope	21/21 (100.0%)	
ENB+rEBUS+fluoroscopy+ultrathin bronchoscope	6/10† (60.0%)	
ENB+rEBUS+thin bronchoscope	5/6 (83.3%)	
ENB+rEBUS+GS+thick bronchoscope	3/4 (75.0%)	
ENB+rEBUS+GS+fluoroscopy+thick bronchoscope	0/2 (0.0%)	
Overall diagnostic yield	359/479 (74.9%)	

*Two cases used standard bronchoscope, four cases used cone-beam CT.
†One case used cone-beam CT.
ENB, electromagnetic navigation bronchoscopy; GS, guide sheath; rEBUS, radial endobronchial ultrasound.

(leading to the lesion) were relevant factors affecting the diagnostic yield (table 5).

Complications occurred in 16 (3.3%) patients, including 15 with moderate bleeding (grade 2) during bronchoscopy without further therapeutic intervention and 1 with pneumothorax that required tube drainage (grade 2). No complications were induced by TBNA or cryobiopsy.

DISCUSSION

This study was performed to evaluate the performance of a novel ENB system for the diagnosis of PPNs in clinical practice. The ENB system carries a 1.45 mm LW that can be used in combination with a thin or ultrathin bronchoscope, allowing the bronchoscope to reach the deeper bronchus and increasing the visibility of the peripheral bronchus. Under direct vision of proximal bronchus and ENB navigation in distal bronchus, it might reduce the difficulty of operation, shorten examination time and improve operational accuracy. Therefore, the approach is generalisable to operators who are familiar with TBLB, especially for operators experienced in VBN or traditional ENB. The overall diagnostic yield and sensitivity for malignancy were 74.9% and 75.2%, respectively, which were comparable with the previously published pooled ENB diagnostic yield of 73.9% and sensitivity of 71.1%–77.0%,[11 19] slightly lower than the diagnostic yield of robot bronchoscope 77%[23] and 81.7%.[24] Notably, all lesions in our study were ≤30 mm, whereas the previously published meta-analysis included lesions of >30 mm. In total, 96.2% of nodules were sampled with a thin bronchoscope. Although no significant difference was found in the diagnosis of PPNs among the different bronchoscopes, operators preferred to use this ENB system with a thin bronchoscope. The results also demonstrated that ENB with a thin bronchoscope had high diagnostic value. The GS used in combination with this ENB system did not have prefabricated bending angles, making it difficult to introduce a thick GS into tortuous and peripheral bronchus. This might be why the operators did not prefer a thick bronchoscope. Unavailability and inability to combine with a GS also limited the use of the ultrathin bronchoscope.

Multiple studies showed that the combination of ENB with other ancillary techniques improves the diagnostic yield.[25 26] However, this superiority was not always demonstrated in clinical practice.[27] Although a significant difference was found among guided strategy, the number of cases among that was unbalanced, as two of the seven guidance strategies were used in 91.0% of patients. Therefore, we failed to demonstrate that a greater combination of diagnostic methods increased the diagnostic yield. A possible explanation for this may be selection bias in this study. Clinicians tended to use multiple ancillary techniques when nodules were difficult to diagnose. Ost *et al* also reported that the diagnostic yields of ENB and rEBUS were lower than expected, even after adjustment, which might have been due to patient selection, with more difficult cases being selected for ENB and rEBUS.[28] In addition, ENB–rEBUS was used in all nodules,

Table 4 Diagnostic yield by each clinical parameter

	Diagnostic yield (%)	Univariable p value
Lesion size		
>8 to ≤20 mm	151/226 (66.8%)	<0.001
>20 to ≤30 mm	208/253 (82.2%)	
Lesion density		
Solid	305/386 (79.0%)	<0.001
Mixed ground-glass opacity	49/80 (61.3%)	
Pure ground-glass opacity	5/13 (38.5%)	
CT bronchus sign		
Leading to	314/394 (79.7%)	<0.001
Adjacent to	34/61 (55.7%)	
Outside	11/24 (45.8%)	
Distance to the hilum		
Central	56/71 (78.9%)	0.71
Intermediate	175/236 (74.2%)	
Peripheral	128/172 (74.4%)	
Distance to the pleura		
≤20 mm	239/318 (75.2%)	0.88
> 20 mm	120/161 (74.5%)	
Lobar location		
RUL+LUS	208/276 (75.4%)	0.69
RML+LLS	56/72 (77.8%)	
RLL+LLL	95/131 (72.5%)	
Lesion nature		
Malignant	278/368 (75.5%)	0.58
Benign	81/111 (73.0%)	
Anaesthesia type		
General anaesthesia	282/371 (76.0%)	0.32
Local anaesthesia with or without moderate sedation	77/108 (71.3%)	
Bronchoscope		
Thick	3/6 (50.0%)	0.19
Thin	350/463* (75.6%)	
Ultrathin	6/10 (60.0%)	
rEBUS position		
Within	293/359 (81.6%)	<0.001
Adjacent to	64/113 (56.6%)	
Outside	2/7 (28.6%)	
GS		
Yes	327/442 (74.0%)	0.09
No	32/37 (86.5%)	
Fluoroscopy		
No	262/353 (74.2%)	0.54
Yes	97/126 (77.0%)	
Rapid on-site evaluation		
Yes	166/213 (77.9%)	0.18
No	193/266 (72.6%)	

Data are presented as numbers with positive result/numbers examined (%).
*Two cases used standard bronchoscope.
GS, guide sheath; LLL, left lower lobe; LLS, left lingular segment; LUS, left upper segment; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

Table 5 Multivariable analysis for predictors of diagnostic yield.

Variable	OR	95% CI	P value
Lesion size (>20 mm vs ≤20 mm)	2.27	1.40 to 3.68	<0.001
Lesion density			<0.001
Pure GGO			Ref
Solid	7.21	2.00 to 25.97	0.003
Mixed GGO	2.72	0.73 to 10.12	0.13
CT bronchus sign			<0.001
Adjacent to			Ref
Leading to	3.10	1.68 to 5.71	<0.001
Outside	1.07	0.37 to 3.07	0.90
Distance to the hilum			0.97
Peripheral			Ref
Central	1.09	0.51 to 2.30	0.83
Intermediate	1.00	0.57 to 1.75	0.99
Distance to the pleura (≤20 mm vs >20 mm)	0.86	0.50 to 1.48	0.58
Lobar location (RUL+LUS vs others)	1.02	0.65 to 1.60	0.95
Lesion nature (malignant vs benign)	0.75	0.42 to 1.32	0.31
Anaesthesia type (general vs local±sedation)	1.03	0.60 to 1.79	0.90
GS (yes vs no)	0.61	0.20 to 1.84	0.38
Fluoroscopy (yes vs no)	1.69	0.91 to 3.15	0.10
Rapid on-site evaluation (yes vs no)	1.23	0.76 to 2.01	0.40

The multivariable analysis was performed by a full logistic regression model.
GGO, ground glass opacity; GS, guide sheath; LUS, left upper segment; Ref, reference; RUL, right upper lobe.

indicating the important role in diagnosis, which also made it difficult to cause difference in diagnostic yields. There was no significant difference in nodules sampled with or without fluoroscopy or ROSE. As some studies have not shown that fluoroscopy could significantly improve the diagnosis yield of PPL.[12 19] Several studies showed that ROSE could improve the diagnostic yield and shorten the operation time of bronchoscopy for PPLs.[29–31] However, the use of ROSE was not a significant multivariable predictor of increased diagnostic yield for PPLs in the NAVIGATE study.[12 32] Gildea *et al* reported that ROSE was concordant with final pathology in only 71% of cases in the NAVIGATE study.[32] Therefore, robust studies are required to demonstrate the role of fluoroscopy or ROSE in the diagnosis of PPLs.

The diagnostic yield of PPLs is associated with the sampling tools used. Some studies showed that a multitool strategy was more effective than a single-tool strategy.[33 34] Our results are consistent with this. The top two highest diagnostic yields among single-tool strategies were obtained by TBNA (75.0%) and cryobiopsy (73.1%). Cryobiopsy was able to obtain a large specimen, which has been demonstrated to be efficient in the diagnosis of PPLs,[35] especially for GGNs. Our pilot study revealed a diagnostic yield of 82.6% for GGNs using a 1.1 mm ultrathin cryoprobe.[22] Theoretically, cryobiopsy may increase the incidence of complications because of its powerful traction, but we found it to be a safe procedure, possibly because the 1.1 mm cryoprobe was safe and most frequently used in this study with the accurate guidance of ENB. TBNA increased the diagnostic yield of PPNs when the bronchus was adjacent to or outside the nodule.[36] The diagnostic advantage of TBNA was also obvious when the rEBUS probe was adjacent to the lesions.[37] TBNA was able to penetrate the bronchial wall, making it efficient to sample nodules eccentrically. However, TBNA was largely underused, as reported previously.[28 36] We adopted TBNA in only four nodules; among these, the rEBUS probe was adjacent to the nodule in three and outside the nodule in one.

The diagnostic yield of PPLs is affected by the lesion size, lesion location, lesion density and CT bronchus sign.[19 38] Our study demonstrated that nodules with large size (20–30 mm), solid density and a bronchus leading to them had a higher diagnostic yield. A meta-analysis showed that the diagnostic yield of ENB for the diagnosis of PPLs was affected by the lesion size and bronchus sign.[19] Yoshikawa *et al* reported that solid lesions had a significantly higher diagnostic yield (67%) than non-solid lesions (35%) by rEBUS–GS without fluoroscopy.[38] The NAVIGATE study did not show a difference in diagnostic yield between solid and non-solid lesions.[12] Our study showed a much higher diagnostic yield of solid nodules (79.0%) than non-solid nodules (58.1%). Further randomised study is needed to clarify this.

The median total procedural time was 1325 s, which was shorter than that in the NAVIGATE study and VBN procedures reported previously,[12 39] indicating the easy operation of this novel ENB system. That may be because the ENB system was used in combination with thin bronchoscope, and GS that was manoeuvrable to the operator. Moreover, the GS can be introduced into the invisible peripheral bronchus with the real-time guidance of the ENB system, which cannot be implemented by VBN, thus reducing the operation time. The overall complication rate was 3.3% and all complications were grade 2, similar to the NAVIGATE study and previously reported VBN procedures.[12 39] Notably, 400 patients were with one or more high risk factors of TTNA such as the lesion size≤2 cm, located inner two-thirds from the hilum, concomitant with emphysema, or chronic obstructive pulmonary disease.[1 2]

This study had some limitations. First, all participating centres were academic hospitals in which the operators were experienced in TBLB. The generalisation of the results to non-academic hospitals and inexperienced operators requires further confirmation. Second, some diagnostic modalities had a limited sample size, which had led to biased results. Enrolment of higher numbers of patients might provide a more robust and broader view of the utilisation of the ENB system. Third, there is a lack of comparison with VBN or other ENB systems, and randomised controlled trials can be carried out in the future to confirm the value of this ENB system.

CONCLUSION

This novel ENB system can be used in combination with different bronchoscopes, ancillary techniques and sampling instruments with a high diagnostic yield and safety profile for the diagnosis of PPNs, of which the combination of thin bronchoscope, rEBUS and GS was the most common method in clinical practice.

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