

Comparison of diagnostic performances among bronchoscopic sampling techniques in the diagnosis of peripheral pulmonary lesions

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Background: There are many sampling techniques dedicated to radial endobronchial ultrasound (R-EBUS) guided flexible bronchoscopy (FB). However, data regarding the diagnostic performances among bronchoscopic sampling techniques is limited. This study was conducted to compare the diagnostic yields among bronchoscopic sampling techniques in the diagnosis of peripheral pulmonary lesions (PPLs).

Methods: A prospective study was conducted on 112 patients who were diagnosed with PPLs and underwent R-EBUS-guided FB between Oct 2012 and Sep 2014. Sampling techniques—including transbronchial biopsy (TBB), brushing cell block, brushing smear, rinsed fluid of brushing, and bronchoalveolar lavage (BAL)—were evaluated for the diagnosis.

Results: The mean diameter of the PPLs was 23.5±9.5 mm. The final diagnoses included 76 malignancies and 36 benign lesions. The overall diagnostic yield of R-EBUS-guided bronchoscopy was 80.4%; TBB gave the highest yield among the 112 specimens: 70.5%, 34.8%, 62.5%, 50.0% and 42.0% for TBB, brushing cell block, brushing smear, rinsed brushing fluid, and BAL fluid (BALF), respectively ($P<0.001$). TBB provided high diagnostic yield irrespective of the size and etiology of the PPLs. The combination of TBB and brushing smear achieved the maximum diagnostic yield. Of 31 infectious PPLs, BALF culture gave additional microbiological information in 20 cases.

Conclusions: TBB provided the highest diagnostic yield; however, to achieve the highest diagnostic performance, TBB, brushing smear and BAL techniques should be performed together.

Keywords: Flexible bronchoscopy (FB); peripheral pulmonary lesions (PPLs); endobronchial ultrasound (EBUS); sampling technique; diagnostic yield

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Introduction

Peripheral pulmonary lesions (PPLs) are common problems in clinical practice. Clinical data and radiographic finding, such as chest radiography and computed tomography (CT) can provide some clues for diagnosis. However, in some circumstances, definite diagnosis is required before deciding on the appropriate treatment. Therefore, respiratory specimens are needed to identify the etiology of the lesions. Flexible bronchoscopy (FB) is a widely used, minimally

invasive diagnostic technique for sampling respiratory specimens. Nevertheless, it is still a challenging task for pulmonologists to obtain accurate samplings that represent the etiologies of PPLs using this approach. FB can reach into the airway up to the subsegmental bronchi; beyond the visual range, the airway continually divides into many generations before the peripheral target is reached. Without guidance, FB cannot guarantee an accurate sampling at the exact location of the PPL, as is shown by its low diagnostic yield (1).

FB under fluoroscopic guidance has been implemented since the 1970s. Its overall diagnostic yield was around 78% (2). Nevertheless, the diagnostic efficacy of this approach is affected by the size of the lesion. For PPLs less than 2 cm, this technique provides a rather low diagnostic yield, varying from 11-42% (2-4).

Radial endobronchial ultrasound (R-EBUS) has been developed to enhance the diagnostic yield of PPLs by providing a detail ultrasound image of the lesion. This can confirm that the instrument has reached the target. In addition, R-EBUS generates more informative images to help select the most promising area for sampling, while fluoroscopy provides only the anatomical location. Compare with fluoroscopy-guided FB, bronchoscopy using R-EBUS with fluoroscopy guidance provided significantly higher diagnostic performance, especially for PPLs smaller than 20 mm (5,6).

There are many sampling techniques associated with R-EBUS-guided FB such as bronchoalveolar lavage (BAL), brushing, and biopsy. However, data regarding the diagnostic performances among bronchoscopic sampling techniques is limited. The aim of this study was to compare the diagnostic yields among bronchoscopic sampling techniques in the diagnosis of PPLs.

Methods

A prospective study was conducted on 112 patients who were diagnosed with PPLs and underwent R-EBUS-guided bronchoscopy between October 2012 and September 2014 in Ramathibodi Hospital, Mahidol University, Thailand. A PPL was defined as a pulmonary lesion that was surrounded by pulmonary parenchyma and was not endoscopically visible by bronchoscopy. A CT scan of the chest was performed in all cases, and the sub-subsegmental bronchus feeding to the PPL was selected prior to the bronchoscopic procedure. Only patients who had demonstrated feeding bronchi, regardless of the size, were selected for R-EBUS-guided FB. The size of the lesion was recorded by its longest diameter on the CT scan. All patients provided written, informed consent prior to participation. The study protocol was approved by the Ethics Committee on Human Experimentation at Ramathibodi Hospital, Faculty of Medicine, Mahidol University.

All bronchoscopies were performed in the bronchoscopy room, equipped with a fluoroscopy unit, using a flexible bronchoscope (BF-P180, Olympus, Tokyo, Japan: external diameter, 4.9 mm; channel diameter, 2.0 mm) via the transnasal route under local anesthesia. The bronchial

tree in both lungs was examined down to the level of subsegmental bronchi. Subsequently, a radial ultrasound miniprobe (UM-S20-17S, Olympus, Tokyo, Japan) with a guide sheath (GS) (SG-200C, Olympus, Tokyo, Japan) was inserted through the working channel of the bronchoscope and was advanced to the target sub-subsegmental bronchus until the lesion was located by EBUS and fluoroscopy images. The R-EBUS probe was then moved within the lesion under fluoroscopic control to identify the most suspicious area, in order to obtain the tissue specimens (7,8). Next, the probe was withdrawn under fluoroscopy, leaving the GS in place. A biopsy forceps and a bronchial brush were introduced through the GS to obtain samples from the site marked by fluoroscopy. Five brushings for cytological smear, five brushings for histology, and five biopsy samplings were performed. Finally, the GS was removed and BAL was performed at the target subsegmental bronchus by instilling with 50 mL of normal saline and aspiration into a trap. Either repeated instilling of 50 mL normal saline, filled up to a total of 100-150 mL or receiving 50 mL retrieved fluid indicated adequate lavage.

Specimens from transbronchial biopsy (TBB) were processed as a cell block for pathologic evaluation. They were collected in a microtube filled with 0.5 mL of normal saline and 1 mL of 10% formalin. The samples were centrifuged at 6,000 rpm for 5 min. The pellet was then embedded in paraffin and sectioned. Routine hematoxylin and eosin (H&E) staining was used on all cell block sections. Microbiological and immunohistochemical stains were applied in cases where special staining was indicated. Cell blocks from bronchial brushing samples were also processed in the same way as TBB specimens after the bronchial brush was rinsed in a microtube.

Each bronchial brushing cytology specimen was prepared by smearing on a microscopy slide and fixing immediately in a flask containing 95% alcohol, followed by staining using the Papanicolaou method. The rest of bronchial brushing was then irrigated with 3 mL of sterile normal saline to obtain new sample as rinsed brushing fluid. In addition, 1 mL of sterile normal saline solution was used to flush the material left in the GS into the rinsed brushing fluid sample. This fluid was sent to the laboratory for centrifugation and staining using the Papanicolaou method. The BAL fluid (BALF) was processed for cytology, Gram, acid-fast bacilli and modified Giemsa staining, and also microbial culture in all cases.

All sampling techniques (*Figure 1*), included TBB, brushing cell block, brushing smear, rinsed fluid of

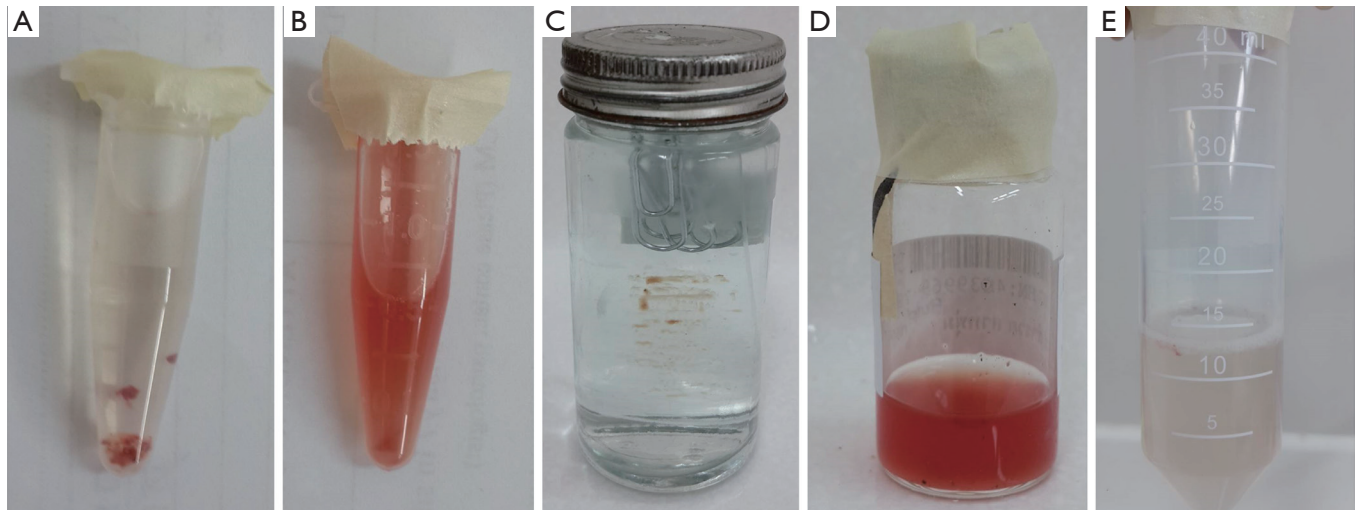


Figure 1 Specimens obtained from various sampling techniques: (A) transbronchial biopsy; (B) brushing cell block; (C) brushing smear; (D) rinsed fluid of brushing; (E) bronchoalveolar lavage (BAL).

Table 1 Final diagnosis of the peripheral pulmonary lesions in 112 patients

Final diagnosis	Number (%)
Malignant	76 (67.9)
Non-small cell lung cancer	70 (62.5)
Small cell lung cancer	0 (0)
Metastases	4 (3.6)
Lymphoma	2 (1.8)
Benign	36 (32.1)
Hamartoma	1 (0.9)
Organizing pneumonia	3 (2.7)
Allergic bronchopulmonary aspergillosis	1 (0.9)
Tuberculosis	18 (16.0)
Cryptococcosis	2 (1.8)
Aspergillosis	3 (2.7)
Nocardiosis	3 (2.7)
Pneumonia	4 (3.5)
Meliodosis	1 (0.9)

brushing, and BAL, were evaluated for the diagnosis. A definite diagnosis was established when histological or cytological results were defined as malignant disease or specific non-neoplastic disease. Histological or cytological diagnosis of non-specific inflammation was considered to be non-diagnostic, although the final diagnosis proved to be a benign process. The result of BALF culture was not

considered for the diagnostic yield, even if it ultimately demonstrated the pathogen relevant to the final diagnosis.

Statistical analysis

All data were analyzed with a statistical software package (SPSS for Windows version 16.0; SPSS, Chicago, IL, USA). Values were expressed as mean \pm standard deviation for continuous variables, and as frequencies and percentages for categorical variables. The effect of size and the etiology of PPLs on the diagnostic yield of each sampling technique were analyzed using a chi-square (χ^2) test. The diagnostic yields of each sampling technique were compared using Cochran's Q test. If statistical significance was reached, the McNemar test was then performed to compare each technique with that achieving the highest diagnostic yield. All statistical tests were two-sided; $P < 0.05$ was considered to be statistically significant.

Results

There were 112 patients comprising 57 males and 55 females, with an average age of 58.2 ± 14.2 years. These included 76 malignancies and 36 benign lesions (Table 1). The mean diameter of the PPLs was 23.5 ± 9.5 mm. Although only patients who had demonstrated feeding bronchi were selected, the R-EBUS probe could not locate the lesion in two cases. For 92 of the lesions, the probe could advance to within the lesion on the EBUS image,

Table 2 Final diagnoses and diagnostic methods of 22 nondiagnostic radial endobronchial ultrasound-guided bronchoscopy peripheral pulmonary lesions

Final diagnosis	Diagnostic method	Number
Malignant		
Non-small cell lung cancer	Open lung biopsy	7
	EBUS-TBNA	2
Metastases	Open lung biopsy	1
Lymphoma	Transthoracic needle aspiration	1
Benign		
Hamartoma	Open lung biopsy	1
Organizing pneumonia	Open lung biopsy	1
Allergic bronchopulmonary aspergillosis	Aspergillus skin test, serum IgE	1
Tuberculosis	Open lung biopsy	1
	Positive BALF culture	2
	Response to antituberculous drugs	1
Cryptococcosis	Open lung biopsy	1
Pneumonia	Positive BALF culture + response to antibiotic	1
	Response to antibiotic	1
Melioidosis	Positive blood culture	1

EBUS-TBNA, endobronchial ultrasound guided transbronchial needle aspiration; BALF, bronchoalveolar lavage fluid.

Table 3 Diagnostic performances of bronchoscopic sampling techniques

Sampling technique	Overall	Diagnostic yield (%)								
		Size			Etiology			Probe location		
		<20 mm (n=45)	>20 mm (n=67)	P value	Benign (n=36)	Malignancy (n=76)	P value	Within (n=92)	Adjacent (n=18)	P value
TBB	70.5	62.2	76.1	0.11	63.9	73.7	0.29	76.1	50.0	0.02
Brushing cell block	34.8	22.2	43.3	0.02	19.4	42.1	0.02	40.2	11.1	0.018
Brushing smear	62.5	55.6	67.2	0.21	27.8	78.9	<0.001	69.6	33.3	0.003
Rinsed brushing fluid	50.0	37.8	58.2	0.03	11.1	68.4	<0.001	57.6	16.7	0.001
BALF	42.0	28.9	50.7	0.02	13.9	55.3	<0.001	47.8	16.7	0.015
All techniques	80.4	75.6	83.6	0.29	69.4	85.5	0.045	87.0	55.6	0.002

TBB, transbronchial biopsy; BALF, bronchoalveolar lavage fluid.

while in the other 18 cases; the probe was adjacent to the lesion.

The overall diagnostic yield of EBUS-guided bronchoscopy was 80.4% (95% CI: 72.9-87.8%). Of the 22 patients with nondiagnostic R-EBUS-guided bronchoscopy, the final diagnoses and diagnostic methods are shown in *Table 2*. The final diagnoses were established on clinical grounds in four infectious diseases (one tuberculosis, two pneumonias, and one melioidosis) and one immunologic process (allergic

bronchopulmonary aspergillosis). All of these PPLs improved after specific treatment.

Table 3 shows the diagnostic yield of different bronchoscopic sampling techniques. Etiology of the PPLs was a significant factor for the diagnostic performance of EBUS-guided bronchoscopy, while lesion size had no effect. As expected, the position of the probe in relation to the PPLs was found to affect the diagnostic yield of all sampling techniques.

Table 4 Diagnostic yield of different bronchoscopic sampling techniques

Sampling technique	Diagnostic yield (%) (95% confidence intervals)	P value (compared with TBB)
BALF	42.0 (32.7-51.2)	<0.001
Rinsed brush fluid	50.0 (40.6-59.4)	<0.001
Brushing smear	62.5 (53.4-71.6)	0.150
Brushing cell block	34.8 (25.9-43.8)	<0.001
TBB	70.5 (62.0-79.1)	–
TBB + BALF	75.0 (66.9-83.1)	0.060
TBB + rinsed brush fluid	75.9 (67.8-83.9)	0.030
TBB + brushing smear	80.4 (72.9-87.8)	0.001
TBB + brushing cell block	72.3 (63.9-80.7)	0.500

BALF, bronchoalveolar lavage fluid; TBB, transbronchial biopsy.

The performance of TBB rendered the highest yield among these specimens ($P < 0.001$, Cochran's Q test). TBB provided high diagnostic yield irrespective of the size and etiology of the PPLs. Although brushing smear achieved lower diagnostic yield compared with TBB, this difference was not statistically significant (*Table 4*). The diagnostic yield of brushing smear for benign lesions was quite low, but the size of the PPLs had no influence on the diagnostic performance of this sampling technique. The combination of TBB and brushing smear achieved the maximum diagnostic yield (*Table 4*).

Of the 36 benign lesions, 31 lesions were caused by infectious diseases. R-EBUS sampling techniques could give the diagnosis in 23 cases (74.2%), while BALF culture provided microbiological information in 20 cases (64.5%). BALF culture provided additional diagnostic yield for R-EBUS sampling techniques in three cases.

There was no major complication in our study during or after the procedure, and no case of pneumothorax. Minimal self-limiting bleeding was occasionally observed. Only one subject developed pneumonia three days later and responded well to antibiotics.

Discussion

Although several sampling techniques can be used, in many recent reports on the diagnostic yield of R-EBUS-guided FB, only TBB was performed (9-12). At present, there are no recommendations regarding sampling techniques for this bronchoscopic approach. Thus, we conducted this study in order to find out the most suitable sampling technique for this procedure.

TBB provided highest diagnostic yield in our study.

Previous reports on the diagnostic yield of this sampling technique for PPLs varied widely, ranging from 46% to 84% (13), and were affected by the lesion size, etiology, CT bronchus sign, and the position of the probe in relation to the PPLs (9,14,15). The recommended number of TBB samplings was at least five biopsy specimens (16).

Since dedicated GS biopsy forceps are smaller than those used in standard biopsies, it is inevitable that the specimens would be smaller. In our early experience, it was difficult for the pathologist to process these samplings as usual standard TBB. Therefore, we adopted the cell block method for this procedure, as previously mentioned. In terms of diagnostic yield, the advantage of the cell block method compared with conventional histological preparation will be a question for future research.

The diagnostic performance of brushing smear cytology in R-EBUS-guided FB has rarely been reported. In two previous studies, brushing smear obtained lower diagnostic yield compared with TBB (14,17). Both TBB and brushing smear sampling techniques have pros and cons. As is the nature of diagnostic methods, histology can reveal not only the morphology of cells, but also additional information such as cell architecture and nearby structure. Moreover, histology sections allow for further investigation of immunohistochemistry and detection of tumor genetic mutations. However, TBB requires that a greater amount of tissue be examined. Although less tissue is obtained via brushing smear, all were smeared in one microscopy slide, which is a sufficient amount for adequate interpretation. Also, a brush can sample the tissue in 360-degree manner with an R-EBUS probe, while TBB can obtain only from a forward angle. Besides, we occasionally observed that for some PPLs, TBB forceps could not be opened inside the

lesion initially, but only succeed in getting at the specimen after the brush had been moved back and forth inside the lesion.

We expected that we could obtain the histology using brush technique. However, after investigating the diagnostic yield of cell blocks obtained from this sampling method, we failed to find the benefit. Cell blocks processed from cellular material rinsed from the sampling instrument showed lower diagnostic yield due to the dilution of cellular material (18). Even when the diluent is reduced and the specimens from the brush are gathered in a micropipette tube, the amount may be insufficient for histology processing.

In our study, rinsed brush fluid that was collected from the remainder of the bronchial brushing smear and the material left in the GS obtained low diagnostic yield. Moreover, there was no additional advantage of rinsed brush fluid over brushing smear. Thus, this sampling process should be discarded due to its low cost-effectiveness.

BAL is a sampling technique that does not require any guidance. Compared with our previous study that was performed without guidance (1), even though the mean diameter of PPLs in the present study was smaller, the diagnostic yield was higher (42.0% *vs.* 29.6%). This might be due to the sequence of the sampling techniques. In the previous study, the routine sequence of bronchoscopic procedure utilized was BAL, brushing, and forceps biopsy. In contrast, in the present study, BAL was performed last, after the lesion had been manipulated by the other sampling instruments, so more cytologic diagnostic cells were detached and could be collected.

There are few data regarding to the diagnostic yield of combine diagnostic sampling modalities. Tay *et al.* (14) and Kurimoto *et al.* (17) demonstrated superior yield when brushing and TBB were combined, as in our study. Although the combination of brushing and BAL achieved the maximum diagnostic yield in the study of Kuo *et al.*, TBB plus brushing was not significantly inferior (19).

Although BALF had a lower cytologic diagnostic yield than TBB and brushing smear and did not provide additional benefits for this combination, BALF culture could give additional microbiological information that the other sampling techniques could not. Thus, we suggest that BAL should be a routine procedure after TBB and brushing are performed.

There were some limitations in our study, so that the results may not be directly comparable with previous findings. First, we enrolled only patients who had demonstrated feeding bronchi, because we realized that

there had been a diagnostic yield as low as 12% in case of having a negative CT bronchus sign (15). Therefore, in most cases we were able to reach the target confirmed by the EBUS image, which caused the diagnostic yield in our study to be higher compared with the others. Second, the number of PPLs that the probe could reach within the lesion was quite high, compared with previous reports. In fact, we could not place the probe within the lesion on the first attempt in all cases. When an adjacent or negative EBUS image was detected, we moved the bronchoscope with R-EBUS upward and downward and also rotated it in order to find the direction that brought it closer to the target. The R-EBUS probe was then removed slightly and reinserted in that direction. Third, most of PPLs in our study appeared on CT scans as solid PPLs. Limited data regarding the diagnostic yield on ground-glass PPLs indicated unfavorable results, i.e., only 18-65% (9,20). Therefore, our findings are not applicable to all PPLs. Next, we did not randomize the sequence of sampling techniques which might influence to the diagnostic yield. After repeated samplings, the GS sometimes migrates from the proper position due to deep breath or cough, resulting in lower diagnostic yield in late samplings. Therefore, first sampling bias was an issue to debate in our study. Finally, although histology from TBB provided highest the diagnostic yield, we did not perform further processing for immunohistochemical stain and tumor genetic mutations analysis in all cases. Therefore, we did not have data in efficiency and usefulness of TBB on this issue.

In conclusion, we demonstrated that TBB rendered the highest diagnostic yield in R-EBUS-guide FB. The combination of TBB and brushing smear achieved the maximum diagnostic yield. In addition, BAL can provide microbiological data for the appropriate selection of antibiotics in infectious diseases that can present as PPLs. Therefore, to achieve the highest diagnostic performance, TBB, brushing smear and BAL should be performed together.

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Ethic consideration: This study protocol was approved by the Ethics Committee on Human Experimentation of Ramathibodi Hospital, Faculty of Medicine, Mahidol University.

Authors' contributions: V Boonsarngsuk: designed and conducted study, performed R-EBUS guided bronchoscopy, analyzed data, prepared and reviewed manuscript.

W Kanoksil: processed and reviewed cytology and histology. S Laungdamerongchai: conducted study, assisted R-EBUS guided bronchoscopy.

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