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Article

## Transbronchial Needle Aspiration through a Guide Sheath with Endobronchial Ultrasonography (GS-TBNA) for Peripheral Pulmonary Lesions

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**Purpose:** Although, endobronchial ultrasonography with a guide sheath is becoming a common procedure for the diagnosis of peripheral pulmonary lesions, there remain to be some inaccuracies in cases wherein the probe is located outside the lesion. We tested whether adding transbronchial needle aspiration through a guide sheath to the conventional technique increases efficacy for diagnosing peripheral pulmonary lesions.

**Methods:** We performed transbronchial needle aspiration through a guide sheath for 37 subjects with peripheral pulmonary lesions between September 2012 and April 2013. The devices used were as follows (all Olympus Ltd., Tokyo, Japan): 1T-260 or LF-TP bronchoscope, K203 guide sheath kit and NA-1C-1 needle apparatus, customized by cutting the guide sheath 30 mm from the proximal end to fit well with the needle.

**Results:** The endobronchial ultrasound probe was located within the lesion in 21 cases (56.8%) and outside in 16 cases (43.2%). Overall accuracy was 86.5 percent; 90.5% in “within” cases compared to 81.3% in “outside” cases with no significant difference ( $P = 0.42$ ). Pneumothorax occurred in 2 cases and pneumonia in 1 case.

**Conclusion:** Transbronchial needle aspiration through a guide sheath is an effective and safe diagnostic procedure for peripheral pulmonary lesions, especially when the guide sheath is outside the lesion.

**Keywords:** peripheral pulmonary lesion, EBUS-GS, GS-TBNA, computed tomography-guided transthoracic needle biopsy, transbronchial biopsy

### Introduction

The chances of detecting peripheral pulmonary lesions (PPLs) are increasing and so are the chances to collect samples from them.<sup>1)</sup>

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However, PPLs are challenging to diagnose as compared to central lesions. One way to collect samples from PPLs is through bronchoscopy. The paradigm shift brought about by the use of radial probe endobronchial ultrasonography and a guide sheath (EBUS-GS) increased detection rates of bronchoscopy for PPLs.<sup>2,3)</sup> The new guidelines of the American College of Chest Physicians now recommends radial EBUS as an emerging technology to diagnose PPLs.<sup>4)</sup> It has been noted that when the EBUS probe location is adjacent to the lesion the diagnostic yield is lower compared to when the probe is within the lesion.<sup>5)</sup> An “adjacent to” EBUS image is thought to imply that the GS is only touching the surface

of the lesion and that no bronchus leads to the lesion, like in cases of pulmonary metastasis.

Computed tomography-guided transthoracic needle biopsy (CTNB) is another choice for diagnosing PPLs. It may be useful for diagnosing PPLs because CTNB can be done regardless of the bronchus location in relation to a pulmonary lesion. However, the diagnostic sensitivity of CTNB ranges from 64% to 93% and the complication rate is relatively high; pneumothorax occurs in 18%–47%, and hemoptysis in 13%–20%.<sup>6–8)</sup>

Both procedures have strong and weak points, and the challenge is to combine the respective strong points of bronchoscopy and CTNB. In cases wherein the EBUS probe is adjacent to lesions, the combination of EBUS and transbronchial needle aspiration (TBNA) has been demonstrated to be useful and safe.<sup>9)</sup> The use of guide sheath is becoming a common procedure in Japan, but usually the GS used is of the thin type (K201; Olympus, Japan). The lumen of the thin GS, however, is too narrow for a TBNA needle to fit in so there have been no studies yet to evaluate the effectiveness of combining EBUS, TBNA and GS. As the use of EBUS-GS increased the diagnostic yield for PPLs,<sup>5)</sup> we hypothesize that TBNA through a GS with radial EBUS (GS-TBNA) would further increase the diagnostic yield of bronchoscopy without compromising safety.

In this study, we evaluated the efficacy of GS-TBNA with the use of a GS with a larger lumen as a new way to collect samples from PPLs. We hope to make good use of the chances to collect samples from PPLs by increasing our diagnostic yield.

## Materials and Methods

### Subjects

We defined PPLs as lesions that are not visible through the bronchoscope. In this study, we included 37 subjects with PPLs who underwent bronchoscopy from September 2012 to April 2013 at the National Cancer Center Hospital, Tokyo, Japan. This study was approved by the Institutional Review Board, and informed consent was obtained from all subjects.

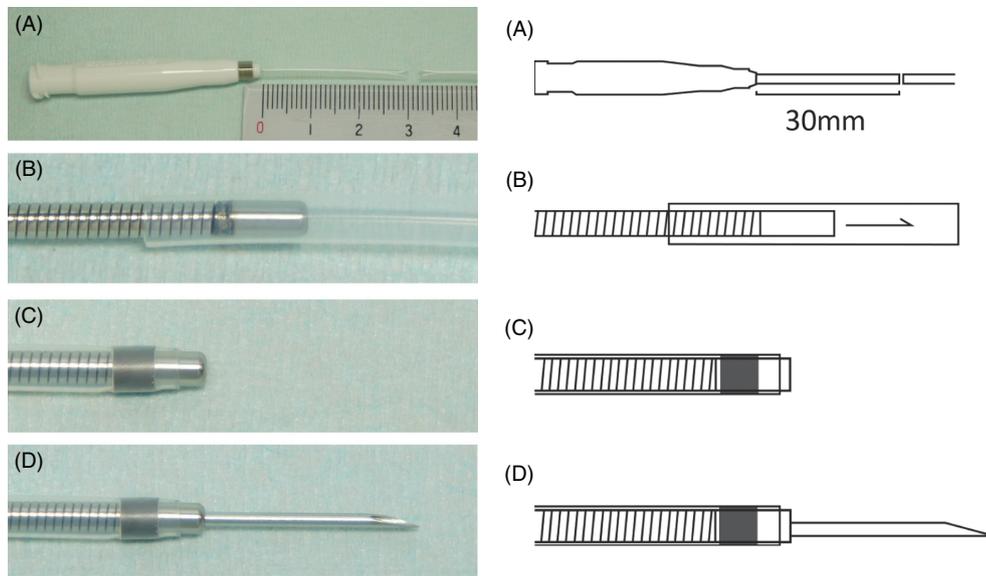
### Equipment and methods

All procedures were carried out using either a BF-1T260 bronchoscope (Olympus Ltd., Tokyo, Japan) with 2.8 mm working channel or an LF-TP bronchoscope (Olympus, Japan) with 2.6 mm working channel. The radial EBUS probe had a diameter of 2.0 mm (UM-S20-

20R; Olympus, Japan) and the guide-sheath measured 2.2 mm in diameter (K203 Kit; Olympus, Japan). Disposable biopsy forceps (FB-231D; Olympus, Japan) and bronchial brush (BC-202D-2010; Olympus, Japan) were used. TBNA procedures were performed using a 13-mm long 21-G needle without a side hole through a metallic sheath (NA-1C-1; Olympus, Japan). The length of the GS was adjusted to accommodate the length of the TBNA sheath by cutting the proximal end of the GS by about 30 mm; this would facilitate insertion of the needle apparatus through the GS up to the appropriate distance needed for TBNA (**Fig. 1**).

### Procedures by bronchoscopy

The bronchial route was planned by reviewing the chest CT scan images before bronchoscopy. In 5 cases, virtual bronchoscopic navigation system was used for planning the route. The size of each PPL was determined by measuring the largest diameter on cross-sectional CT images. The distance from the lateral edge of the pulmonary lesion to the visceral pleura was recorded for each case. Subjects were given meperidine and midazolam as pre-medications. During bronchoscopy, X-ray fluoroscopy was used to confirm the location of the distal tip of the bronchoscope, the EBUS probe, and the sampling devices. For purposes of simplicity, we designated the term “within” when the EBUS probe was determined to be located in the lesion; otherwise, or when the EBUS probe was shown to be adjacent to the lesion, they were designated as “outside”. After scanning the PPL with EBUS, the probe was removed while keeping the GS in place. First, TBNA through the GS was performed, then transbronchial biopsy (TBB) and brushing followed. All sampling procedures -TBB, brushing and TBNA- were performed in all cases regardless of the EBUS probe location. The procedure of GS-TBNA was done as follows: the needle was inserted through the guide sheath and into the lesion under X-ray fluoroscopy guidance. For cases in which the probe was “outside” the lesion the GS was set beside the lesion. Insertion of the needle was done towards the direction of the lesion, as determined by X-ray fluoroscopy and radial EBUS guidance. After pushing the needle into the PPL and while applying negative pressure through a 20 mL syringe, aspiration by moving the needle back and forth was done. To avoid pneumothorax, the distance between the needle and the pleura was monitored by fluoroscopy, and for small PPLs near the pleura the needle was not completely extended from the metallic sheath during aspiration.



**Fig. 1** Preparation of Guide Sheath (GS) for transbronchial needle aspiration (TBNA). (A) Cut 30 mm from the proximal end. (B and C) When the TBNA sheath is inserted to the GS, note that the tip of the metallic sheath will coincide with the distal tip of GS. (D) This way, the needle will not damage the guide sheath during aspiration.

Samples of TBNA were smeared on glass slides. When a core of tissue was obtained, it was fixed in formalin. Needles were flushed with saline and the specimens were sent for genetic testing whenever indicated. After collecting samples, the GS was left in place for 2 minutes for hemostasis before subsequently removing it. X-ray fluoroscopy guidance was intermittently used during sampling procedures (e.g., TBB, brush, TBNA) and during the removal of the guide sheath.

### Statistical analysis

The final diagnosis was made from bronchoscopic specimens or surgical specimens. Fisher's exact test and Mann-Whitney U test were used and statistical significance was set at  $p < 0.05$ . IBM SPSS Statistics 21 (IBM Corporation, New York, USA) was used for all statistical analyses.

### Results

The summary of the baseline characteristics of subjects is shown in Table 1. There were 37 subjects in total (26 men, 11 women). The mean age was  $68.6 \pm 10.1$  years. Malignancy was the diagnosis in 31/37 subjects (84%). The mean size of the PPLs was  $37.9 \pm 17.5$  mm; 22 lesions (59%) were  $>30$  mm. The locations of the PPLs were distributed as follows: 30% in right upper

lobe ( $n = 11$ ), 5% in right middle lobe ( $n = 2$ ), 16% in the right lower lobe ( $n = 6$ ), 27% in left upper lobe ( $n = 10$ ) and 22% in left lower lobe ( $n = 8$ ). When distance of the PPL to the pleura was noted, 24% were adjacent to pleura ( $n = 9$ ), 54% were  $<10$  mm away from pleura ( $n = 20$ ), and 22% were  $>10$  mm away from the pleura ( $n = 8$ ). With regards the EBUS scanning images, 21 cases were within the lesion and 16 were outside the lesion.

The characteristics of cases associated with EBUS images are also shown in Table 1. For within cases, the mean size of the PPL was  $41.5 \pm 19.1$  mm; for outside cases, the mean size was  $33.3 \pm 14.5$  mm. Mean procedure time was  $27.2 \pm 9.35$  minutes. The procedure time was significantly longer in outside cases than that of within cases ( $32.2$  vs.  $23.4$  minutes;  $P = 0.003$ ).

According to the EBUS probe location (Table 2), the overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy of all the sampling procedures for within cases were 89.5%, 100%, 100%, 50%, 90.5%, respectively, and 78.6%, 100%, 100%, 40%, 81.3%, respectively for outside cases. None of them were significantly different. Pneumothorax that did not necessitate chest tube insertion occurred in 2 cases and pneumonia in 1 case. Major bleeding or air embolism was not detected.

For lesions  $>30$  mm, the procedures had a combined sensitivity of 85%, 100% specificity, 100% positive

**Table 1** Baseline characteristics of subjects with peripheral pulmonary lesions

Variables	All cases	Within cases	Outside cases	P value
Number of subjects	37	21 (56.8)	16 (43.2)	
Age (in years $\pm$ SD, range)	68.6 $\pm$ 10.1 (41–86)	71 $\pm$ 10.6 (41–86)	68 $\pm$ 9.6 (48–81)	0.77
Male/Female	26/11	15/6	11/5	0.86
Lesion size (mm $\pm$ SD, range)	37.9 $\pm$ 17.5 (13–74)	41.5 $\pm$ 19.1 (13–74)	33.3 $\pm$ 14.5 (13–63)	0.16
Lesion location				
Right upper lobe (%)	11 (19.7)	9/21 (42.9)	2/16 (12.5)	
Right middle lobe (%)	2 (5.4)	1/21 (4.8)	1/16 (6.3)	
Right lower lobe (%)	6 (16.2)	5/21 (23.8)	1/16 (6.3)	0.05
Left upper lobe (%)	10 (27.0)	2/21 (9.5)	6/16 (37.5)	
Left lower lobe (%)	8 (21.6)	4/21 (19.0)	6/16 (37.5)	
Distance from pleura				
adjacent to pleura (%)	9 (24.3)	5/21 (23.8)	4/16 (25)	
<10 mm away from pleura (%)	11 (29.7)	8/21 (38.1)	3/16 (18.8)	0.41
$\geq$ 10 mm away from pleura (%)	17 (45.9)	8/21 (38.1)	9/16 (56.3)	
Procedure time (min $\pm$ SD, range)	27.2 $\pm$ 9.35 (9–45)	23.4 $\pm$ 8.32 (9–42)	32.2 $\pm$ 8.45 (18–45)	0.003

**Table 2** Prediction of lesions according to the EBUS image

	Total (N = 37)	Within (N = 21)	Outside (N = 16)	P value
Sensitivity (%)	84.8	89.5	78.6	0.39
Specificity (%)	100	100	100	1.0
Positive predictive value (%)	100	100	100	1.0
Negative predictive value (%)	44.4	50.0	40.0	0.76
Accuracy (%)	86.5	90.5	81.3	0.42

EBUS: endobronchial ultrasonography

**Table 3** Prediction according to the size of lesions

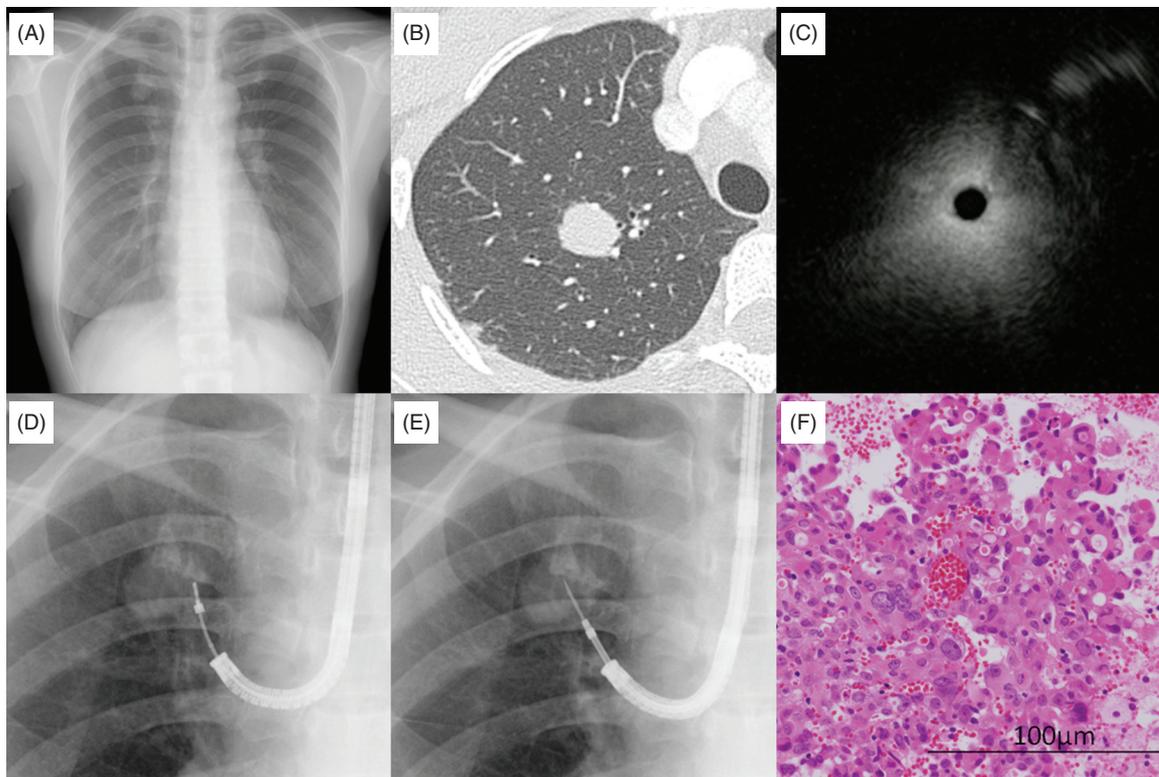
	Total (N = 37)	>30 mm (N = 22)	$\leq$ 30 mm (N = 15)	P value
Sensitivity (%)	84.8	85.0	84.6	0.98
Specificity (%)	100.0	100.0	100.0	1.0
Positive predictive value (%)	100.0	100.0	100.0	1.0
Negative predictive value (%)	44.4	40.0	50.0	0.76
Accuracy (%)	86.5	86.4	86.7	0.98

predictive value, 40% negative predictive value, and 86.4% accuracy. For lesions <30 mm, the sampling procedures had 84.6% sensitivity, 100% specificity, 100% positive predictive value, 50% negative predictive value, and 86.7% accuracy. No significant difference was seen (**Table 3**).

A representative outside case is shown in **Fig. 2**: a 51 year-old woman with a 20 mm PPL on the right upper lobe. On EBUS scanning through the guide sheath, the probe was noted to be adjacent to the target lesion. With the GS located outside the lesion, GS-TBNA was performed. Histopathologic specimen for the GS-TBNA showed adenocarcinoma.

## Discussion

To our knowledge, this is the first report on the efficacy of GS-TBNA for peripheral pulmonary lesions. This study examined the hypothesis that GS-TBNA provides a high diagnostic yield by using the same principle of CTNB while preserving the safety of bronchoscopy, by enabling confirmation of the tumor location by EBUS, and by making it possible to insert sampling devices to the same place multiple times through a guide sheath. Our results show that adding TBNA to usual EBUS-GS sampling has an overall accuracy of 86.5%, without major complications. Of note is the relatively high accuracy (81.3%) of



**Fig. 2** A representative case of transbronchial needle aspiration through a guide sheath (GS-TBNA). (A and B) A pulmonary nodule (20 mm in size) in right upper lobe. (C and D) A radial endobronchial ultrasound (EBUS) probe with a guide sheath (GS) was inserted to the leading bronchus and the generated EBUS image was outside. (E) GS-TBNA was performed on the nodule. (F) Histopathologic specimen from the GS-TBNA showed adenocarcinoma. (Hematoxylin-Eosin stain,  $\times 200$ ).

GS-TBNA for outside cases when compared to previous reports of EBUS-GS on adjacent cases.

When we look back at the historical improvements in the diagnosis of a PPL, the development of flexible bronchoscopy in 1966 was probably the first paradigm shift in the realm of pulmonary diagnostics.<sup>2)</sup> It brought about an approach to a PPL that is easy and less invasive. The technological advancement of the CT scan made it convenient to identify the bronchus leading to the PPL, but still it was difficult to obtain samples with an acceptable accuracy.

The second paradigm shift was when the radial EBUS was developed to assist the operator in determining more accurately whether the sampling device has reached the target lesion. The addition of GS to EBUS brought about further improvement of the diagnostic yield.<sup>10)</sup> But for cases that do not have a bronchus directly leading to the tumor, the challenge is to go beyond the bronchial wall to obtain the sample. In addition to forceps and brush, a sampling device that could serve this purpose would be ideal.

In contrast, CTNB is another approach for diagnosing PPLs. This has a good accuracy and may be done regardless of the bronchus structure.<sup>11)</sup> Since the access is through the percutaneous route with the use of a needle, the incidence of pneumothorax and hospitalization have been reported frequently.<sup>8)</sup> Although rare, a severe complication of CTNB which should always be noted is air embolism.

A similar principle of using a needle is by TBNA, but this time the access is through the airways leading to or adjacent to the target peripheral tumor. For the latter cases, the involved bronchial wall is punctured to get samples from an adjacent tumor. The efficacy and safety of TBNA for PPLs were shown previously; TBNA was diagnostic in 35%–69% cases and pneumothorax occurred in only 0%–0.5%.<sup>12–14)</sup> The strength of TBNA is that it showed higher sensitivity than transbronchial biopsy, especially in cases with lesions lacking bronchus sign.<sup>15,16)</sup> Adding TBNA to conventional EBUS diagnostic procedures has demonstrated a potential for good

diagnostic yields ranging from 60.6% to 78.4%.<sup>9)</sup> Noticeably, these numbers can be improved. One possible way is to overcome the obstacle of limited endoscopic visualization because of bleeding while the EBUS probe and TBNA sheath are inserted alternately.

This study introduces the GS-TBNA technique which combines the techniques of all these emerging methods: CTNB, EBUS and GS. As shown in **Table 2**, when GS-TBNA was added to our usual diagnostic bronchoscopy procedures for PPLs, the yield was relatively high regardless of the location of the EBUS probe. A previous study showed a significantly lower diagnostic yield when the EBUS probe was adjacent to the tumor as compared to when the probe was within (42% vs. 87%).<sup>5)</sup> Based on our results, we infer that adding GS-TBNA to the usual TBB and brushing procedures can increase yield, especially for PPLs that do not have a direct bronchus.

Guide sheath-TBNA is effective not solely by itself but in combination with other devices. Performing TBNA before biopsy and brushing penetrates the bronchial wall towards the lesion. Repeated TBB may cut open a route inside the lesion. Thus, TBNA may enable collection of specimens from inside the lesion and it enhances the accuracy of all the procedures combined. Furthermore, using the GS keeps the view of the bronchoscope clear, controls the bleeding, and leads the different sampling devices quickly to the same place.

Virtual bronchoscopic navigation (VBN) may not affect the diagnostic yield. One study showed that in combination with ultrathin bronchoscopy, VBN did not improve the diagnostic yield for peripheral pulmonary lesions.<sup>17)</sup> In our study, 5 cases were assisted by VBN but this factor may not affect the results. Thus, delicate route selection with VBN may not be necessary for PPLs that do not have a bronchus sign because GS-TBNA can reach the PPL directly by piercing through the bronchial wall.

The diagnostic yield of usual TBB and brushing declines as the size of the PPLs decreases, while that of GS-TBNA may be unaffected by PPL size. This observation may be explained by the fact that for the usual procedures of TBB and brushing, more meticulous bronchus selection is needed as size of the PPL becomes 30 mm or less. This may not hold true for GS-TBNA because of reasons just mentioned in the previous paragraph.

The technique of GS-TBNA per se is similar for both outside and within cases. The difference lies in the longer procedure time for outside cases, wherein the direction of the needle towards the PPL had to be adjusted several times to determine the optimal position prior to sampling.

For within cases, on the other hand, there was already a bronchus directly leading to the PPL, obviating the need for time-consuming positional changes.

This new method has a similar safety profile as the usual bronchoscopy. Majority (78.4%) of our study cases were either adjacent to or  $\leq 10$  mm from the pleura, but even then, pneumothorax occurred in only 5% ( $n = 2$ , both were 0–6 mm away from the pleura and were shown to be “outside” on EBUS scanning). No major bleeding occurred. When we review previous studies on pneumothorax as a complication, TBNA without GS had a 2% rate while CTNB had a 15% rate.<sup>4,9)</sup>

There are several limitations in this study. First, this is a retrospective, non-randomized study. Second, this was performed at a single institution and multi-center trial is ideal because operator skill may also be a confounding variable. Third, adjusting the GS-TBNA needle prior to sampling under fluoroscopy guidance poses an additional radiation exposure risk.

## Conclusion

Addition of GS-TBNA technique to the usual procedures of diagnostic bronchoscopy is useful and safe for peripheral pulmonary lesions, especially for lesions that do not have a bronchus directly leading to them.

## Acknowledgement

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## Disclosure Statement

The authors have reported to *Annals of Thoracic and Cardiovascular Surgery* no conflicts of interest.

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