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ORIGINAL ARTICLE

Endobronchial ultrasound-guided transbronchial biopsy and brushing: a comparative evaluation for the diagnosis of peripheral pulmonary lesions

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Abstract

OBJECTIVES: The diagnosis of peripheral pulmonary lesions (PPLs) often involves endobronchial ultrasound (EBUS)-guided transbronchial biopsy (TBB), washing and brushing. Certain echoic features of PPL have been associated with biopsy yield. This study compared yields of TBB and bronchial washing (TBBW) with those of TBBW plus bronchial brushing and analysed the associations between clinical and echoic features and yield.

METHODS: We performed a retrospective review of 271 patients undergoing TBB for PPL. TBBW was performed in 139 patients and 132 underwent TBBW plus brushing.

RESULTS: The diagnostic yield of TBBW plus brushing was superior to that of TBBW (80.3 vs 66.2%, $P < 0.01$). In TBBW patients, lesions <3 cm (57.1 vs 73.7%, $P < 0.05$), EBUS probe adjacent to the lesion (47.6 vs 74.2%, $P < 0.01$), continuous margin (56.5 vs 75.7%, $P < 0.01$) and homogeneous echogenicity (51.0 vs 75.0%, $P < 0.01$) predicted lower yields, but adding bronchial brushing rendered the diagnostic yields similar, irrespective of EBUS echoic features, leaving lesion size of <3 cm (odds ratio 2.81; 95% confidence interval 1.08–7.31, $P < 0.05$) as the single independent predictor of lower yield by multivariate regression analysis. TBB plus brushing was not inferior to TBBW plus brushing (78.8 vs 80.3%, $P = 0.88$).

CONCLUSIONS: Bronchial brushing boosted diagnostic yields, particularly for PPLs with echoic features previously associated with a reduced biopsy yield.

Keywords: Endobronchial ultrasound • Peripheral pulmonary lesion • Transbronchial biopsy • Brushing

INTRODUCTION

The diagnosis of peripheral pulmonary lesions (PPLs), that are not visible by conventional bronchoscopy, is clinically challenging. Radial probe endobronchial ultrasound (EBUS) has been documented as a valuable technique for approaching PPLs in this situation. The diagnostic yield of EBUS-guided transbronchial biopsy (TBB) for PPLs is comparable with that of traditional fluoroscope-guided TBB, but avoids the accompanying radiation exposure [1, 2].

However, yields of EBUS-TBB reported in studies, to date, have varied widely, from 50 to 80% [3–6]. Apart from the effects of operational differences at various institutions, the characteristics of PPLs also affect the yield considerably [7]. Our previous work showed that PPLs possessing certain echoic features are associated with disadvantages to the TBB yield. Indicators of these disadvantages include homogeneous echogenicity and continuous margin, which suggest firmer and more mobile (i.e. less fixed to the neighbouring lung) tumour attributes that will handicap a biopsy [8]. EBUS probe location is another significant factor. When the EBUS probe is within the PPL, the TBB yield will be superior to the yield anticipated when the EBUS probe is adjacent to the lesion [4, 8, 9].

The development of the guide sheath has improved the TBB technique with regard to greater precision in securing a path through which the biopsy forceps are advanced to the lesion. Previous studies of TBB with guide sheath assistance have reported diagnostic yields ranging from 60 to 80% [2, 9–11], which suggests certain improvement in biopsy stability compared with traditional EBUS-TBB. However, the yield of TBB assisted by the guide sheath is still affected by the EBUS probe location [9]. Furthermore, this equipment is not readily available at every institution.

Bronchial brushing is also frequently used to diagnose PPLs. The brushing technique can be used to collect cells and

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microorganisms that are either located inside the lesion or shed around the periphery of the lesion [12]. This technique is different from the biopsy technique, because it does not require a precise EBUS probe position with respect to the biopsy target. Previous studies have shown that the yield obtained by brushing is higher than the biopsy yield recorded when the EBUS probe is adjacent to the lesion [11] or when the lesion has a sharp margin [13], both of which are associated with a reduced biopsy specimen yield.

Herein, we aimed to investigate the performance of bronchial brushing separately from TBBW for the diagnosis of PPL. The clinical features and echoic features of PPLs that are reportedly relevant to the diagnostic yield were also analysed.

MATERIALS AND METHODS

Study participants and design

A cohort of 338 patients with PPLs referred for TBB was retrospectively reviewed from November 2009 to December 2011. During this period, two separate bronchoscopic examination rooms were available for TBB, with one room routinely equipped with brushing catheters. Patients were randomly assigned to either one of the two rooms, free of the physician's designation. Figure 1 shows the number of patients recruited and the given procedure in this study. PPLs were defined as lesions that were proven not to be endobronchial, as well as lesions with extrinsic compression, submucosal infiltration or orifice narrowing. In study cases where a specific diagnosis was not obtained, patients were referred for computed tomography-guided biopsy or surgical intervention. This study was approved by the institutional review board of Chang Gung Memorial Hospital (No. 99-1156B), and all study participants provided their written informed consent.

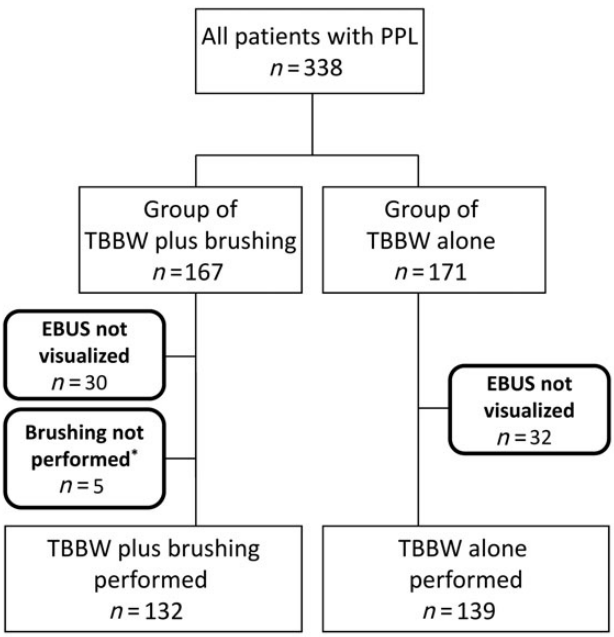

Figure 1: Number of patients who were recruited and underwent the procedure in each group. *Two patients each with severe cough and desaturation, and 1 with intractable bleeding.

Equipment and diagnostic procedures

A flexible fibre-optic bronchoscope (BF-P240 or BF-40, Olympus, Tokyo, Japan) and radial mechanical-type ultrasound probe (model UM-S20-S20R; Olympus) with 20-MHz frequency were used. The bronchoscopic procedures were performed equally by three experienced specialists. The consciousness sedation technique and the procedures used to search for PPLs were standardized methods, described in our previous studies [7, 8]. Biopsy forceps (FB-19C, Olympus) were used, and four to six specimens were obtained during each TBB for all patients. After the TBB, the operator performed bronchial washing in the EBUS-determined segmental bronchus in each patient. The presence of parenchymal lung tissue in biopsy specimens was regarded as evidence of a successful biopsy, and the specimens obtained in all cases were stained and analysed by a pathologist blind to the patient's clinical information. The brushing technique was subsequently used with the patients in the TBBW plus brushing group. If the patients experienced desaturation, active bleeding or severe coughing after TBBW, the operator would then clinically evaluate their tolerance for subsequent brushing. The brushing catheter (BC-202D-5010, Olympus) was standardized, and cells or microorganisms were collected with a back-and-forth motion when the reference distance was reached. This study did not involve the use of either the guided-sheath technique or fluoroscopic guidance.

Echoic features and EBUS probe position

Three echoic features reflecting the structure of PPLs and the EBUS probe position were all recorded (Fig. 2). The operators independently analysed each recorded image and reached a consensus whenever there was a discrepancy [7].

Statistics

The χ^2 test was used to compare the differences in variables between the groups. Multivariate logistic regression was used to identify the independent variables contributing to statistical significance. The odds ratios (ORs) and associated 95% confidence intervals (95% CIs) were determined to assess the contributions of significant factors. All analyses were performed using the SPSS software version 10.0 (Chicago, IL, USA). All reported *P*-values were two-sided, and a *P*-value of <0.05 was considered statistically significant.

RESULTS

Histopathological diagnosis of peripheral lung lesions

A total of 338 patients were referred for EBUS examinations of PPLs. The lesions in 276 (81.6%) patients were localized by EBUS, and 271 were eligible for analysis after excluding 5 patients whose pre-planned brushing technique was aborted due to desaturation, severe cough or intractable bleeding. Of the 271 patients, 139 underwent TBBW procedures, and 132, TBBW plus bronchial

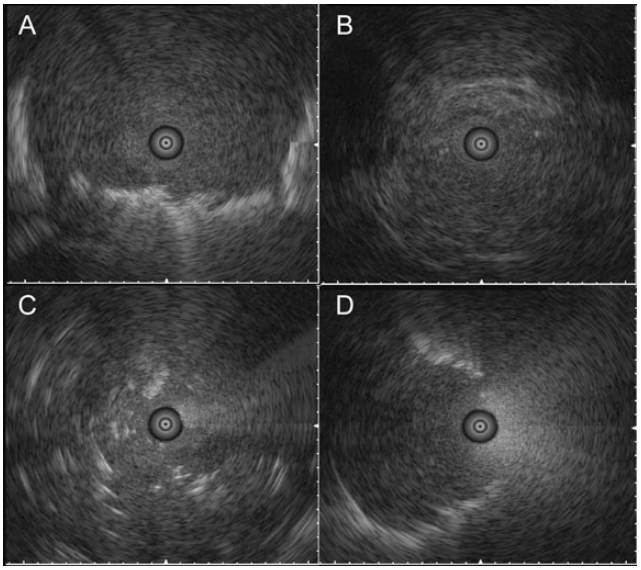

Figure 2: Representations of the three echoic features associated with lower-yield PPL structures. Continuous margins (**A**), heterogeneous echogenicity (**B**; compared with homogeneous echogenicity as shown in A) and linear discrete air bronchogram (**C**). The EBUS probe position is defined as within (A) or adjacent to (**D**) the lesion. The echoic features shown in A and D have been associated with a lower TBB yield in previous reports.

Table 1: Baseline characteristics of all PPLs (*N* = 271)

Lesion diameter (cm)	
Mean ± SD (range)	3.46 ± 0.08 (0.9–9.5)
Diagnosis, *n* (%)	
Malignancy	
Adenocarcinoma	111 (41.0)
Squamous cell carcinoma	47 (17.3)
Undetermined NSCLC	61 (22.5)
Small cell carcinoma	16 (5.9)
Metastasis	9 (3.3)
Benignity	
Organizing pneumonia	12 (4.4)
Pulmonary tuberculosis	7 (2.6)
Non-tuberculosis mycobacterium	2 (0.7)
Anthracosilicosis	2 (0.7)
Cryptococcus	2 (0.7)
Actinomycosis	1 (0.4)
Vasculitis	1 (0.4)

PPL: peripheral pulmonary lesion; NSCLC: non-small-cell lung cancer.

brushing (Fig. 1). The PPLs were malignant in 244 (90%) patients and benign in 27 (10%) (Table 1).

Diagnostic yield of TBBW with or without bronchial brushing

The clinical features of PPLs in each cohort were similar in terms of lesion size, diagnosis and lobar region, where the lesion was located. The EBUS echoic features of interest, i.e. margins, air bronchograms and echogenicity, were also similarly distributed. Therefore, all else being similar, the use of the bronchial brushing technique in combination with TBBW indicated a greater diagnostic yield (80.3 vs 66.2%, $P < 0.01$) than that achieved with TBBW alone (Table 2). Among all patients, procedure-related complications included significant bleeding in 22 (6.5%) and pneumothorax in 7 (2.0%) patients. The distribution of complications between the two groups was similar (Table 3). The practice of wedge compression for 1 min was used to stop significant bleeding at the outset, when bleeding did not stop spontaneously after TBB. This practice was able to successfully manage the bleeding in 20 patients, leaving only two who needed subsequent electrocoagulation to manage the intractable bleeding.

Table 2: Clinical and echoic presentation of PPLs in the TBBW and TBBW/BR cohorts

Variables	TBBW (*N* = 139)	TBBW/BR (*N* = 132)	*P*-value
Age (mean ± SD)	60.4 ± 12.7	59.6 ± 13.0	0.61
Gender (male), *n* (%)	84 (60.4)	90 (68.2)	0.21
Lesion diameter (cm), mean ± SD	3.43 ± 0.11	3.47 ± 0.12	0.81
Diagnosis, *n* (%)			
Malignancy	124 (89.2)	120 (90.9)	0.69
Location of lesion, *n* (%)			
RUL	27 (19.4)	31 (23.5)	0.65
RML	15 (10.8)	18 (13.6)	
RLL	32 (23.0)	24 (18.2)	
LUL	40 (28.8)	32 (24.2)	
LLL	25 (18.0)	27 (20.5)	
EBUS probe location, *n* (%)			
Within lesion	97 (69.8)	91 (68.9)	0.90
Echoic features, *n* (%)			
Continuous margin	69 (49.6)	68 (51.5)	0.81
Linear discrete air bronchogram	48 (34.5)	38 (28.8)	0.36
Homogeneous echogenicity	51 (36.7)	52 (39.4)	0.71
Diagnostic yield	92 (66.2)	106 (80.3)	<0.01

PPL: peripheral pulmonary lesion; TBBW: transbronchial biopsy and bronchial washing; TBBW/BR: transbronchial biopsy, bronchial washing and brushing.

Table 3: Procedure-related complications of TBBW and TBBW/BR cohorts

Complications	TBBW, *n* (%)	TBBW/BR, *n* (%)	*P*-value
Pneumothorax	4 (2.3)	3 (1.8)	0.99
Significant bleeding[a]	12 (7.0)	10 (6.0)	0.81

TBBW: transbronchial biopsy and bronchial washing; TBBW/BR: transbronchial biopsy, bronchial washing and brushing.
[a]Patients required electrocoagulation or wedge compression to stop bleeding.

Clinical and echoic features associated with a diagnostic yield

Among the patients with PPLs that received TBBW, the predictors of a lower diagnostic yield were lesion size of <3 cm, EBUS probe

Table 4: Diagnostic yield of TBBW and TBBW/BR cohorts presenting with different echoic and clinical features of PPLs

Variables	TBBW		TBBW/BR	
	Diagnostic, *n* (%)	*P*-value	Diagnostic, *n* (%)	*P*-value
Lesion size (cm)				
<3	36 (57.1)	0.04	47 (72.3)	0.03[a]
≥3	56 (73.7)		59 (88.1)	
Location of lesion				
RUL	18 (66.7)	0.68	26 (83.9)	0.73
RML	8 (53.3)		14 (77.8)	
RLL	24 (75.0)		17 (70.8)	
LUL	26 (65.0)		27 (84.4)	
LLL	16 (64.0)		22 (81.5)	
EBUS probe location				
Within	72 (74.2)	<0.01	73 (80.2)	0.99
Adjacent	20 (47.6)		33 (80.5)	
Margin				
Continuous	39 (56.5)	<0.01	54 (79.4)	0.83
Non-continuous	53 (75.7)		52 (81.3)	
Air bronchogram				
Linear discrete	29 (60.4)	0.35	30 (78.9)	0.81
Nonlinear discrete	63 (69.2)		76 (80.9)	
Echogenicity				
Homogeneous	26 (51.0)	<0.01	37 (71.2)	0.04
Heterogeneous	66 (75.0)		69 (86.3)	

PPL: peripheral pulmonary lesion, TBBW: transbronchial biopsy and bronchial washing, TBBW/BR: transbronchial biopsy, bronchial washing and brushing.
[a]OR 2.81; 95% CI 1.08–7.31, $P < 0.05$ by the multivariate logistic regression test.

adjacent to the lesion, a continuous margin and homogeneous echogenicity. The addition of the brushing technique increased the diagnostic yield, leaving only lesion size of <3 cm and homogeneous echogenicity as predictors of a lower yield. Multivariate regression analysis revealed a lesion size of <3 cm (OR 2.81; 95% CI 1.08–7.31, $P < 0.05$) as the only independent predictor of a lower yield (Table 4).

Diagnostic performance of each technique

The yields for TBB ($n = 271$), bronchial washing ($n = 271$) and bronchial brushing ($n = 132$) were 62.4, 31.0 and 57.6%, respectively. The yield for TBBW was similar to that of TBB alone (65.3 vs 62.4%, $P = 0.53$), but adding bronchial brushing to TBB significantly improved the yield vs TBBW (78.8 vs 65.3%, $P < 0.01$). In addition, bronchial brushing plus TBB was not inferior to the use of all the three techniques in combination with diagnosing PPLs (78.8 vs 80.3%, $P = 0.88$; Table 5).

Inter-rater reliability

Inter-rater reliability assessed the degree of interoperator consistency in defining the echoic features of the margin, the air bronchogram and the echogenicity of the PPLs. The consistency rates were 95.7, 96.8 and 95.2% with κ coefficients of 0.91, 0.93 and 0.91, respectively.

Table 5: Comparison of diagnostic yields among the three procedures alone or in combination

Procedures (no.)	Diagnostic yield (%)	*P*-value[a]
BW (271)	31.0	<0.01
BR (132)	57.6	<0.01
TBB (271)	62.4	<0.01
TBB/BR (132)	78.8	0.88
TBBW (271)	65.3	<0.01
TBBW/BR (132)	80.3	NA

TBBW: transbronchial biopsy and bronchial washing; TBBW/BR: transbronchial biopsy, bronchial washing and brushing.
[a]All *P*-values are in comparison with TBBW/BR.

DISCUSSION

In the current study, a significantly higher diagnostic yield was achieved in patients with PPLs who underwent TBBW plus bronchial brushing than in those undergoing TBBW alone. Our findings indicated that bronchial brushing can boost a yield irrespective of the echoic features that hamper TBBW. Although TBBW plus bronchial brushing resulted in the highest yield, the combination of the two techniques, i.e. bronchial brushing and TBB, achieved comparable efficacy.

Tolerance for interventional bronchoscopy varies widely among individuals. If patients can tolerate a combination of three diagnostic procedures, the highest yield will be achieved, but certain trade-offs are necessary if patients cannot tolerate it. In the present study, we found that TBB yield was marginally improved with bronchial washing. The clinical significance of this study includes our finding that bronchial brushing can take priority over bronchial washing as a diagnostic practice of choice in conjunction with TBB for diagnosing PPL. The addition of the brushing procedure resulted in similar diagnostic yields, even among patients with lesions presenting various echoic features, boosted the yield to a plateau and left lesion size of <3 cm as the only independent factor related to a lower yield. Our analyses showed that when PPLs demonstrated EBUS features associated with a reduced TBB yield, i.e. homogeneous echogenicity, continuous margins and placement of the EBUS probes adjacent to the lesions, the brushing procedure boosted the yields from 51 to 71.2%, 56.7 to 79.4% and 47.6 to 80.5%, respectively (Table 3). This indicated that even the firmer and more mobile PPLs that can handicap TBB access can be amenable to diagnosis by adding the brushing technique to collect cells and microorganisms that have disengaged from the lesion, both inside the lesion and along the periphery.

Kurimoto *et al.* [11] reported a greater diagnostic yield for bronchial brushing vs TBB (37 vs 7%) when lesions were adjacent to the EBUS probes. The yield from brushing is also reported to be superior to the TBB yield (45 vs 32%) when lesions display sharp margins [13]. Figure 3 shows 2 representative cases in whom the PPL was immediately adjacent to the EBUS probe and displayed continuous borders and homogeneous echoic features. In these 2 cases, the brushing technique, but not TBBW, was able to yield a definitive diagnosis. Therefore, if a PPL presents EBUS features associated with hindering the TBB yield, bronchial brushing should be essential rather than merely ancillary to TBB when

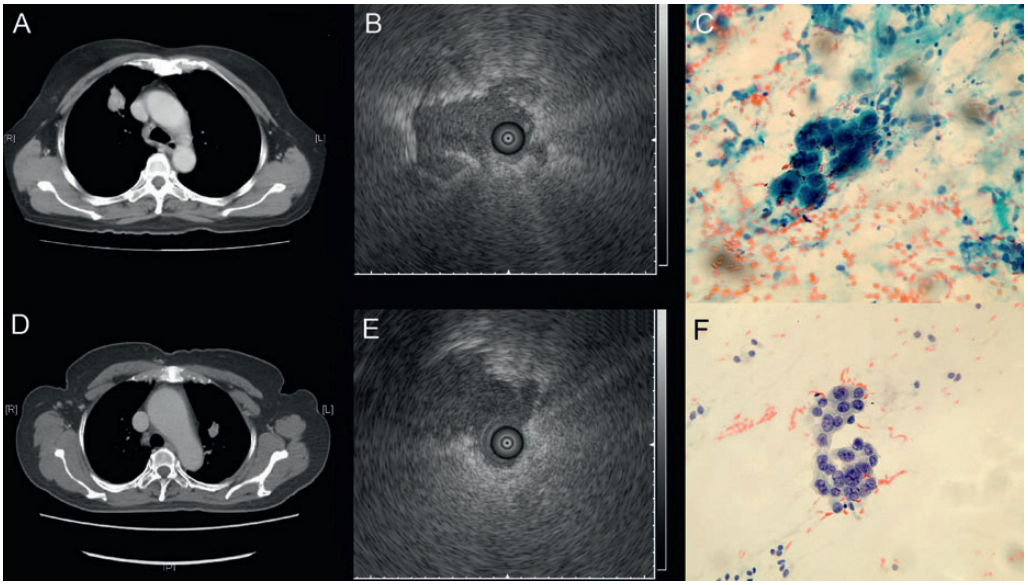

Figure 3: A representative case of a PPL measuring 2.6 × 2.2 cm located on the right upper lobe (**A**). Only a part of the lesion was detected by EBUS with the probe just adjacent to the lesion. The lesion featured continuous margins and homogeneous echogenicity (**B**). The cytological examination revealed clusters of adenocarcinoma cells with pleomorphic nuclei and foamy cytoplasm (Papanicolaou stain, ×400) (**C**). A representative case showing a PPL measuring 1.7 × 1.4 cm located on the left upper lobe (**D**). The lesion had a continuous margin and homogeneous echogenicity when the EBUS probe was placed adjacent to it (**E**). The cytological examination revealed sheets of adenocarcinoma cells with enlarged nuclei and an acinar growth pattern (Papanicolaou stain, ×400) (**F**).

skilled operators and appropriate equipment are available. The limitation of the current study is its inherent bias, as the study uses a retrospective design. However, despite the absence of randomization, the baseline characteristics were comparatively equal, as shown by the similar distribution of variables between the two groups.

In conclusion, bronchial brushing in combination with TBBW outperformed TBBW alone in the specimen yield for the diagnosis of PPLs. The brushing technique can be essential if PPLs display continuous echoic margins or homogeneous echogenicity or in cases in which the EBUS probe is placed adjacent to the lesion.

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Conflict of interest: none declared.

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