Original Article

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for the Diagnosis of Central Intrapulmonary Lesions not Visible by Conventional Bronchoscopy

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Background: The diagnosis of the central intrapulmonary lesion is technically challenge. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is useful for diagnosis of mediastinal lesion and staging before lung cancer surgery. The usefulness of EBUS-TBNA for central intrapulmonary lesion will be evaluated.

Objective: To evaluate the diagnostic performance and safety of convex probe endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of central intrapulmonary lesion and the usefulness of rapid on-site evaluation for samples taken during EBUS-TBNA.

Materials and Methods: The present prospective cross-sectional study was conducted to enroll 175 patients with central intrapulmonary lesions underwent EBUS-TBNA at Vachira Phuket Hospital from June 2013 to May 2017. The diagnostic yield, sensitivity, specificity, PPV, NPV, diagnostic accuracy and associated factors were analyzed.

Results: EBUS-TBNA was performed to 175 patients with central intrapulmonary lesion. The overall diagnostic yield of EBUS-TBNA was 90.3%. The diagnostic yield in the benign lesion was 82.1% and malignant lesion was 91.8%. The sensitivity, specificity, PPV, NPV, and diagnostic accuracy for detecting intrapulmonary lesion were 91.8%, 100%, 100%, 70%, and 91.4%, respectively. Rapid on-site evaluation (ROSE) was available in 52 patients. ROSE was the most important factor that helped enhance EBUS-TBNA diagnostic accuracy ($p = 0.005$). A logistic regression analysis revealed that heterogenous echogenicity and ill-defined margin from EBUS image were predictive factors for malignant lung lesion with the hazard ratio of 26.136 ($p<0.001$) and 3.947 ($p = 0.001$), respectively. The availability of ROSE resulted in a significant reduction in the number of passes per lesion (mean: 3.40±0.66 vs 6.07±1.34, $p<0.001$) and the duration of procedure (mean: 32.33±6.50 vs 50.32±4.99, $p<0.001$). The cytologic result from ROSE was false negative in 2 samples with the sensitivity and specificity were 92% and 100%, respectively.

Conclusion: EBUS-TBNA is an effective and safe procedure for the diagnosis of central intrapulmonary lesion not visible by conventional bronchoscopy. It is minimally invasive and improves the diagnostic performance.

Keywords: Endobronchial ultrasound-guided transbronchial needle aspiration, Central intrapulmonary lesion, Rapid on-site evaluation, Convex probe endobronchial ultrasound

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Transbronchial lung biopsy via flexible bronchoscopy is the most commonly used for the diagnosis of intrapulmonary lesions, especially peripheral pulmonary lesions. Endobronchial ultrasound with a guide sheath with or without fluoroscopy is a modality applied to improve diagnostic yield of bronchoscopic biopsies[1-5]. However, the central intrapulmonary lesions are not visible with conventional bronchoscopy due to locate adjacent to the airway, conventional bronchoscopy usually fails to give a definite diagnosis[6]. Computerized tomography-guided transbronchial needle biopsy can be used for the diagnosis of central intrapulmonary lesion, but there is a high risk for pneumothorax and hemoptysis[7]. Transbronchial needle aspiration (TBNA) is one of the procedure for the diagnosis of intrapulmonary lesion adjacent to the central airway, but the diagnostic yield is variable and operator-dependent [8,9].

Convex probe endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been shown to be useful for mediastinal lymph

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node staging in patients with lung cancer and for the diagnosis of mediastinal lymphadenopathy[10-12]. EBUS-TBNA is a minimally invasive procedure performed under local anesthesia and conscious sedation enabled mediastinal and hilar lymph node assessment with a high sensitivity. In addition to mediastinal and hilar lymph nodes, EBUS-TBNA can assess peritracheal and peribronchial lesions as long as it is within the reach of the EBUS-TBNA scope[13-16]. But the data from clinical researches are limited. In the present study, the author tried to evaluate the value of EBUS-TBNA for the diagnosis of central intrapulmonary lesion located near the airway and not visible by conventional bronchoscopy.

Materials and Methods

Patients

The present study was a prospective cross-sectional study aimed to evaluated the diagnostic performance of EBUS-TBNA in patients with central intrapulmonary lesions, detected by computed tomography (CT) of the chest. The central intrapulmonary lesions were defined as an intrapulmonary nodule, mass or infiltration located adjacent to the tracheobronchial tree (Figure A). The lesions were not visualized by conventional bronchoscopy (no evidence of endobronchial lesion). The patients with central intrapulmonary lesions underwent EBUS-TBNA from June 2013 to May 2017 at the Department of Medicine, Vachira Phuket Hospital were enrolled. The patients who had contraindication for bronchoscopy were excluded.

The previous retrospective study with the highest number of sample size, Zhao H, et al. reported the diagnostic yield of EBUS-TBNA for the diagnosis of intrapulmonary lesions was 89.4%[15]. The sample size was calculated from standard formula with 5% margin of error and 10% of missing or incomplete data, the minimal sample size required for the present study was 166 patients.

The present study was approved by the Ethics Committee of Vachira Phuket Hospital. Written informed consent was obtained from all the patients prior to performing the procedure.

Equipment

EBUS-TBNA was performed using curvilinear ultrasound bronchoscope (BF UC180F; Olympus, Tokyo, Japan). The bronchoscope was connected to EU-ME1 ultrasound unit (Figure B). The 22-gauge needle was used for aspiration the targeted lesions. Before EBUS-TBNA, a standard conventional flexible bronchoscope (BF-180, Olympus, Tokyo, Japan) was prior used to examine the abnormality of tracheobronchial tree.

Bronchoscopic procedure and EBUS-TBNA

All patients were in supine position. Local anesthesia with 4% lidocaine was used and the procedures were mostly performed under moderate sedation using intravenous midazolam (2 mg) and fentanyl (25 mg). Oxygen was administered by a nasal device, and the flow was adjusted to maintain the pulse oximetric saturation more than 92%. Electrocardiogram and blood pressure were monitored continuously during the procedure.

A standard conventional bronchoscope was first used to examine the tracheobronchial tree to ensure that no endobronchial lesion. If the endobronchial lesion was visible by conventional bronchoscopy, this patient was excluded from the study and the biopsy was done for definite diagnosis. If no endobronchial lesion, the curvilinear ultrasound bronchoscope was subsequently advanced through the vocal cord. For paratracheal lesion, the scope was positioned endotracheally. For peribronchial lesion, the scope was positioned in the respective bronchi in order to visualized the lung lesion. Doppler ultrasound was used to identify vessels, if necessary. TBNA was performed using a 22-gauge needle. Once the needle inside the lesion, the stylet was removed and negative pressure was applied by a syringe (Figure C). The needle was moved back and forth inside the tumor. Finally, the needle was removed from the working channel of ultrasound bronchoscope. The rest of the aspirated material was smeared onto glass slides for cytological examination. For histopathological examination, the aspirated specimens were pushed onto the filter paper for processing the cell block and fixed with 10% formalin and stained, using hematoxylin and eosin (H&E). The specimens on glass slide were air-dried and fixed in 95% alcohol and stained using H&E. If rapid on-site evaluation was available, dried smears were evaluated by an on-site cytolopathologist to confirm that the cell material obtained was adequate quality and made the initial diagnosis (positive for malignancy or negative). If ROSE was unavailable, the specimens were sent to the department of pathology later. Immunohistochemical staining was also performed when necessary. The complications (bleeding, hypoxemia, pneumothorax or pneumomediastinum) and final diagnosis of each cases were reviewed.

The cytological and histological specimens from

EBUS-TBNA were categorized as malignant and benign. The diagnostic standard for benign disease was cytopathological or microbiological confirmation of a specific benign disease, surgical confirmation of lesions showing no malignant cells, or spontaneous regression of lung parenchymal lesion after EBUS-TBNA during follow-up of more than 3 months. Malignant disease was defined as confirmation of malignant cells or tissues from EBUS-TBNA, bronchoscope with transbronchial lung biopsy, CT-guided transthoracic needle biopsy or surgical lung biopsy.

Statistical analysis

The data were presented as number (%) or mean±SD (range). Pearson's Chi-square test was used to test the association between categorical factors and diagnostic results; *p*-value <0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy rate with 95% confidence interval were calculated using the standard definitions in the diagnosis of the intrapulmonary lesions and ROSE. Logistic regression analysis was used to evaluation the effect of influencing factors on the prediction of malignancy. All statistical analyses were performed using the SPSS software, version 21.

Results

Patients characteristics

From June 2013 to May 2017, total of 175 patients underwent EBUS-TBNA for central intrapulmonary lesions. There were 131 (74.9%) males and 44 (25.1%) females. The mean age was 59.4±14.65 years (range 19 to 87 years). Among 175 subjects, 117 (66.9%) patients were smoker and 58 (33.1%) patients were non-smoker. Characteristic of the central intrapulmonary lesions were nodule or mass in 151 (86.3%) cases and infiltrate in 24 (13.7%) cases. The majority of lesions were more than 3 cm in short diameter. The mean diameter of pulmonary lesions was 4.95±1.75 cm (range 2.20 to 10.90 cm). The lesions were localized in the right upper lobe in 76 lesions (43.4%), the right middle lobe in 12 lesions (6.9%), the right lower lobe in 28 lesions (16.0%), the left upper lobe in 31 lesions (17.7%), the lingular segment in 9 lesions (5.1%), and the left lower lobe in 19 lesions (10.9%). The baseline characteristics were summarized in Table 1.

Table 1. Baseline characteristics of patients undergoing EBUS-TBNA

Baseline characteristic	Number (%) or mean±SD (range)
Number of patients	175
Age	59.45±14.65 (19-87)
Sex	
Male	131 (74.9)
Female	44 (25.1)
Patients disposition	
Inpatient	37 (21.1)
Outpatient	138 (78.9)
Size of the lesion	4.95±1.75 (2.20-10.90)
≤ 3 cm	22 (12.6)
> 3 cm	153 (87.4)
Characteristic of the lesions	
Nodule or mass	151 (86.3)
Infiltrate	24 (13.7)

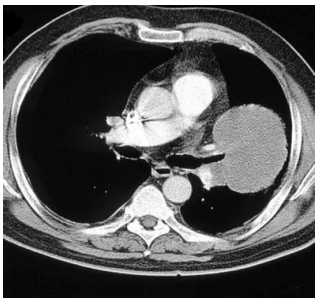

Figure A. Chest CT scan of 65-year-old male showing a mass in the left upper lobe, adjacent to LUL bronchus

Figure B. Curvilinear ultrasound bronchoscope

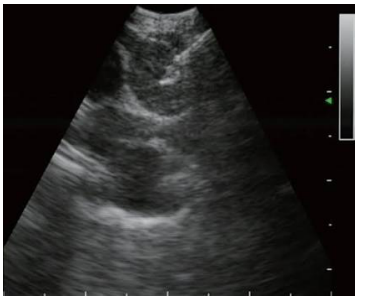

Figure C. Ultrasonography from EBUS-TBNA of the lesion showing the 22-gauge needle within the lesion

Chronic cough was the most common clinical presentation in patients undergoing EBUS-TBNA (146 cases, 83.4%); 58 cases (33.1%) presented with progressive dyspnea; 50 cases (28.6%) presented with weight loss; 38 cases (21.7%) presented with anorexia; 7 cases (4.0%) presented with hoarseness and 14 cases (8%) were asymptomatic, the pulmonary lesions were found from yearly checkup.

Endobronchial ultrasound-guided transbronchial needle aspiration procedures

EBUS-TBNA was successful performed in all 175 intrapulmonary lesions. The location of pulmonary lesions sampled by EBUS-TBNA and puncture sites were shown in Table 3. The most lesions were located in right upper lobe and punctured predominantly through the trachea. Right lower lobe lesions were sampled through right main bronchus, bronchus intermedius and right lower lobe basal trunk. The smallest number of lesions were located in right middle lobe and sampled through right middle lobe lobar bronchus and bronchus intermedius. Left upper lobe lesions were sampled through left second carina, distal left main bronchus and the left side of trachea. Left lower lobe lesions were targeted through left upper lobe lobar bronchus and left lower lobe lobar bronchus. The complication from EBUS-TBNA procedure was found in 26 patients (14.9%). Twelve patients experienced minor bleeding and fourteen patients experienced transient desaturation. All patients recovered from their complication uneventfully. No major or life-threatening complications associated with EBUS bronchoscopy were documented.

The procedure-related findings of patients undergoing EBUS-TBNA were shown in Table 4. Rapid on-site evaluation was available in 52 lesions (29.7%). The mean number of TBNA puncture per lesion was 5.27±1.69 times (range, 2 to 10). The majority of the patients were punctured at central core within the lesion (107 patients, 61.1%) and 68 patients (38.9%) were punctured at peripheral site. The mean time of procedure was 44.97±9.89 minutes (range 20 - 60 minutes). The most common echogenicity of EBUS image was heterogenous echo (130 patients, 74.3%) and ill-defined margin (98 patients, 56%).

Table 2. Baseline characteristics of patients undergoing EBUS-TBNA

Baseline characteristic	Number (%) or mean±SD (range)
Location of the lesion	
Right lung	116 (66.3)
Upper lobe	76 (43.4)
Middle lobe	12 (6.9)
Lower lobe	28 (16.0)
Left lung	59 (33.7)
Upper lobe	31 (17.7)
Lingular segment	9 (5.1)
Lower lobe	19 (10.9)
Smoking status	
Smoker	117 (66.9)
Current smoking	62 (53.0)
Stop smoking	55 (47.0)
Non-smoker	58 (33.1)
Number of cigarette in smoker (pack-year)	35.32±12.33 (7-100)
Clinical presentation	
Asymptomatic	14 (8.0)
Chronic cough	146 (83.4)
Progressive dyspnea	58 (33.1)
Weight loss	50 (28.6)
Hoarseness	7 (4.0)
Anorexia	38 (21.7)

Table 3. Location of lung parenchymal lesion and puncture sites of EBUS-TBNA

Pulmonary lesion location	Puncture site	Number (%)
Right upper lobe (n = 76)	Trachea (right side)	33 (18.9)
	Right main bronchus	11 (6.3)
	Right upper lobe bronchus	19 (10.8)
	Bronchus intermedius	13 (7.4)
Right middle lobe (n = 12)	Right middle lobar bronchus	7 (4.0)
	Bronchus intermedius	5 (2.8)
Right lower lobe (n = 28)	Right main bronchus	3 (1.7)
	Bronchus intermedius	13 (7.4)
	Right lower lobe basal trunk	12 (6.9)
Left upper lobe (n = 40) (include lingular segment)	Left second carina	16 (9.1)
	Distal left main bronchus	12 (6.9)
	Trachea (left side)	12 (6.9)
Left lower lobe (N=19)	Left upper lobe lobar bronchus	8 (4.6)
	Left lower lobe lobar bronchus	11 (6.3)

Table 4. Procedure-related findings of patients undergoing EBUS-TBNA

Procedure details	Number or Mean±SD (range)
Rapid on-site evaluation (ROSE)	52 (29.7)
Number of passes per lesion	5.27±1.69 (2 to 10)
Location of the puncture site within the lesion	
Central core	107 (61.1)
Peripheral site	68 (38.9)
Time to procedure completion (minute)	44.97±9.89 (20 to 60)
Echogenicity of EBUS image	
Heterogenous echogenicity	130 (74.3)
Homogenous echogenicity	45 (25.7)
Margin of EBUS image	
Ill-defined	98 (56.0)
Well-defined	77 (44.0)
Result of EBUS image in all patients	
Diagnostic	158 (90.3)
Undiagnostic	17 (9.7)

The final diagnosis and diagnostic performances of EBUS-TBNA

The final diagnosis of all lesions were shown in Table 5. The established diagnosis was benign in 28 patients (16%) and malignancy in 147 patients (84%). In the malignant group, the patients were diagnosed with lung cancer in 128 cases (37 cases with small cell lung cancer, 91 cases with non-small cell lung cancer), metastatic carcinoma in 9 cases, lymphoma in 2 cases, neuroendocrine tumor in 5 cases, sarcomatoid carcinoma in 1 case, round cell sarcoma in 1 case and mucoepidermoid carcinoma in 1 case.

Diagnose were made by EBUS-TBNA in 158 patients and overall diagnostic yield was 90.3%. The subgroup analysis in benign and malignant lesions, the definitive diagnosis rate of EBUS-TBNA for intrapulmonary lesions near the central airway was 82.1% (23/28) in benign lesions and 91.8% (135/147) in malignant lesions. The diagnosis in the EBUS-TBNA finding-negative patients (17 patients) were made by other methods of specimen collection such as thoracotomy with lobectomy in 12 patients (70.6%), computerized tomography-guided transthoracic needle biopsy (TTNB) in 4 patients (23.5%) and bronchoscopy with transbronchial lung biopsy in 1 patients (5.9%).

The sensitivity (95% CI), specificity (95% CI), positive predictive value (95% CI), negative predictive value (95% CI), and diagnostic accuracy rate (95% CI) of EBUS-TBNA for the diagnosis of central intrapulmonary lesions were 91.8% (86.3-95.3), 100% (87.9-100.0), 100% (97.2-100.0), 70% (54.6-81.9) and 93.1% (88.3-96.4), respectively (Table 6). The factors which influenced diagnostic performance of EBUS-TBNA were shown in Table 7. The diagnostic yield in the rapid on-site evaluation (ROSE) group was higher than in the non-ROSE group (100% and 86.2%, respectively, $p = 0.005$). The characteristic of the lesion, size of the lesion, location of the lesion, type of EBUS image, image margin, and final diagnosis (benign or malignant lesion) did not affect the diagnosis yield by EBUS-TBNA. Procedurally, there was no significant difference in positivity when the location of puncture site was obtained from center or periphery of the lesion.

The morphological characteristics of the sample intrapulmonary lesions were detailed in Table 8. For the radiographic size of the lesion, the lesions ≤ 3 cm and > 3 cm were not effected on the diagnosis of benign or malignancy. For echogenicity, the malignant and benign lesions were characterized as heterogenous echogenicity in 125 cases (96.2%) and 5 cases (3.8%), respectively, but homogenous echogenicity in 22 cases (48.9%) and 23 cases (51.1%), respectively. The lesions were characterized as heterogenous echogenicity tended to suggest malignant intrapulmonary lesion (hazard ratio 26.136) and homogenous echogenicity tended to suggest benign intrapulmonary lesion ($p < 0.001$).

For image margin, the malignant lesions were ill-defined in 90 cases and well-defined in 57 cases, the benign lesions were ill-defined in 8 cases and well defined in 20 cases. The lesions were characterized as ill-defined margin tended to suggest malignant intrapulmonary lesion than the lesion with well-defined margin (hazard ratio 3.947, $p = 0.001$)

Table 5. Established diagnosis in all patients

Final diagnosis	Number (%)	Diagnostic yield by EBUS-TBNA (%)
Benign lesion	28 (16.0)	23/28 (82.1)
Pulmonary tuberculosis	26 (14.9)	
Pulmonary nocardiosis	1 (0.6)	
Pulmonary cryptococcosis	1 (0.6)	
Malignant lesion	147 (84.0)	135/147 (91.8)
Non-small cell lung cancer	91 (52.0)	
Adenocarcinoma	59 (33.7)	
Squamous cell carcinoma	27 (15.4)	
Non-small cell carcinoma, NOS	5 (2.9)	
Small cell lung cancer	37 (21.1)	
Neuroendocrine tumor		
Low-grade neuroendocrine tumor	2 (1.1)	
Atypical carcinoid tumor	2 (1.1)	
Large cell neuroendocrine carcinoma	1 (0.6)	
Sarcomatoid carcinoma	1 (0.6)	
Round cell sarcoma	1 (0.6)	
Mucoepidermoid carcinoma	1 (0.6)	
Metastatic carcinoma		
Metastatic breast cancer	1 (0.6)	
Metastatic thymic carcinoma	3 (1.7)	
Metastatic ovarian carcinoma	1 (0.6)	
Metastatic thyroid carcinoma	1 (0.6)	
Metastatic gastric carcinoma	1 (0.6)	
Metastatic renal cell carcinoma	2 (1.1)	
Lymphoma	2 (1.1)	
Total	175	158/175 (90.3)

Table 6. Comparison of EBUS-TBNA* results of intrapulmonary lesions with final diagnosis

EBUS-TBNA results (N)	Final diagnosis (N)		
	Malignant (Number)	Benign (Number)	Total (Number)
Malignant	135	0	135
Benign	12	28	40
Total	147	28	175

*Endobronchial ultrasound-guided transbronchial needle aspiration

Sensitivity (135/147)*100 = 91.8% (95% CI = 86.3-95.3), Specificity (28/28)*100 =100% (95% CI = 87.9-100.0), PPV (135/135)*100 = 100% (95% CI = 97.2-100.0), NPV (28/40)*100 = 70% (95% CI = 54.6-81.9), Accuracy [(135+28)/175]*100 = 93.1% (95% CI = 88.3-96.4)

The utility of rapid on-site evaluation (ROSE) in EBUS-TBNA was shown in Table 9. EBUS-TBNA provided diagnostics to all 52 patients available for ROSE. In the ROSE group, the mean number of punctures was lower than in non-ROSE group (mean: 3.40 ± 0.66 versus 6.07 ± 1.34, $p < 0.001$). The time taken to complete the procedure showed the ROSE group was less than the non-ROSE group statistically (mean: 32.33 ± 6.50 minutes versus 50.32 ± 4.99 minutes, $p < 0.001$).

The cytologic result from ROSE was false negative in 2 cases (Table 10). The diagnostic performance of central intrapulmonary lesion, the concordance rate between the cytologic result of ROSE and the final histopathological diagnosis from cell block was 96.2%.

The sensitivity (95% CI) and specificity (95% CI) of ROSE compared to final histopathology from cell block were 92% (81.2-96.8) and 100% (34.2-100.0), respectively. ROSE had a positive predictive value (95% CI) of 100% (92.3-100), negative predictive value (95% CI) of 33.3% (9.7-70.0) and accuracy rate (95% CI) of 92.3% (81.5-97.9).

Discussion

The diagnosis of centrally located intrapulmonary lesions adjacent to the tracheobronchial tree has many modalities. The yield of conventional bronchoscopy with bronchial biopsy is nearly 100% in endoscopically visible lesions, but the yield is drop to 60% - 75% for invisible intraparenchymal lesion even with fluoroscopy

Table 7. Effect of the influencing factors on the accuracy of EBUS-TBNA

Factors	Positive diagnosis Number (%)	Negative diagnosis Number (%)	*p*-value
Characteristic of the lesion			0.708
Nodule and mass	137 (90.7)	14 (9.3)	
infiltrate	21 (87.5)	3 (12.5)	
Size of the lesion			0.237
≤ 3 cm	18 (81.8)	4 (18.2)	
> 3 cm	140 (91.5)	13 (8.5)	
Location of the lesion			0.885
Right lung	105 (90.5)	11 (9.5)	
Left lung	53 (89.8)	6 (10.2)	
Type of EBUS image			0.772
Heterogenous echo	118 (90.8)	12 (9.2)	
Homogenous echo	40 (88.9)	5 (11.1)	
Image margin			0.434
Ill-define	90 (91.8)	8 (8.2)	
Well-defined	68 (88.3)	9 (11.7)	
Rapid on-site evaluation (ROSE)			0.005
Available	52 (100.0)	0 (0.0)	
Unavailable	106 (86.2)	17 (13.8)	
Location of the puncture site			0.075
Central core	100 (93.5)	7 (6.5)	
Peripheral site	58 (85.3)	10 (14.7)	
Final diagnosis			0.155
Benign	23 (82.1)	5 (17.9)	
Malignancy	135 (91.8)	12 (8.2)	

Table 8. Effect of influencing factors and logistic regression analysis on the diagnosis and prediction of malignancy

Factors	Malignancy Number (%)	Benign Number (%)	Hazard ratio for predict malignancy	95% CI	*p*-value
Size of the lesion			1.662	0.558-4.951	0.357
≤ 3cm	17 (77.3)	5 (22.7)			
>3 cm	130 (85.0)	23 (15.0)			
Type of EBUS image			26.136	8.983-76.046	< 0.001
Heterogenous echo	125 (96.2)	5 (3.8)			
Homogenous echo	22 (48.9)	23 (51.1)			
Image margin			3.947	1.630-9.560	0.001
Ill-defined	90 (91.8)	8 (8.2)			
Well-defined	57 (74.0)	20 (26.0)			

[17-18]. Transthoracic needle aspiration (TTNA) is mainly used for the peripheral lesions, reported the yield of 92.1% [19]. For centrally lesions, TTNA increases the risk of pneumothorax and bleeding due to the need to puncture a needle through a significant amount of lung tissue [20]. Transbronchial needle aspiration (TBNA) is one of the modalities for diagnosis of the central lesions. The diagnostic yield of the blind TBNA has been reported to be 45.6% - 69.3%, depend on the size and location of the lesion, but the blindly performing TBNA through the bronchoscope increases the risk of penetration into the vascular structure and other structures in the thorax, especially there are no mucosal changes to guide the site of puncture [21-23]. EBUS-TBNA is a real-time transbronchial needle aspiration technique that can be used safely to the diagnosis of the central lesion.

The present study demonstrated EBUS-TBNA for central intrapulmonary lesions provided the diagnostic yield of 90.3%. The sensitivity and specificity to diagnose central lesions were 91.8% and 100%, respectively. The PPV, NPV, and accuracy of the procedure were 100%, 70%, and 93.1%, respectively. EBUS-TBNA is a relative safely procedure because it can identify the vascular structure by using doppler mode. EBUS-TBNA is the real-time procedure allows for continuous visualization of the needle throughout the lesion sampling, resulting in a higher diagnostic yield than blind TBNA.

In the previous study, Nakajima T, et al. [13] reported the sensitivity, specificity and diagnostic accuracy rate of EBUS-TBNA for diagnosis of intrapulmonary lesions were 94.1%, 100%, and 94.3%, respectively. Tournoy KG, et al. [14] reported a sensitivity of 82% and NPV of 23%. Verma A, et al. [24] reported a diagnostic yield of 86.4% and sensitivity of 86.5% for EBUS-TBNA in diagnosing central lung parenchymal lesions. The study sample was similar to the present study. The previous studies were summarized in Table 11.

About the morphologic findings of EBUS, the most literatures were studied in the mediastinal lymph nodes. When lymph nodes had the following features : short axis of more than 1 cm, round shape, distinct margin, heterogenous echogenicity, absence of central hilar structure or presence of coagulation necrosis sign, they tended to suggest metastatic lymph nodes [25]. The present study was the first study to investigate the influencing factors on the diagnosis and prediction

Table 9. The utility of ROSE in EBUS-TBNA

Parameters	ROSE group*	Non-ROSE group*	*p*-value
Accuracy of EBUS-TBNA**			0.005
Diagnosis, Number (%)	52 (32.9)	106 (67.1)	
Undiagnosis, Number (%)	0 (0.00)	17 (100.0)	
Number of passes per lesion (Mean±SD)	3.40±0.66	6.07±1.34	< 0.001
Duration of the procedure (Minutes)	32.33±6.50	50.32±4.99	< 0.001

*Rapid on-site evaluation

**Endobronchial ultrasound-guided transbronchial needle aspiration

Table 10. ROSE and correlation to final diagnosis

ROSE* result (N)	Final diagnosis		
	Malignant (Number)	Non-malignant (Number)	Total (Number)
Positive for malignancy	46	0	46
Negative for malignancy	4	2	6
Total	50	2	52

*Rapid on-site evaluation

Sensitivity (46/50) *100 = 92% (95% CI = 81.2-96.8), Specificity (2/2)*100 = 100% (95% CI = 34.2-100.0), PPV =(46/46)*100 = 100% (95% CI = 92.3-100.0), NPV = (2/6)*100 = 33.3% (95% CI = 9.7-70.0), Accuracy = [(46+2)/52]*100 = 92.3% (95% CI = 81.5-97.9)

Table 11. The study of EBUS-TBNA in central intrapulmonary lesion

Study	Study design	Number of patients	Diagnostic yield or accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Nakajima T, et al. [13]	Retrospective study	35	94.3	94.1	100	100	33.3
Tournoy KG, et al. [14]	Retrospective study	60	77	82	NA	NA	23
Verma A, et al. [24]	Retrospective study	37	86.4	86.5	NA	NA	NA
Zhao H, et al. [15]	Retrospective study	66	89.4	93.7	100	100	42.9
The present study	Prospective study	175	90.3	91.8	100	100	70

of malignancy. The author reported that heterogenous echogenicity and ill-defined margin from EBUS image tended to suggest malignant lung lesion, but no effect by the size of the lesion. Thus, the appearance of heterogenous echogenicity and ill-defined margin of sonographic feature from EBUS have the likelihood of being malignancy.

In the present study, the rapid on-site evaluation (ROSE) was available in 52 patients. In the patients of ROSE available, the diagnostic accuracy was higher than the unavailable group. The use of ROSE was associated with reduction in the number of needle passes per lesion (3.40 ± 0.66 vs 6.07 ± 1.34, $p < 0.001$) and less time to do procedure (32.33 ± 6.50 vs 50.32 ± 4.99, $p < 0.001$). The sensitivity, specificity, PPV, NPV and diagnostic accuracy of ROSE were 92%, 100%, 100%, 33.3%, and 92.3%, respectively. Wong RWM, et al. [26] studied the utility of ROSE on EBUS-TBNA in 188 patients. The sample patients including both intrathoracic lymph nodes and lung mass, but the patients with lung mass were enrolled in 37 patients (pre-ROSE 18 patients and post-ROSE 19 patients). The overall sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 94.4%, 100%, 100%, 95%, and 94%, respectively. In the post-ROSE group, the mean number of puncture was lower than in the pre-ROSE group, similar to the present study, but the duration of procedure was not applicable.

Conclusion

According to the current study, EBUS-TBNA is a safe procedure and the technique can increase the diagnostic performance of central intrapulmonary lesions not visible by conventional bronchoscopy. Rapid on-site evaluation is improved the diagnostic performance, decreased number of passes per lesion and decreased the time of procedure.

What is already known on this topic?

EBUS-TBNA is a real-time bronchoscopic procedure that can be used for the diagnosis of central intrapulmonary lesion with a high diagnostic yield. This procedure is minimal invasive and can be performed as outpatient setting with no major complication.

What is this study added?

1. Confirm the diagnostic performance of EBUS-TBNA for the diagnostic of central intrapulmonary lesion with a high diagnostic yield.
2. Availability of ROSE is increase diagnostic yield of EBUS-TBNA in central pulmonary lesion.
3. The appearance of heterogenous echogenicity and ill-defined margin of sonographic feature from EBUS have the likelihood of being malignancy.
4. The use of ROSE is associated with a reduction in the number of needle passes per lesion and less time to do procedure.
5. ROSE is very useful in conjunction with EBUS-TBNA with high sensitivity, specificity and diagnostic accuracy.

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Potential conflict of interest

The authors declare no conflict of interest.

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