Am J Transl Res 2020;12(8):4604-4611
www.ajtr.org /ISSN:1943-8141/AJTR0115799

Original Article

Comparison in efficacy and safety of forceps biopsy for peripheral lung lesions guided by endobronchial ultrasound-guided sheath (EBUS-GS) and electromagnetic navigation bronchoscopy combined with EBUS (ENB-EBUS)

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Received June 7, 2020; Accepted July 22, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Endobronchial ultrasound-guided sheath (EBUS-GS) and electromagnetic navigation bronchoscopy combined with EBUS (ENB-EBUS) are two diagnostic methods used to obtain lung tissue for biopsy of peripheral lung lesions. This study retrospectively summarized the case data of patients who underwent EBUS-GS or ENB-EBUS, both procedures performed at the respiratory endoscopy center of Tangdu Hospital, and the study compared the diagnostic efficacy and complications of the two methods. The study included 93 patients who underwent EBUS-GS and 26 who underwent ENB-EBUS. The diagnostic rates of EBUS-GS and ENB-EBUS were 71.1% and 65.4%, respectively, with no statistical difference (P=0.581). Furthermore, 89.2% of patients in the EBUS-GS group were diagnosed with malignant disease, which was significantly higher than 23.5% diagnosed with malignant disease in the ENB-EBUS group (P=0.00). An analysis of the factors influencing the diagnosis rate showed that the diagnosis rate of EBUS-GS in cases with bronchial signs was 82.5%, which was significantly higher than the 42.9% in the cases in the ENB-EBUS group with bronchial signs (P<0.05). An analysis of the complications showed that the incidence of complications in the EBUS-GS group was 8.4%, and the incidence of complications in the ENB-EBUS group was 3.8%, with no statistical difference (P>0.05). Both EBUS-GS and ENB-EBUS can be used for the diagnosis of peripheral pulmonary disease. However, the diagnostic rate of EBUS-GS is significantly higher than ENB-EBUS in cases with bronchial signs associated with the lesion, and the diagnostic rate of ENB-EBUS in cases with no bronchial signs was higher than that of EBUS-GS with no statistical difference.

Keywords: Bronchoscopy, image-guided biopsy, electromagnetic navigation bronchoscopy, lung cancer, solitary pulmonary nodule

Introduction

Pulmonary nodules found on low-dose CT scans [1] require further examination to determine whether they are benign or malignant [2]. Commonly used diagnostic methods include flexible fiber bronchoscopy (FFB), CT-guided transthoracic biopsy, bronchoscopy with bronchial ultrasound (EBUS), and thoracoscopy and thoracotomy [3]. Each of these methods has its advantages and disadvantages, and the guidelines recommend the use of the least invasive method for particular conditions [4]. The biggest challenge in employing these conventional methods is to ensure minimal invasiveness while obtaining sufficient tissue samples for pathological diagnosis and genetic testing.

Standard flexible bronchoscopy is limited in its ability to evaluate small lung nodules [5]. However, electromagnetic navigation enables bronchoscopy physicians to guide endoscopic tools to target lung lesions; therefore, the use of electromagnetic navigation bronchoscopy (ENB)

can theoretically improve the diagnostic rates of conventional flexible bronchoscopy. The results of studies of the diagnostic rates of ENB on peripheral small pulmonary nodules show that the reported diagnostic yield of ENB is currently between 59% and 94% [6]. Moreover, importantly, the reported incidence of ENB complications is low; that of pneumothorax is about 3%, and 1.6% of those undergoing ENB require placement of a chest tube [7].

The endobronchial ultrasound-guided sheath (EBUS-GS), another valuable guided technique, extends the radial probe into the distal end of the bronchus to reach the lung lesion(s), and can display a 360° view image around the lumen of the bronchi [8]. EBUS-GS is widely used in the diagnosis of peripheral lung lesions [8], and the diagnostic yields of guided bronchoscopy have increased to more than 70% currently [9]. The guidelines of the American College of Chest Physicians (ACCP) state that the diagnostic rate of lung lesions under the guidance of endobronchial ultrasound is greater than 70% [4].

While both ENB and EBUS-GS are established guidance methods used in the diagnosis of peripheral lung lesions, at present there have been few studies on the diagnostic accuracy of combining EBUS-GS with ENB. This single-center study retrospectively summarized case data of patients undergoing ENB and EBUS-GS guided pulmonary biopsy at Tangdu Hospital, and compared the diagnostic efficacy and complications of the two diagnostic methods.

Material and methods

Study design

This single-center, retrospective clinical study enrolled 109 patients who agreed to undergo either EBUS-GS or ENB-EBUS for investigation of peripheral lung lesions. The study was approved by the ethics committee of the Tangdu Hospital affiliated to the Air Force Military Medical University, and was registered in the Chinese Clinical Trial Registry (ChiCTR) (registration number ChiCTR1900023937).

Patients

We enrolled 109 patients who agreed to EBN-EBUS or EBUS-GS for the investigation of peripheral pulmonary nodules in Tangdu Hospital from March 2017 to January 2019. The inclusion criteria used in the data collection were: (1) the chest CT showed peripheral lung nodules with lung diameter in the range 0.8 cm to 3 cm; (2) lesions were surrounded by lung parenchyma. Exclusion criteria were: (1) severe arrhythmia or myocardial ischemia; (2) uncontrollable hypertension (systolic blood pressure >180 mmHg); (3) severe organ dysfunction; (4) severe breathing difficulties; (5) allergy to anesthetic drugs; and (6) difficulty in complying with clinical instructions and procedures. All subjects provided written informed consent before undergoing EBUS-GS or ENB-EBUS.

Diagnostic equipment

Diagnostic equipment was as follows: bronchoscope (BF-1T260-0L8, outer diameter 5.9 mm, working aperture 3.9 mm), endoscopic ultrasound host (EndoEcho EU-M2000), endobronchial ultrasound probe (UM-S20-17S), bronchoscope (BF- P260, outer diameter 4.9 mm, working aperture 2.8 mm), and the electromagnetic navigation system-V7 (Super Dimension, USA) including 1 computer with Super Dimension-V7 software, 1 electromagnetic positioning plate, 3 Edge catheters and 1 ENB host.

Preparation of patients

Before bronchoscopy, all patients underwent a 64-slice (layer thickness 0.625 mm) CT scan of the chest. All patients agreed to and underwent the following examinations: blood clotting time, routine blood biochemistry, HIV, syphilis, hepatitis serology, liver and kidney function, electrocardiogram and cardiac ultrasound. In addition, patients fasted for no less than 6 hours before EBUS-GS or ENB-EBUS examinations. EBUS-GS and ENB-EBUS were performed under general anesthesia.

ENB-EBUS

The path of the patient's bronchus and registration points were marked using Super Dimension software. A triplet sensor was placed on the sternal stalk and the chest wall on both sides to ensure that the sensors were inside the magnetic field. During the examination, ultrasound probe, puncture needle, cell brush or biopsy forceps were placed into the EWC working channel in advance, so that it just exposed the

Table 1. Basic information of patients from EBUS-GS and ENB-EBUS group

Characteristics	EBUS-GS	ENB + EBUS	*P* Value
Gender (male/female)	45/38	16/10	0.512
Age (year)	59.6 ± 12.59	52.76 ± 18.04	0.081
Smoking rate	37.3% (31/83)	46.2% (12/26)	0.423
family history of cancer	8.4% (7/83)	0	0.194
Lesion long diameter (cm)	2.32 ± 0.58	2.09 ± 0.96	0.252
Distance from the pleura (cm)	1.91 ± 1.51	1.13 ± 1.36	0.02
bronchus sign	75.9% (63/83)	26.9% (7/26)	0.000
Metastasis	56.6% (47/83)	7.7% (2/26)	0.000

Note that the distance of the lesion from the pleura, bronchus sign and suspicious metastases in patients undergoing EBUS-GS and ENB-EBUS were statistically different.

head of the pipe. Electronic bronchoscopy was first carried out as a routine examination. Then, the operator inserted the Edge catheter connected to the ENB host into the bronchoscopy biopsy channel, so that the front end of the bronchoscope protruded about 1 cm to automatically match those 6 registration points. Then the bronchoscope was placed at the relevant section of the lesion, and the forward direction of the catheter adjusted according to the set path, until it finally reached the lesion. After the endoscopic adapter was fixed, the LG catheter was withdrawn, the EBUS probe entered the EWC working channel, and it was confirmed whether the lesion had been reached. Only when an abnormal echo around the bronchus was seen under ultrasound, was it determined to have reached the lesion. Biopsy forceps and brush forceps were used to obtain tissue samples via operating catheters. After completing all procedures, and confirmation that there was no bleeding in the lumen, the operation tube and bronchoscope were withdrawn.

EBUS-GS

EBUS-GS was introduced into the target site according to the lesion location determined by chest CT. After exploring the hypoechoic area, and the GS sheath tube was fixed, the EBUS probe was withdrawn, and the biopsy forceps placed according to the depth of the EBUS probe into the sheath, then biopsy was carried out in the targeted area. All specimens were examined and sent to the pathology department for exfoliation cytology and liquid-based cytology.

Statistical analyses

To compare the efficacy of EBUS-GS and ENB-EBUS in diagnosing adhering pulmonary space-occupying lesions, the study population was divided into EBUS-GS and ENB-EBUS groups. The diagnostic accuracy, specificity, sensitivity and complication rate of the two approaches were evaluated. In order to clarify the influence of the lesion diameter on the results, the patients were divided into groups according to the diameter (d) of the lesion; thus into d<10 mm, d>10 mm and <20 mm, and d>20 mm groups. Continuous variables were expressed by mean ± standard deviation (SD). Differences among the groups were analyzed by one-way analysis of variance (ANOVA) followed by Student's t test. Classification variables were analyzed by Chi-square test or Fisher exact test. P<0.05 was considered as statistically significant based on two-tail tests. All statistical procedures were performed using SPSS software (version 17.0; SPSS Inc., Chicago, Illinois, USA).

Results

Characteristics of the patients and lung lesions

A total of 109 patients were enrolled in this study, of whom 93 were in the EBUS-GS group (45 male and 38 female), with an average age of 59.6 ± 12.59 years, of whom 37.3% were smokers, and 8.4% of patients had a family history of tumors. Of the 26 patients in the ENB + EBUS group, 16 were males and 10 were females. The average age of the patients in this group was 52.76 ± 18.04 years, and 46.2% had a history of smoking. None of the patients in this group reported a family history of tumors. There was no statistical difference between the two groups of patients in these attributes (**Table 1**).

The characteristics of the lung space-occupying lesions are set out in **Table 1**. The long diameter of lesions in the EBUS-GS group was 2.32 ± 0.58 cm, and 2.09 ± 0.96 cm in the ENB-EBUS group, with no statistical difference between the two groups. The distance of the lesion from the pleura was 1.91 ± 1.51 cm in

Table 2. Analysis on the diagnostic rates of EBUS-GS and ENB-EBUS

Category	EBUS-GS (*n*, %)	ENB-EBUS (*n*, %)	*P* Value
Percentage of successfully sampled patients	92.8% (77/83)	100%	0.332
Overall diagnosis rate	71.1% (59/83)	65.4% (17/26)	0.581
Diagnosis rate in successfully sampled patients	76.6% (59/77)	61.5% (16/26)	0.201

Note that EBUS-GS and ENB-EBUS had similar diagnostic rates.

Table 3. Pathology results of patients in the EBUS-GS and ENB-EBUS groups

Category	EBUS-GS (*n*, %)	ENB-EBUS (*n*, %)	*P* Value
Malignant	58/65 (89.2)	4/17 (23.5)	0.00
Endocrine cancer	1 (12.5)	0	1
Adenocarcinoma	45 (77.6)	3 (75)	1
Squamous cell carcinoma	3 (5.2)	1 (25)	0.239
Small cell lung cancer	4	0	
Unclassified lung cancer	1	0	
Carcinoid	1	0	
Sarcomatoid carcinoma	1	0	
Metastasis	2	0	
Benign	7/65 (10.8)	13/17 (76.5)	0.00
Tuberculosis	2 (28.6)	5 (38.5)	1
Chronic inflammation	4 (57.1)	6 (46.2)	1
Hamartoma	0	1	
Mycotic infection	1	1	

Note that the difference in the proportion of malignant or benign diseases between the two groups of patients was statistically significant.

the EBUS-GS group, and 1.13 ± 1.36 cm in the ENB-EBUS group, with a statistically significant difference between the two groups (P=0.02). In addition, 75.9% of the CT images of patients in the EBUS-GS group showed bronchial signs, while 26.9% of the patients in the ENB-EBUS group showed bronchial signs, with a statistical difference between the two groups (P=0.000). In terms of metastases, 56.6% of patients in the EBUS-GS group had suspicious metastases, while 7.7% of patients in the ENB-EBUS group had suspicious metastases. The difference was statistically significant (P=0.000).

EBUS-GS and ENB-EBUS have similar diagnostic rates

As shown in **Table 2**, tissue samples were successfully obtained in 77 out of 93 cases in the EBUS-GS group, with a success rate of 92.8%, while in the ENB-EBUS group, all 26 cases were successfully sampled. However, there was no statistical difference in the success rate of the two groups (P=0.332). The pathological results of the specimens obtained from the EBUS-GS and ENB-EBUS examinations were compared with the patient's final discharge diagnosis to determine the accuracy of the two methods of diagnosis. A total of 65 patients in the EBUS-GS group had a pathological diagnosis consistent with the discharge diagnosis, with a confirmed rate of 71.1% (n=83); a total of 17 cases in the ENB-EBUS group had a pathological diagnosis consistent with the final diagnosis, with a confirmed rate of 65.4% (n=83). There was no statistical difference between the groups (P=0.581). Moreover, no statistical difference was observed between the two groups in those cases of successful sampling.

In addition, we compared the sensitivity and specificity of EBUS-GS and ENB-EBUS for diagnosing peripheral space occupying lesions in the lungs, and found no statistical difference in sensitivity and specificity (P>0.05).

Pathological results of patients in the EBUS-GS and ENB-EBUS groups

The pathological results of patients receiving EBUS-GS or ENB-EBUS are summarized in **Table 3**. In 58 out of 65 patients (89.2%), lesions diagnosed in the EBUS-GS group were malignant, while in the ENB-EBUS group 4 cases out of 17 patients diagnosed in were malignant (23.5%). The difference in the proportion of malignant diseases between the two groups of patients was statistically significant (P=0.00). Correspondingly, the proportion of benign diseases between the two groups was also statistically different (P=0.00).

Impact of long diameter of lesions on the diagnosis

We also examined other factors influencing the diagnostic rates of EBUS-GS and EBN-EBUS.

Table 4. Impact of long diameter of lesions on the diagnosis

Long diameter	EBUS-GS (*n*, %)	ENB-EBUS (*n*, %)	χ^2	P_1
d<1 cm	0/1	2/2	3	0.333
1≤d<2 cm	19/23 (82.6)	6/10 (60)	1.94	0.205
d≥2 cm	46/59 (78)	9/14 (64.3)	1.14	0.312
χ^2	3.865	1.194		
P_2	0.19	0.4		

Note there was no statistical difference observed in the diagnosing efficacy of EBUS-GS and ENB-EBUS biopsy among the different long diameter groups.

Table 5. Influence on the diagnosis of distance from lesion to pleura

Distance	EBUS-GS (*n*, %)	ENB-EBUS (*n*, %)	χ^2	P_1
d<1 cm	18/25 (72)	11/15 (73.3)	0.008	1
1≤d<3 cm	32/40 (80)	4/9 (44.4)	4.765	0.043
d≥3 cm	15/18 (83.3)	2/2 (100)	0.392	1
χ^2	0.921	3.221		
P_2	0.636	0.151		

Note that when the lesion was d≥1 cm and situated <3 cm from the pleura, the diagnostic rate of EBUS-GS (80%) was higher than the diagnostic rate of ENB-EBUS (44.4%).

Table 6. Impact of bronchial sign on the diagnosis rate of EBUS-GS and ENB-EBUS

Bronchial sign	EBUS-GS (*n*, %)	ENB-EBUS (*n*, %)	χ^2	P_1
Yes	52/63 (82.5)	3/7 (42.9)	5.89	0.034
No	13/20 (65)	14/19 (73.7)	0.345	0.557
χ^2	2.75	2.148		
P_2	0.122	0.188		

Note the diagnostic rate of EBUS-GS was statistically higher than that of ENB-EBUS when there was a bronchial shadow beside the lesion.

We analyzed the influence of the long diameter of the lesion; the results (**Table 4**) showed no statistical difference in the efficacy of EBUS-GS and ENB-EBUS biopsy diagnosis among different long diameter groups (P>0.05). More importantly, diagnosis yields of EBUS-GS and ENB-EBUS were not statistically different in each long diameter group (P>0.05).

Influence on the diagnosis of distance from lesion to pleura

We further analyzed the influence of the distance from the lesion to the pleura on the diagnosis rate (**Table 5**), and the results showed that there was no statistical difference in lesions with d<1 cm, d≥1 cm and <3 cm, and d≥3 cm to the pleura when examined by EBUS-GS or ENB-EBUS (P>0.05). However, when the lesion was d≥1 cm and <3 cm from the pleura, the diagnostic rate of EBUS-GS was 80%, which was higher than the diagnostic rate of ENB-EBUS (44.4%). The difference was statistically significant (P< 0.05).

Impact of bronchial sign on the diagnosis

Since EBUS-GS and ENB-EBUS both need to extend the biopsy forceps to the lesion through the bronchus, we analyzed the influence of the presence of bronchial shadow beside the lesion on the CT image on the diagnosis rate. The results (**Table 6**) showed that, when there was a bronchial shadow beside the lesion, the diagnosis rate of EBUS-GS was 82.5%, which was statistically higher than the diagnosis rate of ENB-EBUS (42.9%) (P< 0.05). However, when there was no bronchial shadow beside the lesion, the diagnostic rate of ENB-EBUS was 73.7% and the diagnostic rate of EBUS-GS was 65%, but the difference was not statistically significant (P> 0.05).

Complications of EBUS-GS and ENB-EBUS

We further analyzed the complications and differences between the two diagnostic methods. The results (**Table 7**) showed that the overall complication rate of EBUS-GS was 8.4% (mainly due to hemoptysis), and the incidence rate was 8.4%. The overall complication rate of ENB-EBUS was 7.7% (mainly due to pneumothorax and hemoptysis) and the incidence rate was 3.8% for both pneumothorax and hemoptysis. Importantly, there was no statistical difference in the incidence of complications between EBUS-GS and ENB-EBUS (P>0.05).

Discussion

With the development of molecular targeted therapy, patients with advanced lung cancer have the welcome prospect of effective new

Table 7. Comparisons on the complications of EBUS-GS and ENB-EBUS

Complication	EBUS-GS (*n*, %)	ENB-EBUS (*n*, %)	*P* Value
Complication rate	8.4% (7/83)	7.7% (2/26)	1
Pneumothorax	0	3.8% (1/26)	0.239
Hemoptysis	8.4% (7/83)	3.8% (1/26)	0.677

Note there was no statistical difference in the incidence of complications between EBUS-GS and ENB-EBUS.

treatments [10]; meanwhile, the demand for tumor specimens for diagnosis and treatment screening has also increased [11]. Less invasive methods for sampling, such as lung biopsy and bronchoscopy, have received increasing attention [12]. More specifically, sampling methods under bronchoscopy include radial endobronchial ultrasonography (EBUS), virtual navigation or electromagnetic navigation bronchoscopy (navigation systems), virtual bronchoscopic navigation (VBN) or electromagnetic navigation (EMN), ultrathin bronchoscopes, and endoscopic ultrasound-guided transbronchial needle aspiration This study retrospectively compared the diagnosis of peripheral lung mass lesions by EBUS-GS and ENB-EBUS, and clarified the differences in diagnostic efficacy and complications between the two methods.

Traditional bronchoscopy has a low diagnostic rate for lung cancer. According to the guidelines issued by the American Association of Chest Physicians (ACCP), the overall sensitivity of bronchoscopy in diagnosing central lung cancer is 88%. In addition, its sensitivity in the diagnosis of lesions with a diameter of less than 2 cm is only 34% [3]. However, the radial EBUS probe provides an image of the tissue around the probe tip, and the location of the surrounding lung lesions can be identified by comparing EBUS images of normal lung tissue with cancerous tissue [8]. Therefore, radial EBUS (EBUS-GS) with ultrasound-guided sheaths is widely used for the diagnosis of lung diseases [13, 14]. In this method, an EBUS probe with an outer diameter of 1.4 mm is guided into the sheath, and after the lesion is positioned by ultrasound images, a biopsy forceps or bronchial brush is extended into the lesion to take a biopsy of the lesion. It has been reported that the diagnosis rate of peripheral lesions in the lung using EBUS-GS is around 70% [8]. In addition, the results of a study by Steinfort et al. show that the diagnosis rate of EBUS-GS is not lower than that of CT-guided biopsy, with a lower incidence of complications than CT-guided biopsy [15]. In our study, we retrospectively analyzed the data of 93 patients undergoing EBUS-GS examination, and found that the success rate of EBUS-GS was 92.8%, and the diagnostic accuracy rate of successful patients was 71.1%. Other reports show similar findings [8, 14, 16]. In addition, our results also showed that the distance from the lesion to the pleura, the presence or absence of bronchial signs, and the length of the lesion have no significant effect on the accuracy of the diagnosis.

Electromagnetic navigation is another method used to improve the diagnostic performance of bronchoscopy [16]. This system uses three-dimensional images to navigate the bronchoscope/biopsy forceps to the cancerous area around the pulmonary tissue, improving the accuracy of the biopsy [17]. In a prospective randomized trial involving 120 patients with peripheral pulmonary nodules, the diagnostic rate of electromagnetic navigation was 88%, which was higher than the diagnostic rate of EBUS-GS (59%) [17]. Moreover, in the 2013 edition of the American Thoracic Association guidelines, electromagnetic navigation is recommended for the diagnosis of grade 1 C peripheral pulmonary lesions that are difficult to reach with ordinary bronchoscopy, and the results of a meta-analysis study conducted by ACCP showed a diagnostic accuracy of 71% for ENB [4]. In this study, we retrospectively analyzed the data of 26 patients who underwent EBN-EBUS biopsy. The success rate was 100%, and the diagnostic accuracy was 65.4%. The accuracy was slightly lower than that reported in previous studies [4]. We also found that the distance from the lesion to the pleura, the presence or absence of bronchial signs, and the length of the lesion had no significant effect on the accuracy of the diagnosis, although the small number of cases included in this group may be a factor in this finding.

In our study, the diagnostic accuracy of EBUS-GS was higher than ENB-EBUS, however there was no statistical difference, which differs from previous research results [17]. Possible reasons may be that, in our study, ENB-EBUS was selected for patients for whom there was diffi-

culty in using EBUS-GS for biopsy, and also that our study compared the results of these two diagnostic methods retrospectively. We found that the distance from the lesion to the pleura and the length of the lesion itself had no significant impact on the diagnosis rate of EBUS-GS and ENB-EBUS; however, whether there were bronchial signs around the lesion affected both EBUS-GS and ENB-EBUS in that, when there was a bronchial sign next to the lesion, the diagnosis rate of EBUS-GS was greater than that of ENB-EBUS and the difference was statistically significant. However, with no bronchial sign next to the lesion, the diagnostic accuracy rate of ENB-EBUS was higher than that of EBUS-GS, but the difference was not statistically significant. This may be related to the small number of ENB-EBUS cases included in our study. In addition, our finding of the significant effect of bronchial signs on the diagnostic accuracy of navigation bronchoscopy was similar to that of other research results [18]. Our study also compared the incidence of complications of ENB-EBUS and EBUS-GS and we found there was no statistical difference between the two methods in the incidence of complications.

Our study had some shortcomings. Firstly, ours was a retrospective study, and there may have been case selection bias. ENB-EBUS is a more expensive procedure and more complicated to operate than EBUS-GS and most patients underwent ENB-EBUS examination only after EBUS-GS examination was considered too difficult. Secondly, this study only included data from a single center, and the conclusions obtained may be more biased than when extrapolating from data from multi-center studies. Thirdly, the number of ENB-EBUS patients included in this study was relatively small. However, as the diagnostic efficacy of ENB-EBUS is considered to be inferior to that of EBUS-GS, our unit has stopped using ENB-EBUS as the initial diagnostic method.

Both EBUS-GS and ENB-EBUS can be used to diagnose peripheral lung disease. Although the diagnosis rate of the former is slightly higher than the latter, there is no statistical difference between the two approaches; in the case of bronchial signs next to the lesion, the diagnostic rate of EBUS-GS was significantly higher than ENB-EBUS, while in the absence of bronchial signs, ENB-EBUS had a higher diagnosis rate but there was no statistical difference. There were no significant differences in biopsy complications between EBUS-GS and ENB-EBUS.

Disclosure of conflict of interest

None.

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