Comparing Multimodality-Guided Transbronchial Lung Biopsy in Small Peripheral Pulmonary Nodules by Thin Bronchoscopy and Electromagnetic Navigation Bronchoscopy: A Randomised Trial

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Abstract

Background

Various modalities of guided bronchoscopy have been developed to improve the diagnostic yield of peripheral pulmonary nodule (PPN). The present study compared the diagnostic yield between thin bronchoscopy (TB) and electromagnetic navigation bronchoscopy (ENB) in diagnosis of PPN.

Methods

The patients with 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 using ENB (the superDimension) system (ENB group). In both groups, we used radial probe endobronchial ultrasound (R-EBUS) and fluoroscopy to guide transbronchial lung biopsy.

Results

The total of 49 patients were enrolled and randomized into TB group (n=24) and ENB group (n=25). Mean size of PPN was 22 mm. There was no difference in nodule size, location of nodule, the presence of CT bronchus sign and EBUS visualization between groups. The diagnostic yields were 73.9% and 66.7% in TB group and ENB group, respectively. There was no statistically significant difference in the diagnostic yield between two groups and the non-inferiority of the TB group could not be confirmed. Multivariate analysis showed that the diagnostic yield was significantly higher if there is CT bronchus sign (odd ratio 48.82, p = 0.031) and the bronchoscope can reach more airway depth (odd ratio 6.21, p = 0.023). The overall complication was 2% which is pneumothorax in one patient in the TB group.

Conclusions

The thin bronchoscopy has a comparable diagnostic yield as electromagnetic bronchoscopy in diagnosis of peripheral pulmonary nodule without serious complication.

Trial registration

TCTR, TCTR20200224003. Registered 24 February 2020 - Retrospectively registered, https://www.clinicaltrials.in.th/index.php?tp=regtrials&menu=trialsearch&smenu=fulltext&task=search&task2=view1&id=5834.

Background

The prevalence of malignancy in various studies evaluating patients with noncalcified pulmonary nodules ranges from 2-82%.(1-3) PPN is technically challenging with conventional flexible bronchoscopy in obtaining diagnosis which has various diagnostic yields. The important factors that impact the

diagnostic yield include size and location of nodule, the presence of CT bronchus sign and EBUS visualization.

Over the last decade, various bronchoscopic techniques have been developed to improve the diagnostic yield in diagnosis of PPN including radial probe endobronchial ultrasound (R-EBUS), endobronchial ultrasound with guide sheath (EBUS-GS), thin and ultrathin bronchoscopy, virtual bronchoscopic navigation (VBN) and electromagnetic navigation bronchoscopy (ENB). Previous study from our center has reported that the diagnostic yield of R-EBUS in diagnosis of PPN was 66.4%.(4) Combining other bronchoscopic procedures, such as thin bronchoscope and electromagnetic navigation bronchoscopy with R-EBUS may improve the diagnostic yield.(6,7)

Thin bronchoscope (TB) can be advanced to the more distal bronchi compared with conventional bronchoscope. The previous study has reported that the diagnostic yield of 3.4-mm bronchoscope with R-EBUS in diagnosis of PPN was 65%.[6] The ENB method uses electromagnetic field to track a locatable guide in real time, correlating its position in the tracheobronchial tree to the patient's computed tomography (CT). Several studies have reported some improvement in the diagnostic yield of ENB ranging from 54 to 75%.(5) However, the cost of ENB system should be considered. The present study aimed to compare the diagnostic yield of thin bronchoscopy and ENB in diagnosis of PPN.

Methods

Patients

This study is a prospective, single-center, randomized, non-inferiority study. The patients with PPN ≤ 3 cm in the longest diameter and had no evidence of endobronchial lesion who underwent bronchoscopy between April 2016 and January 2017 at Division of Respiratory Disease and Tuberculosis, Faculty of Medicine, Siriraj Hospital were enrolled. The patients who were pregnant or had contraindication for bronchoscopy or transbronchial lung biopsy (TBLB) were excluded. The primary objective is the diagnostic yield of thin bronchoscopy and ENB in diagnosis of PPN. The secondary objectives include factors affected the diagnostic yield and complication of the procedures. All chest radiograph and CT chest were reviewed. Baseline characteristic of patients and PPN, including the longest diameter, characteristics, location and the presence of CT bronchus sign were recorded. All patients provided their written informed consent.

Patients were randomly assigned in 1:1 ratio into 2 groups, TB group and ENB group. Randomization sequence was computer generated in block size of 4. In TB group, thin bronchoscope (BF-MP60, 4-mm diameter, 2.0-mm working channel diameter; Olympus, Tokyo, Japan) was used. In ENB group, 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, Minnesota) were used. In both group, 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 one bronchoscopist.

Procedures

Thin bronchoscopic method (TB group)

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 were performed under fluoroscopic guidance followed by bronchoalveolar lavage.

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

The final diagnoses were established by cytology, histopathology and microbiology. Benign diseases were diagnosed if there was stability or improvement of the lesion on imaging for a minimum period of 24 months.

Electromagnetic navigation bronchoscopy method (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. Bronchoscopic techniques were similar to the TB group except in performing 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

Comparative analysis on the diagnostic yield of ENB and TB in diagnosis of PPN for non-inferiority has been used. The difference of the diagnostic yield between 2 groups were 0.29 (calculated from diagnostic yield of TB and ENB in diagnosis of PPN was 59% and 88%, respectively). Noninferiority 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%. Demonstration of non-inferiority with a statistical power of 80% at a one-sided significance level of 0.05 would require 38 patients per group.

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 categorical variables. Unpaired t-test was used to test the difference in mean of normally distributed quantitative variables.

Results were considered statistically significant when the p-value was less than 0.05. All statistical analyses were performed using statistical software (SPSS for windows, version 20.0; SPSS; Chicago, IL).

This study was approved by the ethics committee of our institution. Written informed consent was obtained in all patients prior to the bronchoscopic procedure.

Results

The study was stopped prematurely because of technical problems and inadequate conditional power. We enrolled a total of 49 patients were enrolled in this study (24 patients in TB group and 25 patients in ENB group). There was no statistically significant difference in characteristic of patients between both groups except for sex (Table 1).

The diagnostic yields were 73.9% and 66.7% in TB group and ENB group, respectively. There was no significant difference in the diagnostic yield between groups. The difference in the diagnostic yield between 2 groups was 7.2% and non-inferiority of the TB group could not be confirmed (95% CI, -14.6-29.1; p = 0.178). The final diagnoses were summarized in Table 2. The prevalence of malignancy was 67% (66% in TB group and 79% in ENB group, p=0.344) which adenocarcinoma was the most common histopathologic result. The most common diagnosis of benign disease was pulmonary tuberculosis. The diagnosis remains unknown in 4 patients (8%) due to loss to follow-up.

The thin bronchoscope could reach more distal segmental bronchi compared to the conventional bronchoscope in ENB group but there was no statistical significance (Table 3). PPN were identified on EBUS image in 90% of cases as shown in table 3, half of them were within the lesion. There was no statistical difference of diagnostic yield according to the EBUS visualization. The mean number of TBLB was 7 pieces in both groups. The overall complication was 2% which is pneumothorax that occurred in one patient in TB group. The multivariate analysis showed that the presence of CT bronchus sign and more distal segmental bronchi reached by bronchoscope associated with the improvement of the diagnostic yield as shown in Table 4.

Discussion

Several studies have reported the multimodality of guided-bronchoscopy improved the diagnostic yield of PPN.(7) In our center, we routinely use the R-EBUS and fluoroscopy to confirm the location of lesion and biopsy forceps before performing TBLB. According to our previous study, the diagnostic yield of R-EBUS combined with fluoroscopy for diagnosis of PPN was only 66.4%.(4) R-EBUS has the limitation of lacking real-time imaging. So, it can be difficult to confirm that the biopsy forceps are in the lesion even the EBUS image shows the probe is within the lesion, especially in small PPN (size $\leq$ 3 cm). The combined use of R-EBUS with other techniques of guided bronchoscopy may improve the diagnostic yield. Several studies have reported the various diagnostic yield using multimodality techniques for diagnosis of PPN depending on the characteristic of PPN and guided techniques.(1-3,7) The present study investigated the

diagnostic yields of the TB and ENB method in diagnosis of small PPN less than or equal to 30 mm when combined with R-EBUS and fluoroscopic guidance. The diagnostic yield of TB method was comparable between the use of TB and ENB (73.9% and 66.7%, respectively). However, the non-inferiority of the TB group could not be confirmed by non-inferiority analysis. The use of thin bronchoscope provides access to more distal bronchi compared with conventional bronchoscopes which may result in a higher diagnostic yield when combined with other techniques of guided bronchoscopy.(10) The addition of navigation platform, such as ENB, has been suggested to provide a higher diagnostic yield. Recent meta-analysis of ENB reported a sensitivity of 69-82% and diagnostic yields ranging from 63-90%.(11-15) When using ENB with R-EBUS, the diagnostic yield was significantly improved compared to ENB or R-EBUS alone.(16) Interestingly, the results of the AQuIRE registry, they have reported a low diagnostic yield when using ENB with R-EBUS for diagnosis of peripheral lung lesions which was only 47%.(17) These might reflect the diagnostic yield of ENB in real world practice especially when ENB was used outside the research center and the procedure needs experiences. Regarding the superDimension® system, the operators need some experiences in choosing and controlling the locatable guide to find target lesion. These might result in a lower diagnostic yield in ENB group compared to that in TB group in the present study. Most of the lesions in the present study can be visualized by EBUS regardless the use of ENB, suggesting that the use of ENB might have no additional benefit in terms of a chance to localize the lesion. However, ENB may have benefit in shortening the time to find the lesion which was not evaluated in the present study.

Several factors were associated with higher diagnostic yield, including size of nodule (> 30 mm), presence of CT bronchus sign, and EBUS visualization.(13-14) The present study demonstrated that the presence of CT bronchus sign and more distal segmental bronchi reached by bronchoscope were associated with the improvement of diagnostic yield. No major complication was found in the present study. The overall complication rate was 2.0% which was similar to the previous studies.(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.

There are some limitations of the present study. Firstly, the sample size is too small because we could not recruit enough patients to carry out the study. Secondly, we did not study the duration of procedure which may shorter in the ENB group.

Conclusions

The thin bronchoscope has a comparable diagnostic yield as electromagnetic bronchoscopy in diagnosis of peripheral pulmonary nodule.

Abbreviations

PPN: peripheral pulmonary nodule; TB: thin bronchoscopy; ENB: electromagnetic navigation bronchoscopy; R-EBUS: radial probe endobronchial ultrasound; CT: computed tomography; EBUS-GS: endobronchial ultrasound with guide sheath; VNB: virtual navigation bronchoscopy; TBLB: transbronchial lung biopsy; EWC: extended working channel; CI: confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board, Faculty of Medicine Siriraj Hospital. Written informed consent will be obtained from all participants.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare they have no competing interest.

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Authors' contribution

Conception and design: S.D., A.R., J.T. Administrative support: J.T. Provision of study materials or patients: S.D., J.T. Collection and assembly of data: S.D., A.R., J.T. Data analysis and interpretation: S.D., A.R. Manuscript writing: S.D., A.R., J.T. Final approval of manuscript: S.D., A.R., J.T.

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Summary at a Glance

It’s challenging in diagnosis of small peripheral pulmonary nodule. Multimodality guided bronchoscopy improve the diagnostic yield. The thin bronchoscopy has a comparable diagnostic yield as electromagnetic navigation bronchoscopy.

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Tables

Table 1 Characteristics of patients and pulmonary nodules

Baseline characteristics	TB group, N (%)	ENB group, N (%)	*p* value
Number	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 2 cm	13 (54.2)	11 (44)	
2-3 cm	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

ENB = electromagnetic navigation bronchoscopy; TB = thin bronchoscope; SD = standard deviation; mm = millimeter; cm = centrimeter; CT = computed tomography

Table 2 Final diagnosis and diagnostic yield

Final diagnosis	TB group, N (%)	ENB group, N (%)	*p* value
Final diagnosis			0.344
Malignancy	14 (66.7)	19 (79.2)	
- Adenocarcinoma	9	11	
- Squamous cell carcinoma	1	2	
- Adenoid cystic carcinoma	0	1	
- Carcinoid tumor	1	0	
- Metastatic carcinoma	1	4	
- Malignant melanoma	1	0	
- Unidentified primary site	1	1	
Benign diseases	7 (33.3)	5 (20.8)	
- Pulmonary tuberculosis	4	3	
- Organizing pneumonia	1	0	
- Other benign diseases	2	2	
Undetermined	3 (12.5)	1 (4)	
Diagnostic yield (%)	73.9	66.7	0.587

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 visualization			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)	

EBUS = endobronchial ultrasound; TBLB = transbronchial lung biopsy

Table 4 Factors associated with diagnostic yield

Variables	OR	*p* value
Univariate analysis		
- Age	0.942	0.086
- Nodule size 2-3 cm	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 2-3 cm	0.459	0.621
- Subsolid nodule	12.439	0.269
- CT bronchus sign	48.82	0.031
- Airway generation	6.21	0.023

OR = odds ratio; CT = computed tomography

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