Multimodality-guided Transbronchial Lung Biopsy in Peripheral Pulmonary Nodules: A Comparison Between using an Electromagnetic Navigation Bronchoscopy and a Thin Bronchoscope

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ABSTRACT

Objective: To compare the diagnostic yield of using a thin bronchoscope (TB) and ENB in the diagnosis of small PPNs combined with routine R-EBUS and fluoroscopy.

Materials and Methods: Patients with a PPN less than or equal to 30 mm were randomly assigned into 2 groups: 4 mm thin bronchoscope (TB group) and 5.9 mm conventional bronchoscope with an ENB (the superDimension®) system (ENB group).

Results: In total, 49 patients were enrolled and randomized into two groups: TB group (n = 24) and ENB group (n = 25). The mean size of the PPNs was 22 mm. There was no difference in nodule size, location of the nodules, the presence of computed tomography (CT) bronchus sign, and EBUS location between the groups. The diagnostic yields were 73.9% and 66.7% in the TB group and ENB group, respectively. There was no statistically significant difference in the diagnostic yield between the two groups. Multivariate analysis showed that the diagnostic yield was significantly higher when there was also a CT bronchus sign (odds ratio 48.82, p = 0.031) and when the bronchoscope could reach a greater airway depth (odds ratio 6.21, p = 0.023). The overall complication was 2%, which was pneumothorax in one patient in the TB group.

Conclusion: Multimodality-guided techniques can improve the diagnostic yield in the diagnosis of PPNs. The PPNs larger than 2 cm with the presence of CT bronchus sign, the ENB provides a similar diagnostic yield compared to the thin bronchoscope. Further analysis and adequately powered prospective studies are required to confirm the advantages of ENB.

Keywords: Electromagnetic navigation; bronchoscopy; peripheral pulmonary nodule; navigation bronchoscopy (Siriraj Med J 2022; 74: 487-494)

INTRODUCTION

The prevalence of malignancy in various studies evaluating patients with noncalcified pulmonary nodules ranges from 2%–82%.[1-3] Peripheral pulmonary nodules (PPNs) are technically challenging to diagnose with conventional flexible bronchoscopy, which has demonstrated varying diagnostic yields, depending on a number of factors, including the size and location of nodules, the presence of the computed tomography (CT) bronchus sign, and endobronchial ultrasound (EBUS) location.

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Over the last decade, various bronchoscopic techniques have been developed to improve the diagnostic yield for the diagnosis of PPNs, including radial probe endobronchial ultrasound (R-EBUS), endobronchial ultrasound using a guide sheath (EBUS-GS), thin and ultrathin bronchoscopes, virtual bronchoscopic navigation (VBN), and electromagnetic navigation bronchoscopy (ENB). A previous study from our center reported a diagnostic yield of R-EBUS in the diagnosis of PPNs of 66.4%.[4] Combining R-EBUS with other bronchoscopic procedures, such as using a thin bronchoscope or electromagnetic navigation bronchoscopy, may improve the diagnostic yield.[5-7]

A thin bronchoscope (TB) can be advanced to the more distal bronchi compared with a conventional bronchoscope. A previous study reported a diagnostic yield of 65% from using a 3.4 mm bronchoscope with R-EBUS in the diagnosis of PPNs.[6] The ENB method uses an electromagnetic field to track a locatable guide in real time, correlating its position in the tracheobronchial tree to the patient's computed tomography (CT) scan. Several studies have reported some improvement in the diagnostic yield from using ENB, ranging from 54% to 75%.[5] The present study aimed to compare the diagnostic yield of using a thin bronchoscope and conventional bronchoscope with ENB in the diagnosis of small PPNs less than or equal to 30 mm.

MATERIALS AND METHODS

Patients

The present study was a prospective, single-center, randomized study. The inclusion criteria were patients with a small PPN defined by a size less than or equal to 30 mm in the longest diameter, with no evidence of endobronchial lesion, and who underwent bronchoscopy between April 2016 and January 2017 at the Division of Respiratory Disease and Tuberculosis, Faculty of Medicine Siriraj Hospital. The exclusion criteria were patients who were pregnant or had a contraindication for bronchoscopy or transbronchial lung biopsy (TBLB). The primary objective was to compare the diagnostic yield of using a thin bronchoscope and conventional bronchoscope with ENB in the diagnosis of small PPNs. The secondary objectives included assessing the factors affecting the diagnostic yield and complications of the procedures. All the chest radiographs and CT chest scans were reviewed. The baseline characteristic of the patients and PPNs, including the longest diameter, type of lesion, location, and the presence of the CT bronchus sign were recorded. All the patients provided their written informed consent.

The patients were randomly assigned in a 1:1 ratio into 2 groups: TB group and ENB group. The randomization sequence was computer generated in block sizes of 4. In the TB group, a thin bronchoscope (BF-MP60, 4 mm diameter, 2.0 mm working channel diameter; Olympus, Tokyo, Japan) was used. In the ENB group, a conventional bronchoscope (BF type TE2, 5.9 mm diameter, 2.8 mm working channel diameter; Olympus, Tokyo, Japan) and electromagnetic navigation system (superDimension®; Medtronic, Minneapolis, MN, USA) were used. In both groups, R-EBUS (UM-S20-20R, 20 MHz, 1.7 mm distal end diameter; Olympus, Tokyo, Japan) and fluoroscopy were used to confirm the location of the lesion and biopsy forceps before performing TBLB. The procedures in both groups were performed by a single bronchoscopist.

Procedures

Thin bronchoscope (TB group)

The bronchoscopic procedures were performed using local anesthesia with lidocaine and moderate conscious sedation with intravenous midazolam and fentanyl. When the target bronchus was located, the R-EBUS probe was inserted through the bronchoscopic working channel. When the EBUS image was obtained, TBLB was performed under fluoroscopic guidance followed by bronchoalveolar lavage. We did not perform brushing and transbronchial needle aspiration.

The bronchus level reached by the bronchoscope, the location of the R-EBUS probe related to the lesion on an EBUS image, and any procedure-related complications were recorded. The biopsy specimens were immersed in 10% formalin and analyzed by pulmonary pathologists. Pneumothorax was screened for using fluoroscopy in all patients immediately after the procedure.

The final diagnoses were established by the cytology, histopathology, and microbiology results. Malignancy was diagnosed based on the histopathology results obtained from the bronchoscopic biopsy. The diagnosis of benign diseases was confirmed by histopathology with or without microbiological evidence of infection. All patients with non-diagnostic bronchoscopy were either subjected to alternative procedures (e.g., repeat bronchoscopy, CT-guided transthoracic core needle biopsy, and surgical resection) or followed up with a combination of clinical data and CT chest for a minimum of 24 months. When an alternative diagnosis was established, these cases were considered to be a negative diagnostic yield. If the patients showed both clinical and radiological stability or improvement, the lesion was considered to be a true benign lesion.

Electromagnetic navigation bronchoscopy (ENB group)

Pre-procedural planning for identification of the target lesion, airway path, and registration points was performed after importing the CT data into the superDimension® software. The bronchoscopic techniques applied were similar to in the TB group except they were performed under real-time navigation. When the bronchoscope was located in the bronchus of interest, the locatable guide was withdrawn and the R-EBUS probe was inserted through the extended working channel (EWC). When the EBUS image was obtained, TBLB was performed under fluoroscopic guidance followed by bronchoalveolar lavage.

Statistical analyses

Initially, we decided to analyze the results using a non-inferiority design based on the diagnostic yields of TB and ENB in the diagnosis of PPNs reported in a previous study (59% and 88%, respectively). Non-inferiority of the TB method was concluded if the lower border of the 95% confidence interval (CI) for the difference in the diagnostic yields exceeded the predetermined non-inferiority border of 5%. We calculated that demonstration of non-inferiority with a statistical power of 80% at a one-sided significance level of 0.05 would require a minimum of 38 patients per group. Unfortunately, we could not recruit enough patients to carry out this study due to the limitation in material support. Thus, finally, we decided to compare the diagnostic yields of TB and ENB using Fisher's exact test. The continuous variables were presented as the mean or median and standard deviation. Pearson's chi-square test or Fisher's exact test were used to test the association between the categorical variables. The unpaired t-test was used to test the difference in means of the normally distributed quantitative variables. Results were considered statistically significant when the p-value was less than 0.05. All the statistical analyses were performed using statistical software (SPSS for Windows, version 20.0; SPSS; Chicago, IL, USA).

The study was approved by the ethics committee of our institution (Si 213/2016). Written informed consent was obtained from all patients prior to the bronchoscopic procedures.

RESULTS

We enrolled a total of 49 patients (24 patients in the TB group and 25 patients in the ENB group). There was no statistically significant differences in the characteristics of the patients between both groups except for sex (Table 1).

The diagnostic yields were 73.9% and 66.7% in the TB group and ENB group, respectively. There was no significant difference in the diagnostic yield between the two groups (p = 0.587). The final diagnoses are summarized in Table 2. The prevalence of malignancy was 71.4% (66.7% in the TB group and 76% in the ENB group, p = 0.344), in which adenocarcinoma was the most common histopathologic result. The most common diagnosis of benign disease was pulmonary tuberculosis. The diagnosis remains unknown in 2 patients (4.1%) due to their loss to follow-up. There was no significant difference in diagnostic yield regarding nodule size, location of the nodules, EBUS location, and diagnosis of malignancy. The presence of the CT bronchus sign had a higher diagnostic yield compared to the absence of the CT bronchus sign (p = 0.05).

In the non-diagnostic group, the final diagnosis was made by repeated bronchoscopy (2 cases), surgical resection (7 cases), CT-guided transthoracic core needle biopsy (1 case), and follow-up CT chest (4 cases).

The thin bronchoscope reached more distal segmental bronchi compared to the conventional bronchoscope in the ENB group, but there was no statistical significance (Table 3). PPNs were identified by R-EBUS in 89.8% of cases (87.5% in the TB group and 92% in the ENB group, p = 0.835). The mean number of TBLBs was 7 in both groups. The multivariate analysis showed that the presence of the CT bronchus sign and more distal segmental bronchi reached by the bronchoscope were associated with an improvement of the diagnostic yield, as shown in Table 5 (OR 48.82, p = 0.031 and 6.21, p = 0.023, respectively). The overall complication was 2%, which was pneumothorax that occurred in one patient in the TB group and which required chest tube drainage.

DISCUSSION

Several studies have reported that the multimodality of guided bronchoscopy can improve the diagnostic yield of PPNs.[7] In our center, we routinely use R-EBUS and fluoroscopy to confirm the location of lesions and biopsy forceps before performing TBLB. R-EBUS has demonstrated various diagnostic yields in the diagnosis of PPNs with some limitations,[7-9] including that R-EBUS is not a real-time guided procedure and the position of tip of the bronchoscope can be lost during EBUS probe withdrawal prior to introduction of the biopsy forceps. Our center previously reported a diagnostic yield of 66.4% for R-EBUS combined with fluoroscopy in the diagnosis of PPNs.[4] The combined use of R-EBUS with other guided techniques may improve the diagnostic yield.[1-3,7] The present study investigated the diagnostic yields of TB and ENB in the diagnosis of small PPNs less

TABLE 1. Characteristics of patients and pulmonary nodules.

Baseline characteristics	TB group, N (%)	ENB group, N (%)	*P* value
N	24	25	
Age, years (mean ± SD)	67 ± 13	63 ± 10	0.318
Male	16 (66.7)	9 (36)	0.032
Size, mm (mean ± SD)	20 ± 6.1	23.36 ± 6.36	0.184
Nodule size			0.477
Less than 20 mm	13 (54.2)	11 (44)	
20-30 mm	11 (45.8)	14 (56)	
Type of nodule			0.613
Solid nodule	23 (95.8)	23 (92)	
Ground glass nodule	0 (0)	1 (4)	
Subsolid	1 (4.2)	1 (4)	
Location of nodule			0.180
Right upper	6 (25)	8 (32)	
Right middle	4 (16.7)	3 (12)	
Right lower	3 (12.5)	10 (40)	
Left upper	5 (20.8)	2 (8)	
Lingula	2 (8.3)	1 (4)	
Left lower	4 (16.7)	1 (4)	
CT bronchus sign	15 (62.5)	14 (56)	0.644

Abbreviations: ENB; electromagnetic navigation bronchoscopy, TB; thin bronchoscope, SD; standard deviation, mm; millimeter, CT; computed tomography

TABLE 2. Final diagnosis.

Final diagnosis	TB group, N (%)	ENB group, N (%)	*P* value
Final diagnosis			0.344
Malignancy	16 (66.7)	19 (76)	
Adenocarcinoma	11	11	
Squamous cell carcinoma	1	2	
Adenoid cystic carcinoma	0	1	
Carcinoid tumor	1	0	
Metastatic carcinoma	2	5	
Malignant melanoma	1	0	
Benign diseases	7 (29.2)	5 (20)	
Pulmonary tuberculosis	4	3	
Organizing pneumonia	1	0	
Other benign diseases	2	2	
Undetermined	1 (4.2)	1 (4)	

TABLE 3. Bronchoscopic results.

Bronchoscopic results	TB group, N (%)	ENB group, N (%)	*P* value
Airway generation (mean ± SD)	5 ± 1	4 ± 1	0.252
EBUS location			0.835
Within the lesion	10 (41.7)	12 (48)	
Adjacent to the lesion	11 (45.8)	11 (44)	
Not seen the lesion	3 (12.5)	2 (8)	
Pieces of TBLB (mean ± SD)	7 ± 1	7 ± 1	0.275
Complications			0.488
Massive bleeding	0 (0)	0 (0)	
Pneumothorax	1 (4.2)	0 (0)	
Severe hypoxemia	0 (0)	0 (0)	
Others	0 (0)	0 (0)	

Abbreviations: SD; standard deviation, EBUS; endobronchial ultrasound, TBLB; transbronchial lung biopsy

TABLE 4. Diagnostic yield.

Variables	TB group,	ENB group, N (%)	*P* value N (%)
N	23	24	
Overall diagnostic yield	17 (73.9)	16 (66.7)	0.587
Nodule size			0.775
Less than 20 mm	9 (75)	6 (60)	
20-30 mm	8 (72.7)	10 (71.4)	
Type of nodule			1.000
Solid nodule	16 (72.7)	15 (65.2)	
Ground glass nodule	-	-	
Subsolid	1 (100)	1 (100)	
Location of nodule			0.246
Right upper	4 (66.7)	5 (62.5)	
Right middle	3 (75)	3 (100)	
Right lower	2 (66.7)	4 (44.4)	
Left upper	5 (100)	2 (100)	
Lingula	1 (50)	1 (100)	
Left lower	2 (66.7)	1 (100)	
CT bronchus sign			0.050
Presence	12 (85.7)	10 (76.9)	
Absence	5 (55.6)	6 (54.5)	
EBUS location			0.714
Within the lesion	8 (80)	9 (75)	
Adjacent to the lesion	8 (80)	7 (70)	
Not seen the lesion	1 (33.3)	0 (0)	
Diagnosis			0.460
Malignancy	12 (75)	13 (68.4)	
Benign	5 (71.4)	3 (60)	

Abbreviations: ENB; electromagnetic navigation bronchoscopy, TB; thin bronchoscope, mm; millimeter, CT; computed tomography, EBUS; endobronchial ultrasound

TABLE 5. Factors associated with diagnostic yield.

Variables	OR	*P* value
Univariate analysis		
Age	0.942	0.086
Nodule size 20-30 mm	4.5	0.028
Subsolid nodule	0.15	0.113
CT bronchus sign	6.9	0.007
Airway generation	2.24	0.115
Multivariate analysis		
Age	0.905	0.126
Nodule size 20-30 mm	0.459	0.621
Subsolid nodule	12.439	0.269
CT bronchus sign	48.82	0.031
Airway generation	6.21	0.023

Abbreviations: OR; odds ratio, mm; millimeter, CT; computed tomography

than or equal to 30 mm when combined with R-EBUS and fluoroscopic guidance. The diagnostic yield of TB was comparable to that of ENB (73.9% and 66.7%, respectively; p = 0.587).

The use of a thin bronchoscope (4 mm outer diameter) and ultrathin bronchoscope (UTB; outer diameter less than 4 mm) might reduce the limitation of R-EBUS compared with using a conventional bronchoscope because they can reach more distal segmental bronchi leading to the lesion, which would result in a more precise direction alignment with the lesion and reducing the chance of displacement of the tip of the bronchoscope.[10-13] The present study found that the use of TB with R-EBUS and fluoroscopy resulted in a higher diagnostic yield in diagnosis of PPNs less than 30 mm compared to the previous study performed at our center (73.9% and 63.8%, respectively).[4] This was similar to the study of Tanner et al., which reported that the use of TB with R-EBUS could improve the diagnostic yield in the diagnosis of PPNs compared to the use of a conventional bronchoscope (49% and 37%, respectively; p = 0.110).[10] The use of UTB combined with multimodality-guided techniques has been reported to provide a significantly higher diagnostic yield compared to the use of TB.[11-13] This advantage might be due to more distal bronchi being reached when using UTB. However, the diagnostic yields of UTB vary depending on the studies and guided methods, ranging from 40%–90%, with a yield of 24%–81% for lesions < 20 mm.[11]

The addition of ENB may have a benefit in helping physicians to identify the target bronchi leading to the lesion. ENB requires the use of a conventional bronchoscope (5.9 mm outer diameter with a 2.8 mm working channel), so the tip of the bronchoscope cannot be advanced to the more distal segmental bronchi. Using a steerable locatable guide in ENB can solve this limitation because the direction of the locatable guide can be adjusted in real time in practical situations to find the target bronchus leading to the lesion. When using ENB combined with R-EBUS, the diagnostic yield was significantly improved compared to ENB or R-EBUS alone.[7,14] The present study found that ENB with R-EBUS had a diagnostic yield of 66.7%, which was similar to our previous study of using a conventional bronchoscope with R-EBUS. Several studies have reported various diagnostic yields of ENB ranging from 65%–90%.[7,16-19] Interestingly, the results of the AQuIRE registry showed a low diagnostic yield when using ENB with R-EBUS for the diagnosis of peripheral lung lesions, which was only 47%.[20] The recent multicenter study in seven countries from the United States and Europe, The NAVIGATE study, has found the global diagnostic yield of ENB was 67.8% (69.8% in the United States and 55.2% in Europe).[21] The NAVIGATE study had some regional practice variations including differences in guided techniques, ENB experience, number of tissue biopsies, and the use of general anesthesia that likely affected the outcomes. These might reflect the diagnostic yield of ENB in real-

world practice, especially when ENB was used outside a research center. Regarding the superDimension® system, the operators need some experience in choosing and controlling the locatable guide to find the target lesion, which might have resulted in the lower diagnostic yield in the ENB group in the present study.

Most of the lesions in the present study could be visualized by EBUS (48% within the lesion and 44% adjacent to the lesion) regardless of the use of ENB (41.7% within the lesion and 45.8% adjacent to the lesion), suggesting that the use of ENB might have no additional benefit in terms of the chances of localizing the lesion. However, ENB may have benefit in shortening the time to find the lesion, which was not evaluated in the present study.

Failure to identify the lesion by R-EBUS was 12.5% and 8% in the TB and ENB group, respectively. The results of the present study were consistent with previous studies, which reported a successful navigation to PPNs with ENB of 97.4%, but the definitive diagnosis could be confirmed in only 64.9% of cases, with a sensitivity to detect cancer of 71% and a negative predictive value of 52%.[19] This discordance between the navigation success and diagnostic yield may depend on the relationship between the airways and lesion, and the actual position of the locatable guide may differ from the virtual location due to the interval duration between CT imaging and the diagnostic procedure and respiratory variation. Conscious sedation during the procedures might result in a high respiratory variation and coughing, which sometimes causes a difficulty to control the locatable guide. The meta-analysis reported that the use of general anesthesia was associated with better diagnostic yields compared to the use of conscious sedation (69.2% and 57.5%, $p = 0.02$).[18] Several studies have reported low diagnostic yields for PPNs located adjacent to the R-EBUS probe location. In contrast, we found that the EBUS location did not affect the diagnostic yield in both groups.

Multivariate analysis demonstrated that the presence of CT bronchus sign and more distal segmental bronchi reached by the bronchoscope were associated with an improvement in diagnostic yield (OR 48.84, $p = 0.031$ and OR 6.21, $p = 0.023$, respectively), which were consistent with several other studies.[16,17,21,22]

No major complications were found in the present study. The overall complication rate was 2.0%, which was similar to in a previous study.[9]

The cost of the ENB system is considerably higher than that of the TB because the ENB system requires disposable instruments, such as a locatable guide and an extended working channel. Further study is needed to identify the cost-effectiveness of these procedures.

The present study has several limitations to note. First, the study involved a single-center experience. However, there was no operable variability because all of the procedures were performed by one bronchoscopists. Second, the sample size was inadequate due to technical problems. Finally, the duration of the procedure was not evaluated in the present study.

CONCLUSION

Multimodality-guided techniques can improve the diagnostic yield in the diagnosis of PPNs. The PPNs larger than 2 cm with the presence of CT bronchus sign, the ENB provides a similar diagnostic yield compared to the thin bronchoscope. Further analysis and adequately powered prospective studies are required to confirm the advantages of ENB.

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