Endobronchial ultrasound-guided transbronchial biopsy with or without a guide sheath for peripheral pulmonary malignancy

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Shareable abstract (@ERSpublications)
In this study, EBUS-guided transbronchial biopsy both with and without a guide sheath provided a similarly favourable diagnostic yield and safety profile for malignant peripheral pulmonary lesions
https://bit.ly/3jpi6Kv

Cite this article as: Huang C-T, Chang L-Y, Chen C-Y, *et al*. Endobronchial ultrasound-guided transbronchial biopsy with or without a guide sheath for peripheral pulmonary malignancy. *ERJ Open Res* 2021; 7: 00267-2021 [DOI: 10.1183/23120541.00267-2021].

Received: 18 April 2021
Accepted: 26 July 2021

Abstract

Endobronchial ultrasound (EBUS)-guided transbronchial biopsy (TBB) is a common procedure used to diagnose peripheral pulmonary lesions (PPLs). However, existing literature did not conclusively show a difference in the ability of EBUS-TBB with and without a guide sheath (GS) to diagnose PPLs. This multicenter cohort study enrolled patients presenting for EBUS-TBB of PPLs that finally proved to be malignant. The diagnostic yield and complication rate were compared between patients undergoing EBUS-TBB with and without a GS (EBUS-TBB+GS *versus* EBUS-TBB−GS). A propensity score matching method was used to balance differences of pertinent clinical features between the two groups. The original cohort consisted of 975 patients (556 in EBUS-TBB−GS; 419 in EBUS-TBB+GS). GS guidance was more likely to be used with smaller (40 mm *versus* 44 mm) and middle or lower lobe (60% *versus* 35%) lesions. After propensity score matching, 720 (360 in each group) patients were included; the diagnostic yields for PPLs were 79% and 78% for EBUS-TBB−GS and EBUS-TBB+GS groups, respectively (p=0.649). The complication rates (5.8% *versus* 7.2% for bleeding; 0.6% *versus* 1.9% for pneumothorax) appeared to be lower in the EBUS-TBB+GS group, but the differences did not reach statistical significance. The procedure time was significantly longer in the EBUS-TBB+GS group than in the EBUS-TBB−GS group (29 min *versus* 24 min; p<0.001). In conclusion, adding a GS to EBUS-TBB did not improve the diagnostic yield for malignant PPLs. GS guidance was seemingly associated with a lower number of complications after TBB but contributed significantly to a longer procedure time.

Introduction

With the increasing use of low-dose computed tomography (CT) for lung cancer screening [1], the incidence of peripheral pulmonary lesions (PPLs) will likely be rising in the coming years. Reaching a diagnosis of PPLs remains a challenging problem in pulmonology practice. Since the introduction of the flexible bronchoscope around 50 years ago [2], bronchoscopy has assumed an important role in the diagnosis of a myriad of lung diseases. However, conventional bronchoscopy with or without fluoroscopic guidance offers a suboptimal diagnostic yield for PPLs [3, 4]. This has led to the development of advanced bronchoscopic techniques, such as endobronchial ultrasound (EBUS), in order to improve the diagnostic yield of PPLs.

The application of EBUS enables visualisation and location of PPLs surrounding or adjacent to the bronchus. Herth *et al*. [5] first described the use of EBUS to guide transbronchial biopsy (TBB) of PPLs

in 2002, and numerous studies since then have shown a superior diagnostic yield of PPLs using TBB under EBUS guidance, as compared to conventional bronchoscopy [6–9]. A notable methodological limitation inherent to EBUS is that it does not provide real-time images for TBB procedures; thus, the biopsy forceps may not always be advanced into the target bronchus from which the EBUS image has been obtained. To overcome this shortcoming, a guide sheath (GS) has been devised and can be regarded as an extension of the bronchoscope [10]. The GS can be left in place after removing the EBUS probe and acts as a conduit for the TBB forceps into the proper site for specimen acquisition.

In theory, EBUS-guided TBB (EBUS-TBB) with a GS can further improve the diagnostic yield of PPLs, compared with EBUS-TBB without a GS [10, 11], and so this method has been widely adopted in studies focusing on EBUS-TBB [6, 8]. However, existing literature does not conclusively show a difference in the ability of EBUS-TBB with and without a GS to diagnose PPLs [7, 12, 13]. In this regard, the aim of the present study was to investigate whether adding a GS to EBUS-TBB provided a superior diagnostic yield for PPLs compared to EBUS-TBB alone in a setting without fluoroscopic guidance. We also sought to compare the procedure time and complication rate between the two diagnostic procedures.

Methods

Study settings and subjects

We conducted a multicenter retrospective cohort study at National Taiwan University Hospital (Taipei), National Taiwan University Hospital Hsin-Chu Branch and National Taiwan University Hospital Yun-Lin Branch. From April 2017 to March 2019, all patients aged 20 years or older and who had undergone EBUS-TBB for PPLs were screened for eligibility. Patients were included in this study if the final diagnosis of the PPLs were malignant using any diagnostic modality. PPLs were defined as lung lesions surrounded by lung parenchyma without evidence of endobronchial involvement. The study subjects were then categorised into two groups: one received EBUS-TBB with a GS (EBUS-TBB+GS) and the other received EBUS-TBB without a GS (EBUS-TBB−GS). The study was approved by the Research Ethics Committee of National Taiwan University Hospital, and informed consent was waived since retrospective data were used and no patient intervention was involved.

Final diagnoses

Patients with a malignant diagnosis established by the index EBUS-TBB procedures were defined to have malignant PPLs. Patients with non-diagnostic bronchoscopy were followed up for 1 year thereafter or until death or loss to follow-up, whichever came first. Those patients whose PPLs were proved to be malignant in the subsequent diagnostic processes, such as CT-guided biopsy, surgery or repeat bronchoscopy, were also classified as having malignant PPLs. Otherwise, patients were considered to have benign PPLs and were excluded from this study.

EBUS-TBB

All bronchoscopic procedures were performed by staff pulmonologists or supervised pulmonary fellows. After local anaesthesia of the upper airway by lidocaine and intravenous administration of fentanyl with or without midazolam for conscious sedation, conventional bronchoscopy (BF-260, BF-P260F or BF-Q290; Olympus, Tokyo, Japan) was conducted first to inspect the bronchial trees. Subsequently, the EBUS probe (UM-S20–20R; Olympus) was inserted through the working channel into the target bronchus to localise the PPLs, and EBUS-TBB with a 1.5-mm (with a GS: FB-233D; Olympus) or 1.8-mm (without a GS: NBF01-11018120; Micro-Tech Co. Ltd., Jiangsu, China) standard biopsy forceps was carried out for specimen acquisition. If possible, at least four adequate samples were to be retrieved. The use of a GS during the EBUS-TBB procedure was left to the discretion of the pulmonologist, who also decided whether or not to perform bronchial brushing or washing along with EBUS-TBB. Fluoroscopic guidance was not utilised throughout the study period. Instead, the distance from the distal end of the EBUS probe to the PPL was determined as previously described [14, 15]. In brief, after precisely identifying the PPL on the EBUS image, the probe was marked at the point of entry to the working channel of the bronchoscope. The probe was then slowly withdrawn to the orifice of the target bronchus and a second mark was made on the probe at its entry point to the working channel. The distance between two marks was measured to guide subsequent biopsy procedures.

Data collection

We collected patient data on age, sex, PPL features (lobar location, size and image patterns) and procedural information (EBUS probe position, complications and procedure time). The image patterns of the PPLs were categorised as solid, part-solid, ground-glass opacity or cavitary. The probe position of the EBUS was classified as within, adjacent to, or outside the PPLs, as previously described [10]. Two complications of interest, *i.e.* pneumothorax and haemorrhage, were defined for this study as follows: pneumothorax

indicates the presence of free air within the pleural cavity as detected by the chest radiograph. Given the favourable safety profile of EBUS-TBB [16], a chest radiograph was taken only on an as-needed basis during the study period. Haemorrhage indicates postprocedural bleeding mandating further intervention, such as bronchoscopic wedging or topical epinephrine spray, and self-limited bleeding was not regarded as a complication in this study [17]. Procedure time was calculated as the time that elapsed between the initial insertion of the bronchoscope and its final withdrawal at the end of the examination.

Outcomes

The main objective of this study was to compare the diagnostic yield of TBB between the EBUS-TBB+GS and EBUS-TBB−GS groups. The diagnostic yield of TBB was defined as any malignant finding, at either cytology or histopathology, from the biopsy, brushing or washing samples during a single bronchoscopy session. Other outcomes of interest included the incidence of procedure-related complications and the procedure time between the two groups of patients.

Statistical analysis

Numerical variables were presented as the mean±SD and compared using the independent-sample t-test. Categorical variables were expressed as number (percentage) and measured using the chi-square test. To identify independent clinical features associated with the diagnostic yield of EBUS-TBB, we constructed a logistic regression model and reported odds ratios with their 95% confidence intervals. Statistical analysis was performed using SPSS statistical software (version 20.0 for Windows; SPSS Inc., Chicago, IL, USA). All of the analyses were two-tailed and p-values of <0.05 were considered to be statistically significant.

Since significant differences may have existed in the baseline characteristics of the patients in the EBUS-TBB+GS and EBUS-TBB−GS groups, propensity score matching was applied to balance potentially confounding variables when comparing the diagnostic yield of EBUS-TBB between the two groups [18]. In this study, the propensity score was the conditional probability of using a GS, as a binary dependent variable, under a set of measurements, including the lobar location, image pattern, and size of the PPLs and EBUS probe position. For 1:1 matching, a caliper width of 0.25 times the standard deviation of the propensity score without replacement was used. The matching process was conducted with Stata software (version 11; StataCorp, College Station, TX, USA).

Results

Study population

During the 2-year study period, there were a total of 1185 patients receiving EBUS-TBB for PPLs. Of those, 118 and 92 patients were excluded from the EBUS-TBB−GS and EBUS-TBB+GS groups, respectively, because they did not have a malignant diagnosis for their PPLs during the follow-up period. Finally, 975 (556 in EBUS-TBB−GS and 419 in EBUS-TBB+GS) patients whose PPLs were proved to be malignant were enrolled in this study (table 1). The mean age of the patient population was 67 years, and 578 (59%) were male. The overall diagnostic yield was 79% and the vast majority (94%) of our study population had a final diagnosis of lung cancer. Compared to the EBUS-TBB−GS group, patients in the EBUS-TBB+GS group were more likely to have smaller PPLs (44 mm *versus* 40 mm; p=0.008) and have PPLs in the middle or lower lobes (35% *versus* 60%; p<0.001). The diagnostic yield of EBUS-TBB was comparable between the two groups of patients (80% *versus* 78% for the EBUS-TBB−GS and EBUS-TBB+GS groups, respectively; p=0.281).

Propensity score-matched cohort

After propensity score matching, we assembled a matched cohort of 720 patients (360 in each group). The baseline features potentially associated with the diagnostic yield of EBUS-TBB were balanced between the two groups (table 2). There was no significant difference in the diagnostic yield of TBB between the EBUS-TBB−GS and EBUS-TBB+GS groups (79% *versus* 78%; p=0.649). The numbers of auxiliary procedures performed during the EBUS-TBB sessions, namely bronchial washing and brushing, were similar between the two patient groups (table 3). Without the auxiliary procedures, the diagnostic yields of TBB alone were also similar between two groups of patients (73% *versus* 74% for EBUS-TBB−GS and EBUS-TBB+GS groups, respectively; p=0.613). The procedure time was significantly longer in the EBUS-TBB+GS group than in the EBUS-TBB−GS group (29 min *versus* 24 min; p<0.001). Numerically, the rates of haemorrhage (5.8% *versus* 7.2%) and pneumothorax (0.6% *versus* 1.9%) appeared to be lower in the EBUS-TBB+GS group than in the EBUS-TBB−GS group, but the differences did not reach statistical significance. No complications related to bronchial washing and brushing were observed in the current study.

TABLE 1 Characteristics of all study patients with and without a guide sheath during EBUS-TBB

Characteristic	EBUS-TBB without a guide sheath	EBUS-TBB with a guide sheath	p-value
Patients n	556	419	
Age years	67±12	66±13	0.032
Male sex	356 (64)	222 (53)	0.001
Lesion location			
Upper lobes	360 (65)	167 (40)	<0.001
Middle/lower lobes	196 (35)	252 (60)	
Lesion character			
Solid	512 (92)	377 (90)	0.250
Others[#]	44 (7.9)	42 (10)	
Lesion size			
<20 mm	48 (8.6)	46 (11)	0.093
20–30 mm	102 (18)	94 (22)	
>30 mm	406 (73)	279 (67)	
EBUS probe position			
Within	457 (82)	354 (85)	0.343
Adjacent to or outside	99 (18)	65 (16)	
Final diagnosis			
Lung cancer	532 (96)	386 (92)	0.019
Non-lung cancer	24 (4)	33 (8)	
Diagnostic yield	447 (80)	325 (78)	0.281

Numerical variables are presented as mean±SD, and categorical variables are expressed as number (%). EBUS-TBB: endobronchial ultrasound-guided transbronchial biopsy. [#]: part-solid, ground-glass opacity, and cavity.

Factors associated with diagnostic yield

In the propensity score-matched cohort, we constructed a multivariate logistic regression model, including the use of a GS, location, character and size of the PPLs, and EBUS probe position, to examine correlates of the diagnostic yield of EBUS-TBB (table 4). The EBUS probe position (OR 3.226, 95% CI 2.207–5.134; within *versus* adjacent to or outside) was the strongest factor associated with the diagnostic yield, followed by lesion size. An increase in the diagnostic odds of EBUS-TBB was observed along with an increase in the lesion size (OR 2.023, 95% CI 1.071–3.824; 20–30 mm *versus* <20 mm and OR 2.333, 95% CI 1.323–4.116; >30 mm *versus* <20 mm).

TABLE 2 Baseline characteristics of study patients after propensity score matching

Characteristic	EBUS-TBB without a guide sheath	EBUS-TBB with a guide sheath	p-value
Patients n	360	360	
Age years	68±11	65±13	0.006
Male sex	220 (61)	196 (54)	0.070
Lesion location			
Upper lobes	167 (46)	167 (46)	1.000
Middle/lower lobes	193 (54)	193 (54)	
Lesion character			
Solid	323 (90)	322 (89)	0.903
Others[#]	37 (10)	38 (11)	
Lesion size			
<20 mm	45 (13)	31 (8.6)	0.148
20–30 mm	72 (20)	86 (24)	
>30 mm	243 (68)	243 (68)	
EBUS probe position			
Within	305 (85)	304 (84)	0.918
Adjacent to or outside	55 (15)	56 (16)	

Numerical variables are presented as mean±SD, and categorical variables are expressed as number (%). EBUS-TBB: endobronchial ultrasound-guided transbronchial biopsy. [#]: part-solid, ground-glass opacity, and cavity.

TABLE 3 Diagnostic yield, auxiliary procedures, procedure time and complications in the matched study cohort

Variable	EBUS-TBB without a guide sheath	EBUS-TBB with a guide sheath	p-value
Patients n	360	360	
Diagnostic yield	286 (79)	281 (78)	0.649
Auxiliary procedures			
Bronchial washing	312 (87)	319 (89)	0.428
Bronchial brushing	320 (89)	323 (90)	0.718
Procedure time min	24±11	29±11	< 0.001
Complications			
Haemorrhage	26 (7.2)	21 (5.8)	0.451
Pneumothorax	7 (1.9)	2 (0.6)	0.094

Numerical variables are presented as mean±SD, and categorical variables are expressed as number (%). EBUS-TBB: endobronchial ultrasound-guided transbronchial biopsy.

Discussion

This study, for the first time, demonstrated that adding GS guidance to routine EBUS-TBB without fluoroscopy did not offer a better diagnostic yield for malignant PPLs in a propensity score-matched cohort. We also found that the use of a GS was seemingly associated with a lower risk of complications during EBUS-TBB, but its use contributed significantly to a longer procedure time. Nonetheless, overall, the diagnostic yield and safety profile in both EBUS-TBB−GS and EBUS-TBB+GS groups were favourable compared to worldwide experience with EBUS-TBB. Taken together, EBUS-TBB both with and without a GS performed well in diagnosing malignant PPLs with a low complication rate; however, the optimal timing and strategy for using a GS during the TBB procedure remain to be established in further studies.

The most important finding in this study was that the diagnostic yield for malignant PPLs in the EBUS-TBB−GS group was noninferior to that in the EBUS-TBB+GS group. In other words, GS guidance did not provide the diagnostic benefits as we thought it would. It is worth considering why we encountered this unexpected result. First, our study did not include fluoroscopy to assist in the EBUS-TBB procedure, and displacement of the GS would possibly go unnoticed while repeatedly manipulating the sheath throughout the biopsy procedure [11, 19]. Thus, the TBB could not be taken from the target site and yielded a lower diagnostic rate for PPLs. Second, EBUS-TBB with a GS may be particularly advantageous in the diagnosis of smaller (*i.e.* ⩽20 mm) PPLs [10, 11, 20]. A major proportion (88%) of the PPLs in our matched cohort had a diameter of 20 mm or larger, which was higher than that (43–74%) in most reported studies [12, 21–25]. Since several reports have shown a favourable diagnostic yield of 74–81% for PPLs in

TABLE 4 Multivariate logistic regression model for the diagnostic yield of EBUS-TBB in the matched study cohort

Variable	OR (95% CI)	p-value
EBUS-TBB		
With a guide sheath	0.893 (0.614–1.300)	0.554
Without a guide sheath	Reference	
Lesion location		
Upper lobes	1.307 (0.892–1.916)	0.169
Middle/lower lobes	Reference	
Lesion character		
Solid	1.505 (0.845–2.679)	0.165
Others[#]	Reference	
Lesion size		
>30 mm	2.333 (1.323–4.116)	0.003
20–30 mm	2.023 (1.071–3.824)	0.030
<20 mm	Reference	
EBUS probe position		
Within	3.226 (2.207–5.134)	<0.001
Adjacent to or outside	Reference	

EBUS-TBB: endobronchial ultrasound-guided transbronchial biopsy. [#]: part-solid, ground-glass opacity, and cavity.

this size range using EBUS-TBB without a GS [12, 14, 17, 26, 27], the beneficial effect of GS guidance may not be observed in our patient cohort. Third, when a GS is used, a regular-sized biopsy forceps cannot be housed within the sheath. To deal with this problem, a smaller-sized TBB forceps has been developed to accommodate the GS. Therefore, the risk of acquiring a smaller, inadequate tissue sample for pathological diagnosis during EBUS-TBB could increase with GS guidance [13, 23], and this may counteract its positive effect on the diagnostic yield of PPLs.

Similar to our study, Oki *et al.* [12]. showed that in terms of the diagnosis of PPLs under fluoroscopic guidance, EBUS-TBB *via* a 3.4-mm bronchoscope was noninferior to EBUS-TBB with a GS through a 4-mm bronchoscope. Zhang *et al.* [13], using a crossover study design, also found a comparable diagnostic rate of PPLs by EBUS-TBB with and without a GS, and fluoroscopy was not used during the procedures. Moreover, although significant between-study heterogeneity existed, a meta-analysis revealed that the diagnostic yield of EBUS-TBB for PPLs was 73% (95% CI 64–82%) when a GS was used and 71% (95% CI 67–76%) when a GS was not used [7]. As such, the existing literature as well as our finding suggest that non-selective application of GS guidance during EBUS-TBB should not be encouraged considering its extra cost and lack of proven diagnostic benefit. Undoubtedly, more studies are needed to refine indications for the use of a GS in EBUS-TBB of PPLs.

An advantage of GS guidance lies in the repeatability of access to the PPLs for EBUS-TBB and, theoretically, GS guidance can be time-saving for the whole procedure [10, 13]. Our procedure time in both groups of patients fell within previously reported ranges (20–33 min) [12, 22, 28, 29]. However, consistent with the results of the Oki *et al.* study [12], we showed an association between GS guidance and a longer procedure time. With a GS, the EBUS probe has a larger calibre and becomes less flexible. Therefore, it is probably more complex than the technique without a GS when exploring some PPLs in a wide-angled branch of the bronchial tree. The GS also requires additional manipulation to adjust and fit the length of various TBB tools during the procedure. And kinking or bending of the GS may occur when the bronchoscope is manipulated at a sharp angle, which would hinder smooth insertion of the biopsy forceps and brush [30]. All of these disadvantages are potentially contributory to the prolonged procedure time in our EBUS-TBB+GS group. Predictors of the diagnostic yield of EBUS-TBB have been widely investigated [6–8]. Some of our findings largely mirror those of previous studies. The diagnostic yield of TBB increased as the size of the PPLs increased. The yield was also significantly higher when the EBUS probe could be placed within the PPLs, as opposed to being positioned adjacent to or outside them. With regard to complications, a lower incidence of bleeding may be anticipated if a GS is used, since trapping of the GS in the bronchus would prevent flushing of blood proximally into a larger airway. We observed fewer cases of postprocedural haemorrhage that required additional intervention in the EBUS-TBB+GS group. Pneumothorax, a well-known and feared event after TBB, occurred in 0 to 5.1% of patients in previous reports [16]. Our study results showed a marginally lower risk of pneumothorax in patients receiving EBUS-TBB with a GS for PPLs. This finding may not be that surprising in that a smaller biopsy forceps is used and lesion location is more secured with GS guidance. However, this study did not really find a difference in the complication rate of EBUS-TBB between the two groups of patients.

The present study has limitations. First, the study was conducted at institutions with great expertise in this area, and experience would improve the performance of EBUS-TBB [17]. Accordingly, our findings may not be generalisable to less-experienced institutions, even though one study showed an acceptable diagnostic yield when the TBB procedure was performed by beginners [28]. Second, although our study adopted a quasi-experimental design using propensity score matching, we cannot exclude the possibility of residual confounding from variables not included in our analysis. Prospective randomised controlled trials are required to validate our results. Last, only patients with malignant PPLs were enrolled in this study, because this would be straightforward in defining the diagnostic yield of EBUS-TBB. Therefore, the role of GS guidance in the diagnosis of benign PPLs remains to be determined.

In conclusion, for malignant PPLs, EBUS-TBB both with and without a GS provided a similarly favourable diagnostic yield and safety profile. Although the use of GS guidance might be associated with a lower number of complications, it significantly prolonged the procedure time during EBUS-TBB. Additional research is required to validate our findings and determine the optimal timing and strategy for GS guidance in EBUS-TBB.

Acknowledgements: We thank the staff of the Eighth Core Lab, Dept of Medical Research, National Taiwan University Hospital, for technical support during the study, and we also thank the staff of the Dept of Medical Research, National Taiwan University Hospital for the Integrated Medical Database.

Conflict of interest: None declared.

Provenance: Submitted article, peer reviewed.

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