Original Article

Endobronchial ultrasound with a guide sheath for small malignant pulmonary nodules: a retrospective comparison between central and peripheral locations

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Objective: Radial endobronchial ultrasound with a guide sheath (EBUS-GS) has improved the diagnostic accuracy of transbronchial biopsy (TBB) for malignant peripheral pulmonary nodules (PPNs). Many underscore the importance of tumor localization but reproducible results on other aspects that affect yield are few. We aimed to analyze the diagnostic performance of TBB with EBUS-GS and to know what group of patients can benefit most.

Methods: The database of patients with malignant PPNs (≤30 mm) who underwent EBUS-GS TBB at the National Cancer Center Hospital, Tokyo, Japan from April 2012 to March 2013 was retrospectively reviewed and analysed based on lesion and procedural characteristics.

Results: Most PPNs (N=212) were adenocarcinoma, measuring 20 mm [mean, standard deviation (SD) 5.45]. Overall diagnostic accuracy was 67.5% (143 of 212 cases). Factors that significantly affected and predicted diagnostic success were EBUS probe within (P=0.001) and parenchymal location that was not adjacent to the costal visceral pleura (P=0.001). When combined, these variables achieved an 87% (59 of 68 lesions) diagnostic yield. CT scan characteristic, lesion size, lobe location, and GS size were non-contributory.

Conclusions: EBUS-GS TBB is an acceptable diagnostic method for small peripheral lung cancer. It can be maximized for PPNs that are away from the pleura and when the EBUS probe can be placed within the lesion.

Keywords: Endobronchial ultrasound (EBUS); ground glass opacity (GGO); lung cancer; pulmonary nodule (PN); transbronchial biopsy (TBB)

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Introduction

Current guidelines in the management of a peripheral pulmonary nodule (PPN) recommend bronchoscopy as one of the non-surgical diagnostic procedures with a more favourable safety profile (1). The addition of various image-guided modalities, one of which is radial endobronchial ultrasound with a guide sheath (EBUS-GS), has improved the diagnostic yield of transbronchial biopsy (TBB) (2-4). Quite a number of researches have assessed the utility of EBUS-GS during TBB and by far, an EBUS probe location that is within the lesion has been the most consistent factor associated with a high accuracy (5-8).

Some issues that can help maximize the benefits of TBB with EBUS-GS have not been unanimously settled yet (9). The effect of lesion size, location, or size of sampling device on diagnostic performance varies among studies (5-8,10-12). Seemingly, a better diagnostic yield would be expected for larger nodules that are closer to the central airways and if biopsy samples are larger, but this hypothesis should be supported by objective data.

Essentially, refinements are needed to help clinicians choose an approach that is best suited for a particular patient. In this study, we aimed to investigate the factors affecting diagnostic yield of TBB with EBUS-GS for small malignant PPNs and to know what group of patients can benefit most.

Materials and methods

Study design and population

A retrospective review of electronic medical records at the National Cancer Center, Tokyo was carried out on consecutive cases of PPNs that underwent TBB with EBUS-GS at the Respiratory Endoscopy division of the hospital, from April 2012 to March 2013.

Cases that had a final diagnosis of malignancy were included in the study population. Those that were benign or had uncertain diagnosis after one year of follow-up and cases that necessitated removal of the GS during sampling were excluded.

Informed consent was sought from every patient and this study was approved by the Institutional Review Board of the hospital.

Study variables and statistical analysis

Data on demographics, radiologic characteristics, procedural findings, and final diagnoses were collected. PPN was defined as an abnormal lung parenchymal lesion measuring ≤30 mm in largest diameter on axial plane CT scan and that was not visible endoscopically. CT scan characteristics were classified as solid or ground glass opacity (GGO). Location in the pulmonary parenchyma was decided based on a previous study and was designated as "central parenchymal" if the nodule was not adjacent to the costal visceral pleura; or "peripheral parenchymal" if the nodule was adjacent to, or within 10 mm from the costal visceral pleura (13). Lobe was recorded as upper, middle/lingula, and lower.

Data gathered from the bronchoscopy procedure were GS size, EBUS probe location, number of tissue samples, and procedure time (from vocal cord insertion to removal of the GS). Primary endpoint was diagnostic accuracy. The study population was divided according to location and examined separately for factors affecting diagnostic yield.

Data was analysed using IBM SPSS Statistics Software Version 21. Frequencies were presented as mean with standard deviation (SD) and percentages; continuous variables were categorized. Univariate analysis was by Fisher's exact test and Pearson chi-square. Multivariate analysis was by logistic regression. A P value of ≤0.05 was considered significant. Sub-group analysis was performed by crosstabs.

EBUS-GS transbronchial sampling procedure

Procedures were performed at the Respiratory Endoscopy Unit of the hospital; most of the time, the operator was a resident/fellow trainee, under the direct supervision of experienced staff members. Bronchoscopy was performed through the oral route under local anesthesia with conscious sedation. For all cases, the bronchial path to the target lesion was planned using 1-5 mm sequential axial CT scan slices. The choice of bronchoscope and devices (all by Olympus, Tokyo, Japan) depended on each case and availability of equipment. The BF 1T260 (5.9 mm outer diameter, 2.8 mm working channel diameter) was used with a UM-S20-20R radial EBUS probe and a large GS Kit (K-203). The BF-Type260 (5.0 mm outer diameter, 2.0 mm working channel diameter) or P260F (4.0 mm outer diameter, 2.0 mm working channel diameter) was used with a UM-S20-17S radial EBUS probe and a small GS Kit (K-201). Fluoroscopy (VersiFlex VISTA, Hitachi, Japan) was used intermittently during each procedure; specifically during tumor localization by EBUS-GS, during sampling, and during removal of the GS after sampling.

The devices were prepared and the sampling site was searched as usual (2,6). To locate the target site, we used the typical radial EBUS images that have been previously described for solid nodules (6) and the Blizzard sign for GGO nodules (14). When the EBUS probe was found to be within the lesion, it was removed from the GS and TBB was started. When the EBUS probe was adjacent to the lesion or invisible, it was adjusted until the closest possible area to the target site was reached.

Specimens for pathology examination were obtained by alternately inserting biopsy forceps and cytology brush through the GS. Rapid on-site evaluation (ROSE) was performed by an experienced cytopathologist. For PPNs that did not have a "within" location of EBUS probe or when ROSE showed inadequate specimen, transbronchial needle aspiration (TBNA) was done using a 21-G aspiration needle (NA-1C-1) through a large GS (15). In cases wherein the initial GS size used was small, the GS was removed prior to TBNA.

The final diagnoses were established by pathologic evidence from bronchoscopic or surgical biopsy, microbiological analysis, or clinical follow-up.

Table 1 Baseline characteristics of patients with small malignant pulmonary nodules (N=212)

Characteristics	No. [%]
Age in years, mean	67.9 (SD 10.47)
Gender	
Male	122 [58]
Female	90 [42]
CT scan characteristic	
Solid	117[55]
GGO	95
Pure GGO	23 [11]
Part-solid GGO	72 [34]
Size in mm, mean	20.45 (SD 5.45)
Lobe	
Upper	113 [53]
Middle/lingula	26 [12]
Lower	73 [34]
Location	
Peripheral parenchymal	91 [43]
Central parenchymal	121 [57]
Location of EBUS probe	
Within	120 [57]
Adjacent to/invisible	92 [43]
Guide sheath kit	
Large	88 [42]
Small	124 [58]
Number of tissue samples per procedure, mean	4.92 (SD 2.05)
Duration of procedure in minutes, mean	24.58 (SD 7.82)
Cases diagnosed by EBUS-GS TBB	143 [67.5]
Final diagnosis	
Adenocarcinoma	163 [77]
Squamous cell carcinoma	29 [14]
Small cell carcinoma	4 [2]
Other primary lung carcinoma	9 [4]
Metastatic	7 [3]

SD, standard deviation; CT, computed tomography; GGO, ground-glass opacity; EBUS, endobronchial ultrasound; EBUS-GS, EBUS with a guide sheath; TBB, transbronchial biopsy.

Results

The study population consisted of 212 patients with a mean age of 67.9 (SD 10.47) years and with PPNs measuring 20.45 (SD 5.45 mm) (*Table 1*). There were 91 nodules that were "peripheral parenchymal", while 121 nodules were "central parenchymal" in location. Overall diagnostic yield of EBUS-GS was 67.5% and majority were adenocarcinoma. There were no major post-procedural complications.

Table 2 shows the factors affecting diagnostic yield of EBUS-GS TBB for small malignant parenchymal nodules. The diagnostic yield for central parenchymal lesions was significantly higher than that for peripheral parenchymal lesions (77% *vs.* 55%, P=0.001). In the univariate analysis, lesions wherein the EBUS probe could be placed within had a significantly higher diagnostic yield compared to when the EBUS probe was adjacent or invisible (68% *vs.* 54%, P=0.001). In the multivariate analysis, central parenchymal location and EBUS probe within were the predictors of a successful TBB. Diagnostic yield was the same regardless of demographics, nodule size, CT scan characteristic, lobar location, or GS kit size used.

A sub-group analysis that compares the diagnostic accuracy between peripheral parenchymal and central parenchymal locations based on nodule and procedural characteristics is shown in *Table 3*. The diagnostic accuracy of EBUS-GS TBB was highest (87%) for central parenchymal lesions that had an EBUS probe within. Representative cases are presented in *Figures 1* and *2*. In addition, the diagnostic yield for central parenchymal was at least 75% and significantly higher than that of peripheral parenchymal when the lesion was <20 mm in size, solid on CT scan, located in the upper and lower lobes, and when a small size GS kit was used.

Discussion

Endobronchial ultrasound has undeniably contributed a great deal to the recent advancement of diagnostic bronchoscopy for PPNs. Systematic reviews on radial EBUS for PPNs have reported an overall diagnostic accuracy of 71%, though with significant inter-study heterogeneity and yields varying widely from 46-86 percent (4,5). With additional use of a GS, localization of the lesion has consistently translated to better diagnostic yields ranging from 73 to 92 percent (5-8).

This one-year study on 212 small malignant PPNs demonstrated that TBB with EBUS-GS has an overall diagnostic performance of 67.5 percent. Our data is consistent with previously published reports (5-7,9,16) that an EBUS probe within was a significant predictor of procedural success. Proximity to the hilum is an important feature mentioned in literature; accuracy of the procedure for lesions that were touching the visceral pleura was only 35-50 percent (5,7,11). From our analysis, an easily

Table 2 Factors affecting diagnostic yield of EBUS-GS TBB for small malignant pulmonary nodules (N=212)

Characteristics	Univariate analysis		Multivariate analysis	
	Accuracy [%]	P value	P value	Odds ratio (95% CI)
Age (years)		0.060		
≥70	79/107 [74]			
<70	64/105 [61]			
Sex		0.550		
Male	80/122 [66]			
Female	63/90 [70]			
Size in major axis (mm)		0.179		
≥20	91/128 [71]			
<20	52/84 [62]			
CT scan characteristic		1.000		
Solid	79/117 [68]			
GGO	64/95 [67]			
Lobe		0.803		
Upper	75/113 [66]			
Middle/lingula	19/26 [73]			
Lower	49/73 [67]			
Location		0.001	0.001	2.85 (1.53-5.31)
Central parenchymal	93/121 [77]			
Peripheral parenchymal	50/91 [55]			
EBUS probe		0.001	0.001	2.79 (1.48-5.27)
Within	93/120 [68]			
Adjacent/invisible	50/92 [54]			
GS kit size		0.460		
Large	62/88 [71]			
Small	81/124 [65]			

EBUS-GS, endobronchial ultrasound with a guide sheath; TBB, transbronchial biopsy; CT, computed tomography; GGO, ground glass opacity; GS, guide sheath.

accessible lesion (central parenchymal) was more likely to be diagnosed successfully than a more distally located lesion. For central parenchymal nodules, diagnostic accuracy increased significantly to 77 percent. This difference in diagnostic yield between peripheral and central parenchymal locations was significant especially for lesions <20 mm in size, solid in character, located in the upper and lower lobes, and when the GS kit used was small. When combined with an EBUS probe that could be precisely localized within the lesion, TBB with EBUS-GS for central parenchymal lesions had a remarkably higher yield of 87 percent. The average number of TBB samples was five per procedure. There were no major complications.

The findings of this study could be helpful when choosing a diagnostic modality for clinically suspected malignant PPNs that are away from the pleura. Transthoracic needle aspiration (TTNA) has a similar diagnostic yield for PPNs but with higher accompanying risks (1,17,18). Our results could also be important for beginner physicians. At the start of the learning curve, it might be prudent to perform TBB with EBUS-GS for patients who are more likely to be diagnosed accurately. For lesions that are adjacent to the pleura, use of virtual bronchoscopic navigation (VBN) may be useful to increase the yield (19).

Nodule size has been cited by some studies (1,4,5,18) to significantly influence diagnostic yield but other researches

Table 3 Comparison of diagnostic accuracy between peripheral and central parenchymal locations based on lesion and procedure characteristics

Characteristics	Peripheral parenchymal (n=91) [%]	Central parenchymal (n=121) [%]	P value
Size			
≥20 mm (n=128)	33/52 [64]	58/76 [76]	0.164
<20 mm (n=84)	17/39 [44]	35/45 [78]	0.002
CT characteristic			
Solid (n=117)	30/55 [55]	49/62 [79]	0.006
GGO (n=95)	20/36 [56]	44/59 [75]	0.070
Lobar location			
Upper (n=113)	19/38 [50]	56/75 [75]	0.012
Middle/lingula (n=26)	9/13 [69]	10/13 [77]	1.000
Lower (n=73)	22/40 [55]	27/33 [82]	0.024
EBUS probe location			
Within (n=120)	34/52 [65]	59/68 [87]	0.008
Adjacent to/invisible (n=92)	16/39 [41]	34/53 [64]	0.040
GS size			
Small (n=124)	32/63 [51]	49/61 [80]	0.001
Large (n=88)	18/28 [64]	44/60 [73]	0.450
Procedure time in minutes, mean	24 (SD 8)	25 (SD 8)	0.500

CT, computed tomography; GGO, ground glass opacity; EBUS, endobronchial ultrasound; GS, guide sheath; SD, standard deviation.

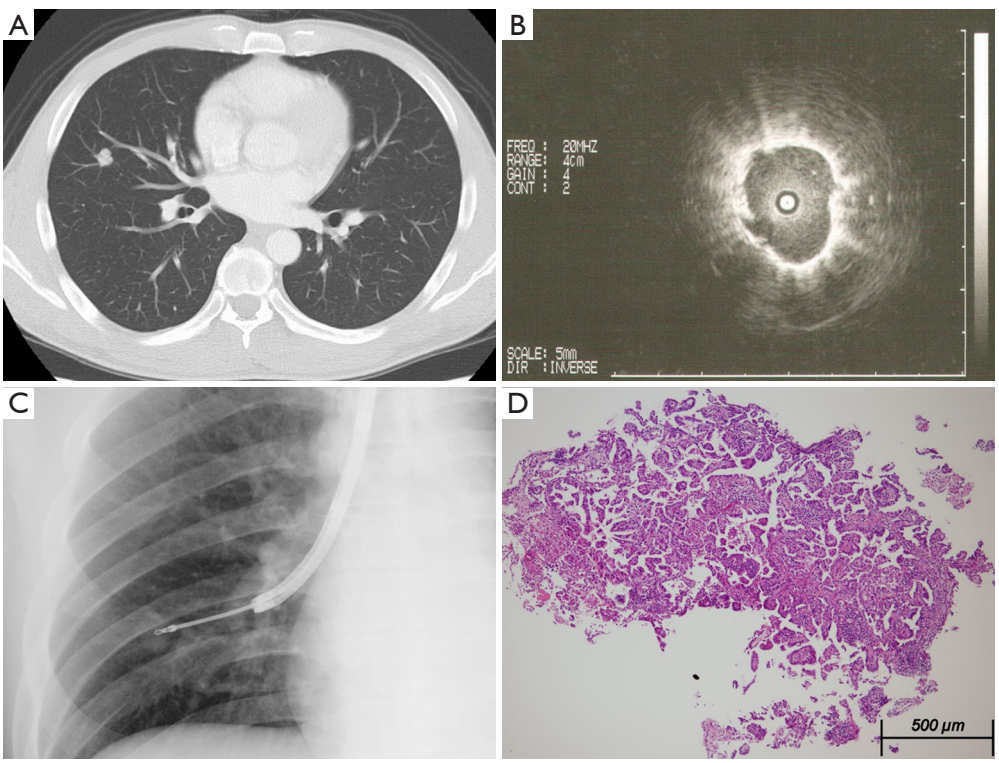

Figure 1 A 43-year-old man with a small solid central parenchymal nodule. (A) CT scan showed a 14-mm lesion in the right segment 3 that was localized by; (B) heterogenous echogenicity, within on radial EBUS; (C) TBB with a large guide sheath kit under fluoroscopy guidance yielded; (D) adenocarcinoma (hematoxylin-eosin stain, ×4). CT, computed tomography; EBUS, endobronchial ultrasound; TBB, transbronchial biopsy.

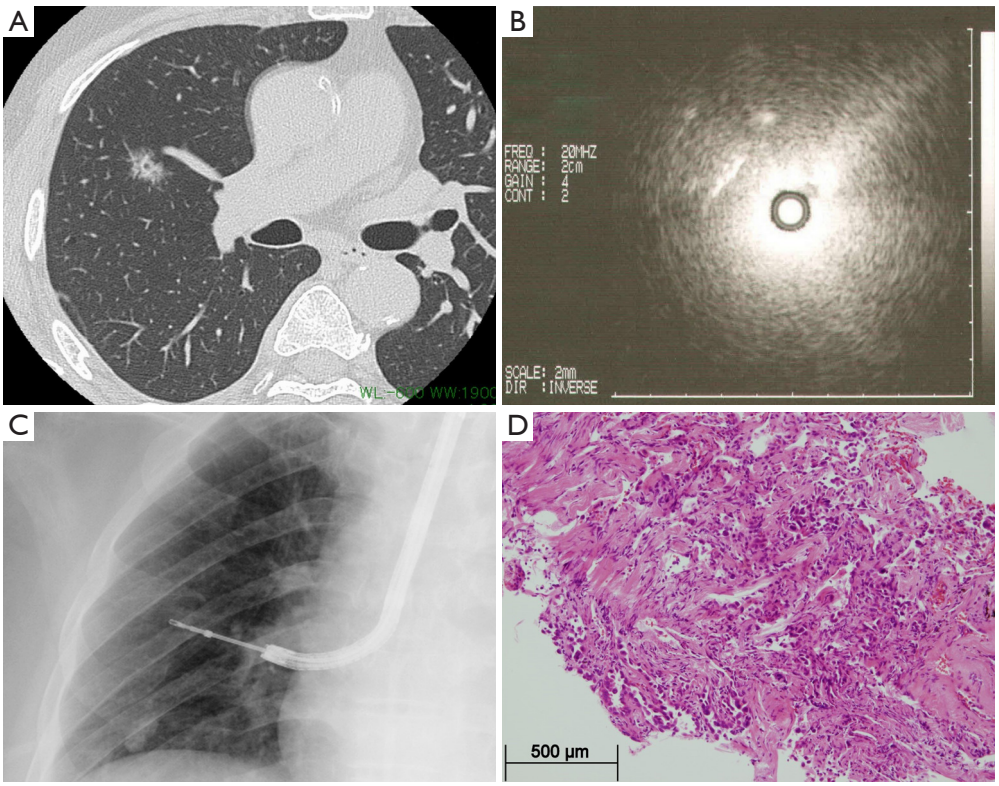

Figure 2 A 79-year-old man with a small, part-solid ground-glass opacity central parenchymal nodule. (A) CT scan showed a 15-mm lesion in the right segment 4 that was localized by; (B) Blizzard sign on radial EBUS; (C) TBB with a large guide sheath kit under fluoroscopy guidance yielded; (D) adenocarcinoma (hematoxylin-eosin stain, ×10). CT, computed tomography; EBUS, endobronchial ultrasound; TBB, transbronchial biopsy.

present opposing results (6,12,20). Also, we hypothesized that using a large GS and its corresponding sampling devices is preferred, especially for GGOs. This study demonstrated that TBB with EBUS-GS is an acceptable diagnostic modality for malignant PPNs regardless of size, CT scan characteristic (solid or GGO), lobar location, or GS kit size.

Our study has some limitations. First, although TBNA was used in some cases in this study population, we did not have sufficient reliable data to include this variable in the analysis. Second, the unequal distribution of patients in each of the subgroups (*Table 3*) should be taken into consideration when analysing these results. Last, it may be noteworthy that our follow-up period was less than the recommended time frame to establish stability of both solid and GGO nodules; thus, false-negative results are possible. Since this was a retrospective, single-center research, we suggest prospective randomized controlled studies in the future.

Nevertheless, this research highlights that precise search of a biopsy site using EBUS is essential when performing TBB for small peripheral lung cancer. Patients with lesions that are not adjacent to the costal visceral pleura may potentially benefit more from the procedure.

Conclusions

EBUS-GS as an aide during TBB has an acceptable diagnostic yield for small malignant PNs. The value of the procedure can be maximized for patients who have parenchymal lesions that are not adjacent to the pleura and can be precisely localized by the radial EBUS probe.

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Matsumoto all substantially contributed to the acquisition, interpretation, and consolidation of data. Statistical analysis was performed by C Chavez and T Izumo. The manuscript was written by C Chavez, was revised critically for important intellectual content by S Sasada, and reviewed by T Izumo, J Watanabe, M Katsurada, Y Matsumoto, and T Tsuchida. All authors approved of the final version of the manuscript.
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