The Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy in Peripheral Pulmonary Lesions

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Background: *Peripheral pulmonary lesions are technically challenging with conventional bronchoscopy in obtaining tissue diagnosis. The recently developed small-caliber ultrasonographic probe can be introduced via the working channel of a flexible bronchoscope to localize peripheral pulmonary lesions (PPLs) prior to transbronchial lung biopsy (TBLB). The endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) is a new diagnostic method for the diagnosis of pulmonary lesions in our center.*
Objective: *To evaluate the diagnostic yield of EBUS-TBLB in pulmonary lesions.*
Study design: *A prospective cross-sectional study*
Material and Method: *We enrolled 152 patients with pulmonary lesions that were beyond the segmental bronchus and had no evidence of endobronchial lesion, who underwent bronchoscopy in our center. With EBUS assisted, transbronchial lung biopsy was performed after localizing and measuring distance from the tip of bronchoscope to the lesion. The diagnostic yield was calculated.*
Results: *The pulmonary lesions were visible on EBUS image in 98.7% of cases. The overall diagnostic yield of EBUS-TBLB was 66.4%. The diagnostic yield in the infiltrative and mass lesions were 86.4% and 63.1%, respectively. The lesions which EBUS probe located within it were diagnosed by EBUS-TBLB about 74.8%. The benign and malignant lesions were diagnosed by EBUS-TBLB about 81.1% and 58.6%, respectively. The average EBUS time was 3.55 $\pm$ 2.29 minutes. No complication of EBUS and transbronchial lung biopsy were observed in this study.*
Conclusion: *EBUS-TBLB is a safe procedure for diagnosing pulmonary lesions. Our results indicate that the EBUS-TBLB improves the diagnostic yield compared to conventional brochoscopy.*

Keywords: *bronchoscopy, endobronchial ultrasound, miniature probe, transbronchial lung biopsy, peripheral pulmonary lesions*

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Peripheral pulmonary lesions (PPL) are technically challenging with conventional bronchoscopy in obtaining tissue diagnosis because the biopsy forceps may not enter the target segmental or subsegmental bronchus. Currently, EBUS has been gradually introduced in the bronchoscopic practice[1-3]. The small-caliber ultrasonographic probe can be successfully introduced into the working channel of a flexible bronchoscope to localize peripheral pulmonary lesions prior to using diagnostic techniques including transbronchial lung biopsy (TBLB)[4-6].

Several studies[7,8] found that endobronchial ultrasound-guided transbronchial lung biopsy (EBUS-TBLB) was a useful new diagnostic tool for the diagnosis of peripheral pulmonary lesions. This procedure may improve the diagnostic yield and save the patients from undergoing operative procedure.

The present study evaluated the diagnostic yield of EBUS-TBLB for diagnosis of pulmonary lesions.

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Material and Method

Patients

This study was a prospective cross-sectional

study aimed to evaluate the role of EBUS-TBLB in patients with pulmonary lesions, detected by chest radiograph or computed tomography (CT) of the chest, that were beyond the segmental bronchus and had no evidence of endobronchial lesion. The patients with pulmonary lesions, as described, who underwent bronchoscopy between August 2007 and March 2009 at Division of Respiratory Disease and Tuberculosis, Faculty of Medicine, Siriraj Hospital were enrolled. The patients who were pregnant or had contraindication for TBLB were excluded from the study.

All chest radiograph or CT of the chest were reviewed. The longest diameter, characteristics, location and distribution of the lesion were recorded. The central distribution of each lesion was defined as the lesion which was located in inner half of hemithorax.

Equipment

A miniature probe (20-MHz, mechanical-radial type) was used. The probe was connected to an endoscopic ultrasound system (EU-M2000; Olympus optical, Japan).

Bronchoscopic procedure and EBUS-TBLB

All patients were in supine position. Local anesthesia with 4% lidocaine was used and sedation with intravenous 2 mg midazolam if needed. Oxygen was administered by a nasal device, and the flow was adjusted to maintain the pulse oximetric saturation > 92%. Blood pressure was measured before and during bronchoscopy. Continuous pulse oximetry was performed during bronchoscopy.

After the bronchoscope was advanced beyond the vocal cords, all segments of the bronchial tree were visualized. A miniature EBUS probe was inserted through the working channel of the bronchoscope into the bronchus identified as interesting based on radiographic findings (Fig. 1).

After localizing the lesion by EBUS image, the location of EBUS probe (Fig. 2) and the distance from the tip of the bronchoscope to the lesion were recorded (Fig. 3). Then the EBUS probe was removed from the working channel and the biopsy forceps was introduced into the corresponding subsegmental bronchus at the same distance and transbronchial biopsy was done. Fluoroscopy was used for confirming the location of EBUS probe and biopsy forceps as needed, depending on the operator. The specimens were obtained (at least 4 pieces) and were immersed in 10% formalin and analyzed by the pathologist. Fluoroscopic screening for pneumothorax, blood pressure measurement and pulse oximetric saturation were assessed after transbronchial lung biopsy. Major complications (significant bleeding, severe hypoxemia or pneumothorax) and final diagnosis of each cases were reviewed.

Fig. 1 EBUS probe was inserted through working channel of the bronchoscope.

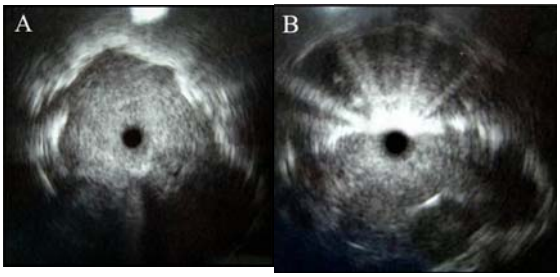

Fig. 2 The location of EBUS probe on EBUS image. A) Within the lesion, B) Adjacent to the lesion

EBUS time

The total time of EBUS-TBLB was defined as the time from inserting EBUS probe into working channel to the time of removal EBUS probe from working channel.

Statistical analysis

The data were presented as the mean $\pm$ SD. Pearson's Chi-square test was used to test the association between categorical factors and diagnostic results (positive and negative); p-value < 0.05 was considered statistically significant. Unpaired t-test was employed to test the difference in mean of normally distributed quantitative variables between positive and negative diagnostic results. All statistical analyses

Fig. 3 The distance from the tip of the bronchoscope to the lesion were measured.

were performed using statistical software (SPSS for windows, version 13.0; SPSS; Chicago, IL).

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

Results

Patient data

A total of 152 patients (85 males and 67 females) with an average age of 60.68 $\pm$ 13.45 years (range 24-88 years) were examined. Characteristic of the pulmonary lesions were mass (85.5%) and infiltrates (14.5%). In the infiltration group, 36.4% were alveolar infiltrates and 63.6% were reticulonodular infiltrates. The mean of the longest diameter of pulmonary lesion was 3.95 $\pm$ 1.99 cm (range 1.0-12.0 cm). The lesions were localized in right lung in 102 lesions (67.1%) and in left lung in 50 lesions (32.9%). The data are summarized in Table 1.

EBUS-TBLB

The lesions were visible on EBUS image in 150 out of 152 recorded patients (98.7%). The EBUS probe was located within the lesion in 103 patients and adjacent to the lesion in 47 patients. The lesion cannot be seen by EBUS image in 2 patients. Fluoroscopy was used in 79 patients (52%). The mean duration of EBUS was 3.55 $\pm$ 2.29 minutes (range 0.33-16.46 minutes). The data are summarized in Table 2.

Diagnosis was made by EBUS-TBLB in 101 patients and the overall diagnostic yield of EBUS-TBLB was 66.4%. The final diagnosis of all lesions is shown in Table 3, 99 cases were diagnosed of malignant disease (65.1%) and 53 cases were diagnosed of benign disease (34.9%). The diagnostic yield of EBUS-TBLB in benign lesions was significantly higher than that in malignant lesions (81.1% and 58.6%, respectively, $p = 0.004$).

The EBUS-TBLB was non-diagnostic in 51 patients (33.6%). The final diagnosis was made by other methods of specimen collection such as cytology of bronchoalveolar lavage fluid or bronchial wash or bronchial brush (8 cases), surgical resection (16 cases), repeated conventional bronchoscopic procedure with fluoroscopy guidance (8 cases), pleural effusion cytology (1 case), pleural biopsy (2 cases), transthoracic fine needle aspiration (7 cases) and EBUS-guided transbronchial needle aspiration (1 case) and clinical course of metastatic disease or benign disease (8 cases).

The factors which influenced the diagnostic yield of EBUS-TBLB are shown in Table 4. The diagnostic yield of EBUS-TBLB in infiltrative lesions was significantly higher than that in mass lesions (86.4% and 13.6%, respectively, $p = 0.024$). The pattern of infiltration did not affect the yield by EBUS-TBLB. The diagnostic yield for the lesions located in the left lung was higher than that located in the right lung. The lesions in left upper lobe, lingula and lower lobe were diagnosed by EBUS-TBLB as 76.5%, 100% and 66.7%, respectively. The lesions in right upper lobe, middle lobe and lower lobe were diagnosed by EBUS-TBLB in 58.1%, 58.8% and 48.0% of cases, respectively. The size of the lesions (< 3 cm or ≥ 3 cm), distribution of the lesions (central or peripheral distribution), distance from the lesion to orifice of working channel and duration of EBUS did not affect the diagnostic yield by EBUS-TBLB.

No significant difference of diagnostic yields were observed whether fluoroscopy was used or not. The diagnostic yield of EBUS-TBLB when the EBUS probe was located within the lesion was significantly higher than that when located adjacent to the lesion (74.8% and 51.1%, respectively, $p = 0.004$).

No major complications, such as significant bleeding, severe hypoxemia or pneumothorax, which related to procedure, were observed in this study.

Discussion

Flexible bronchoscopy with transbronchial lung biopsy (TBLB) was used to diagnose peripheral pulmonary lesions. Fluoroscopic guidance is required in most cases to direct the operator to the target bronchus with a wide range of diagnostic yield. But it is

Table 1. Characteristics of patients undergoing EBUS-TBLB.

Baseline characteristics	Number (%)
Number of patients	152
Age (years)	60.68 ± 13.45 (24-88)*
Sex	
Female	67 (44.1)
Male	85 (55.9)
Characteristic of the lesions	
Mass	130 (85.5)
Infiltrates	22 (14.5)
Alveolar infiltrates	8 (36.4)
Reticulonodular infiltrates	14 (63.6)
Size of the lesions (cm)	3.95 ± 1.99 (1.0-12.0)*
< 3 cm	47 (35.1)
3 cm or more	87 (64.9)
Location of the lesions	
Right lung	102 (67.1)
Upper lobe	48 (31.6)
Middle lobe	22 (14.5)
Lower lobe	32 (21.1)
Left lung	50 (32.9)
Upper lobe	26 (17.1)
Lingula	7 (4.6)
Lower lobe	17 (11.2)
Central or peripheral distribution	
Peripheral lesion	76 (50.0)
Central lesion	76 (50.0)

* mean ± SD (range)

Table 2. Characteristics and results of EBUS-TBLB.

Variables	Number (%)
Distance from tip of bronchoscope to the lesion (cm)	4.10 ± 1.44 (1.0-8.0)*
Location of EBUS probe	
Within the lesions	103 (68.7)
Adjacent to the lesions	47 (31.3)
Not seen from EBUS image	2
Duration of EBUS (minutes)	3.55 ± 2.29 (0.33-16.46)*
Usage of fluoroscopy	79 (52.0)
Major complication	0 (0)
Final diagnosis	
Non-malignancy	53 (34.9)
Malignancy	99 (65.1)
Overall diagnostic yield of EBUS-TBLB***	101/152 (66.4)

* mean ± SD (range)

often difficult to confirm whether the forceps has reached the lesion. In our institution, Sompradeekul et al[10] designed a retrospective study to evaluate the diagnostic yield of TBLB with fluoroscopic guidance

Table 3. Final clinical diagnosis in 152 patients

Final clinical diagnosis	Result (No.)	Lesions diagnose by EBUS-TBLB
Benign	**53**	**43/53 (81.1%)**
- Pulmonary tuberculosis	27	
- Pneumonia	7	
- Inflammatory lesion	7	
- Aspergillosis	2	
- Cryptococcosis	3	
- Chronic eosinophilic pneumonia	1	
- Benign pulmonary nodule	6	
Malignancy	**99**	**58/99 (58.6%)**
- Adenocarcinoma	56	
- Undifferentiated NSCLC	15	
- Squamous cell carcinoma	4	
- Small cell carcinoma	4	
- Neuroendocrine carcinoma	1	
- Metastatic carcinoma	4	
- Malignancy, unspecified	14	
- Myxofibrosarcoma	1	
Total	**152**	**101 (66.4%)**

* NSCLC = non-small-cell lung cancer

(Flu-TBLB) compared with TBLB without guidance by fluoroscopy (NFlu-TBLB) in non-endobronchial lung lesions. They found the diagnostic yield in Flu-TBLB and NFlu-TBLB group were 43.8% and 32.9%, respectively ($p = 0.003$). Recently, the EBUS was used to localize the peripheral pulmonary lesions. In present study, we found the diagnostic yield of EBUS-TBLB was 66.4%.

Several studies reported the diagnostic yield of EBUS-TBLB for diagnosis of pulmonary lesions (Table 5). Herth et al[7] found the diagnostic yields of EBUS-TBLB was 80%. Chung et al[8] found the diagnostic yield of TBLB in group of EBUS, with a measured distance from tip of bronchoscope to the lesion, was significantly higher than that in the group of EBUS-TBLB alone (78.9% and 57.1%, respectively). The overall diagnostic yield was 68.1%. The diagnostic yield of EBUS-TBLB in the present study was lower; the reasons might be due to the lower number of lesions which the EBUS probe located within by EBUS image (68.7% in present study and 76.1% in the study of Chung)[8].

The lesion's size $\geq$ 3 cm and reticulonodular pattern of infiltrates were diagnosed as more than lesion's size < 3 cm and alveolar pattern of infiltrates, but there was no statistical significance. No different results were observed according to central or peripheral distribution of the lesions on chest radiograph, distance from the tip of bronchoscope to the lesion and duration of EBUS.

In our study, the diagnostic yield in infiltrative lesion was higher than mass lesion (86.4% and 63.1%, respectively, $p = 0.024$) because the mass lesion had more localized pathology, so the EBUS probe and biopsy forceps had a higher possibility to slip off from the lesion. The lesions which the EBUS probe located adjacent to it were diagnosed less than lesions which the EBUS probe located within it, this could be explained by the fact that the EBUS probe might only be in contact with outer surface of the lesion. These results consistent with the results in previous studies[9,11-13].

However, the EBUS-TBLB had some limitations. First, the tip of bronchoscope might be dislocated from the target bronchus when the EBUS probe was withdrawn from working channel or when a patient drew a deep breath. Second, although the EBUS probe was located within the lesion on the EBUS image and the biopsy forceps were in the target bronchus, it was possible that the forceps might slip off from the lesion due to patient's respiration.

In order to overcome this disadvantage, addi-

Table 4. Factors influencing the diagnostic yield of EBUS-TBLB.

Variable	Positive diagnosis, number (%)	Negative diagnosis, number (%)	p-value
Characteristic of the lesions			0.024
Mass	82 (63.1)	48 (36.9)	
Infiltrates	19 (86.4)	3 (13.6)	
Pattern of infiltrates			0.291
Alveolar	6 (75.0)	2 (25.0)	
Reticulonodular	13 (92.9)	1 (7.1)	
Size of the lesions	3.81 $\pm$ 1.91*	4.20 $\pm$ 2.13*	
< 3 cm	30 (63.8)	17 (36.2)	0.548
$\geq$ 3 cm	56 (64.4)	31 (35.6)	
Location of the lesions			0.322
Right lung	66 (64.7)	36 (35.3)	
Left lung	35 (70.0)	15 (30.0)	
Distribution of the lesions			0.151
Central	54 (71.1)	22 (28.9)	
Peripheral	47 (61.8)	29 (38.2)	
Usage of fluoroscopy			0.084
Fluoroscopy	57 (72.2)	22 (27.8)	
Non-fluoroscopy	44 (60.3)	29 (39.7)	
Measured distance before biopsy (cm)	4.15 $\pm$ 1.51*	4.02 $\pm$ 1.31*	0.600
Location of EBUS probe on image			0.004
Within the lesion	77 (74.8)	26 (25.2)	
Adjacent to the lesion	24 (51.1)	23 (48.9)	
Duration of EBUS (minutes)	3.23 $\pm$ 2.10*	4.19 $\pm$ 2.53*	0.014
Final diagnosis			0.004
Benign	43 (81.1)	10 (18.9)	
Malignancy	58 (58.6)	41 (41.4)	

* mean $\pm$ SD (range)

Table 5. The diagnostic yield of EBUS-TBLB in pulmonary lesions.

Study	Technique	Number of patients	Diagnostic yield (%)
Herth et al[7]	EBUS-TBLB and fluoroscopy-guided TBLB	50	80
Chung et al[8]	EBUS with and without measuring distance from tip of bronchoscope to the lesion	113	68.1

tional technique such as bronchial brushing with transbronchial lung biopsy may be improve the diagnostic yield. Saita S, et al[14] found that the diagnostic yield of bronchial brushing in visible bronchial lesions is higher than biopsy alone and a combination of these two methods gives the best diagnostic accuracy, however, no study in peripheral pulmonary lesions was established. Currently, the guide-sheath (GS) or curette-loaded GS has been developed to improve the diagnostic yield of EBUS-TBLB. The GS or curette-loaded GS may prevent dislocation of the tip of bronchoscope. Several studies[9,11-13] were conducted to evaluate the diagnostic yield of EBUS with guide-sheath (GS) or curette-loaded GS-guided TBLB in pulmonary lesions and found that the diagnostic yields were 58-77% (Table 6).

According to our results, EBUS-TBLB is a safe procedure and this technique can increase the diagnostic yield for diagnosing pulmonary lesions compared to conventional bronchoscopy with minimal ad-

Table 6. The diagnostic yield of EBUS with guide sheath or curette-loaded GS-guided TBLB in pulmonary lesions

Study	Technique	Number of patients	Diagnostic yield (%)
Herth et al[9]	EBUS with guide sheath-guided TBLB	54	70
Kikuchi et al[11]	EBUS with guide sheath-guided TBLB	24	58.3
Kurimoto et al[12]	EBUS with guide sheath-guided TBLB	150	77
Yoshikawa et al[13]	EBUS with guide sheath-guided TBLB and bronchial brush	123	61.8

ditional time. EBUS-TBLB can be used as a choice of diagnostic procedure for peripheral pulmonary lesions in centers which the guide-sheath are not available on the market.

Conclusion

The endobronchial ultrasound-guided transbronchial lung biopsy is a safe procedure for diagnosis of peripheral pulmonary lesions. Our results indicated that the EBUS-TBLB improves the diagnostic yield compared to conventional brochoscopy.

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การศึกษาประโยชน์ของการใช้อัลตราซาวด์หลอดลมเพื่อช่วยในการวินิจฉัยรอยโรคในปอด

ศุภฤกษ์ ดิษยบุตร, แจ่มศักดิ์ ไชยคุนา, อรรถ นานา

ภูมิหลัง: *การส่องกล้องตรวจหลอดลมเป็นวิธีที่ใช้ในการวินิจฉัยรอยโรคในปอด ที่ไม่สามารถเห็นได้จากการส่องกล้องตรวจหลอดลมซึ่งพบว่ามีข้อจำกัดบางประการ ได้แก่ ไม่สามารถยืนยันตำแหน่งของคีมตัดชิ้นเนื้อได้ว่าอยู่ในหลอดลมที่ไปสู่รอยโรคจริงหรือไม่ ปัจจุบันได้มีการนำหัวอัลตราซาวด์หลอดลมซึ่งมีขนาดเล็ก และสามารถใส่ผ่านกล้องส่องตรวจหลอดลมได้ เพื่อยืนยันตำแหน่งของรอยโรคในปอด ซึ่งอาจทำให้การตรวจ โดยการตัดชิ้นเนื้อจากรอยโรคในปอดเพื่อส่งตรวจทางพยาธิวิทยาทำได้แม่นยำมากขึ้น*

วัตถุประสงค์: *เพื่อศึกษาประโยชน์ของการใช้อัลตราซาวด์หลอดลมร่วมกับการส่องกล้องตรวจหลอดลมเพื่อช่วยในการวินิจฉัยรอยโรคในปอด*

วัสดุและวิธีการ: *มีผู้ป่วยที่มารับการส่องกล้องตรวจหลอดลมที่โรงพยาบาลศิริราชเข้าร่วมการศึกษาทั้งหมด 152 คน ซึ่งเป็นผู้ป่วยที่มีรอยโรคในปอดที่เห็นได้จากภาพรังสีทรวงอก แต่ไม่เห็นความผิดปกติจากการส่องกล้องตรวจหลอดลม ผู้ป่วยจะได้รับการส่องกล้องตรวจหลอดลมตามวิธีมาตรฐาน ร่วมกับการใช้อัลตราซาวด์หลอดลม เพื่อค้นหาตำแหน่งของรอยโรค ภายหลังจากพบตำแหน่งของรอยโรคในปอดโดยดูจากภาพอัลตราซาวด์ และวัดระยะตั้งแต่รอยโรคในปอดจนถึงปลายของกล้องส่องตรวจหลอดลมแล้ว แพทย์จะทำการตัดชิ้นเนื้อในปอดเพื่อส่งตรวจทางพยาธิวิทยา และรวบรวมข้อมูลเพื่อคำนวณหาโอกาสที่จะได้การวินิจฉัยจากวิธีการดังกล่าว (diagnostic yield)*

ผลการศึกษา: *สามารถตรวจพบรอยโรคในปอดจากภาพอัลตราซาวด์หลอดลมทั้งหมด 98.7% และสามารถให้การวินิจฉัยได้ (diagnostic yield) 66.4% โดยรอยโรคที่เป็น infiltrates สามารถให้การวินิจฉัยได้มากกว่ารอยโรคที่มีลักษณะเป็นก้อน (86.4% และ 63.1% ตามลำดับ) ภาพอัลตราซาวด์ที่หัวอัลตราซาวด์อยู่ภายในรอยโรคจะสามารถให้การวินิจฉัยรอยโรคในปอดได้มากกว่า กรณีที่หัวอัลตราซาวด์อยู่ข้างรอยโรค (74.8% และ 51.1% ตามลำดับ) และจากผลการตรวจทางพยาธิวิทยาพบว่าการใช้อัลตราซาวด์หลอดลม ร่วมกับการส่องกล้องตรวจหลอดลมสามารถให้การวินิจฉัยรอยโรคที่เป็นมะเร็งและรอยโรคที่ไม่ใช่มะเร็งได้ 81.1% และ 58.6% ตามลำดับ และใช้เวลาการทำอัลตราซาวด์หลอดลมโดยเฉลี่ยเท่ากับ 3.55 $\pm$ 2.29 นาที และไม่พบว่ามีภาวะแทรกซ้อนที่รุนแรงจากการทำอัลตราซาวด์หลอดลมและการตัดชิ้นเนื้อจากรอยโรคในปอด*

สรุป: *การใช้อัลตราซาวด์หลอดลมร่วมกับการส่องกล้องตรวจหลอดลม เพื่อช่วยในการวินิจฉัยรอยโรคในปอดเป็นวิธีที่ปลอดภัย และช่วยเพิ่มโอกาสในการวินิจฉัยรอยโรคในปอดที่ไม่สามารถเห็นได้จากการส่องกล้องหลอดลมเมื่อเทียบกับการส่องกล้องตรวจหลอดลมโดยวิธีเดิม*