# Radial EBUS combined with a GS and VBN for diagnosis of peripheral lung lesions: a retrospective study

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**Research article**

**Keywords:** Radial endobronchial ultrasound, Guide sheath, Virtual bronchoscopic navigation, Peripheral pulmonary lesion, Transbronchial biopsy

**Posted Date:** July 24th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-45673/v1

## Abstract

# Background

More and more peripheral pulmonary lesions (PPL) have been found following the increased utilization of chest CT in China. But how to identify the nature of PPL accurately, safely and economically is the concern of Chinese doctors. The combination of radial endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation was a deluxe scheme to indicate the pathology of peripheral pulmonary lesions in nation's current medical level. This study aimed to compare the diagnostic yield, safety and health economics of EBUS-GS-VBN versus radial ultrasonic small probe plus thin bronchoscopy (EBUS) for diagnosis of PPLs.

# Methods

This study was a single-institution retrospective review of PLLs examined by using EBUS-GS-VBN or radial EBUS between March 2018 and September 2018 consecutive. The diagnostic yields, accuracy, operation time, complications, factors influencing the diagnostic outcome, tissue genetic test rate and medical cost were analyzed separately.

# Results

there was no significant difference in the diagnostic yield between the two groups (92.31% vs 88.57%, $p = 0.594$). Although the searching time of EBUS-GS-VBN was shorter (1.47 ± 0.49 min vs 2.12 ± 1.36 min, $p < 0.001$), procedure time was extended (24.07 ± 5.53 min vs 17.41 ± 4.38 min, $p < 0.001$). The diagnosis yield of malignancy and benign disease were equal (84.62% vs 100% and 95.35% vs 84%). There was no difference in the rate of gene testing between the two groups (75% vs 70.58%), while the incidence of Intrapulmonary hemorrhage in the EBUS-GS-VBN group was significantly descended. Moreover, the average expense of EBUS-GS-VBN was higher than that of EBUS-GS (6315 ± 1817 RMB vs 3128 ± 1086RMB).

# Conclusion

When performing TBLB of PLLs, we found EBUS-GS-VBN to be similar to EBUS in accuracy. Although the founding lesion time of EBUS-GS-VBN group were significantly shorter, the total examination time was longer. Furthermore, the complications of EBUS-GS-VBN group were fewer. There was no difference in genetic testing between the two groups. It is worth noting that the cost and radiation exposure was lower of EBUS group patients.

# Trial registration:

retrospectively registered

## Introduction

Lung cancer is one of the most common cancer worldwide both in terms of incidence and mortality [1]. Advances in computed tomography equipment and the prevalence of national physical examination have increased the detection of peripheral pulmonary lesions (PPLs) and even lung cancers. These make it urgent to diagnosis those lesions quickly and accurately, in order to avoid misdiagnosis and missed diagnosis. Although bronchoscopy is a routine method to diagnose pulmonary lesions in light of lung biopsy tissue, many lung cancers in early stage are in the periphery of the lung, leading to a failure for operators to detect the lesions with conventional bronchoscope [2]. Fortunately, diagnosis methods of peripheral lung lesions have been improved due to the emerging of endobronchial ultrasonography with a guide sheath (EBUS-GS), it allows repeated accurate biopsy of a lesion [3]. In order to further escalate accuracy of EBUS-GS in detecting periphery lesions, virtual bronchoscopic navigation (VBN) was proposed, which is regarded as a novel technology that can create a virtual bronchoscopic image and guide a pathway to the lesion. Remarkable results have been reported for VBN used in combination with EBUS-GS in many reports [4], indicating its underlying efficacy in diagnosing PPLs.

Although advanced examination inspections improve accuracy in precise diagnosis, the corresponding medical costs should also be taken into account. As a developing country with incomplete civil hospitalization insurance, many families cannot afford such high medical fees, being eager to spend relatively low medical expenses and get high diagnostic accuracy. How to resolve this conflict from the perspective of health economics concerns a specialty-based clinical decision in selecting proper inspection approaches and perfecting the speed of final diagnosis.

In the present study, we evaluated the diagnostic yield for PPLs by EBUS-GS-VBN, and analyzed the clinical factors associated with diagnosis of such lesions. We aimed to differentiate the clinical characteristic of PPLs by EBUS-GS-VBN and EBUS alone, and to explore the clinical application

value of EBUS combined with VBN guiding TBLB for PPLs. The priority of this study is to enable each patient with PPLs to get the optimal examinational and therapeutic approaches, based on merits and drawbacks of each EBUS, aiming to improve diagnosis efficiency of PPLs.

## Materials And Methods

Study design and patients

This study was a retrospective analysis of a maintained medical records database at our department. Consecutive patients who underwent a diagnostic bronchoscopy for peripheral lung lesions in the department of Pulmonary and Critical Care Medicine of Xijing Hospital, between March 2018 and September 2018 were retrospectively identified. Among them, cases with PLLs that were visible on Chest CT were enrolled, 96 patients with pulmonary lesions in the peripheral zone of the lungs (found on the CT images within the last 3 months). Patient baseline demographic characteristic data and lesion image characteristics, including type, maximum diameter, lobes, segments, and presence of bronchus sign, were evaluated on thin-section chest CT images were recorded. Ultrasound images and operating time were also recorded. The different bronchoscopy protocols were explained to each patient before performing, then each patient signed informed consent.

EBUS plus thin bronchoscopy

A flexible thin bronchoscope (BF-H290, Olympus, Tokyo, Japan) and radial mechanical-type ultrasound probe (UM-S20-17S; Olympus) were used. Based on the CT scan, endoscopists insert the EBUS probe through endoscopic channel to detect the PLLs after advancing the bronchoscope to the suspected bronchi. then the EBUS probe was removed and forceps were introduced. When the bronchoscopic procedures were performed, several specimens were obtained during each TBLB for all patients. Then performed bronchial washing was performed in the EBUS-determined segmental bronchus of each patient. After that, the brushing technique was subsequently used with the patients. The operator performed bronchial lavage or mucosal brushing according to the specific pathological changes under bronchoscopy. This study did not involve the use of either the guided-sheath technique or fluoroscopic guidance.

EBUS-GS

EBUS-GS was performed using an endoscopic ultrasound system (EU-ME2 PREMIER PLUS; Olympus) equipped with a 20 MHz mechanical radial-type probe (UM-S20-17S; Olympus: external diameter, 1.7 mm) and a guide sheath (K-201; Olympus: external diameter, 1.9 mm). The guide sheath-covered EBUS probe was inserted through the bronchoscope working channel and advanced to the peripheral pulmonary lesion to obtain an EBUS image. After localizing the lesion using EBUS imaging, the probe was removed, leaving the guide sheath in the peripheral lesion. Biopsy forceps (FB-233D; Olympus) and a bronchial brush (BC-204D-2010; Olympus) were introduced via the guide sheath to provide specimens for pathological and cytological examination. When the lesion could not be visualized by EBUS, we considered that the probe did not reach the lesion and stopped the inspection immediately, then changed to conventional TBLB.

Virtual Bronchoscopic Navigation

Patients underwent high resolution chest CT to generate virtual bronchoscopy images to guide bronchoscopy. Based on chest CT data, we used DirectPath VBN system (Olympus, Tokyo, Japan) to detect the bronchial route to the target lesion. When the bronchus involved by the lesion was unclear, virtual bronchoscopy images of the bronchus closest to the lesion were produced.

Diagnosis

Final diagnosis was established according to pathologic results from the biopsy specimen, including TBLB or subsequent surgical operation. We define benign lesions as pathological findings of granuloma or chronic inflammation. In addition, if tissue microbial culture is positive, it is also considered as benign. If the lesion with no typical pathologic or microbiological conclusions reduced after anti-infective or anti-inflammatory treatment in the follow-up period of six months, it is also considered as benign. Some patients who could not be diagnosed by bronchoscopy or with lesions that did not decrease in size after a CT follow-up examination were diagnosed by computed tomography-guided transthoracic needle aspiration (CT-TTNA) or surgical biopsy. All of the patients were followed up for 6 months if they refused further examination.

Statistical analysis

After data collection, statistical analysis of the data was performed using a statistical software package [(SPSS for Windows, version 21.0; SPSS Inc. (IBM SPSS, Chicago, USA)]. Descriptive statistics was used for the baseline clinical characteristics. Enumeration data were described by percentage or rate. Chi-square test was used to compare the rates. $p < 0.05$ was considered statistically significant.

# Results

### Patient characteristics

A total of 96 patients were enrolled and analyzed in this study. There were 26 cases in the EBUS-GS-VBN group, which consisted of 20 (76.92%) males and 6 (23.07%) females. The ages ranged from 23 years to 83 years, with a median age of 54 years (Table 1). There were 70 cases in the EBUS plus thin bronchoscopy group, which consisted of 42 males (60%) and 28 females (40%). The ages ranged from 25 years to 85 years, with a median age of 56 years. For all patients, the ECOG PS was mostly 0-1 score and there were not significant PS scores between the two groups ($p$ = 0.92). A summary of their baseline characteristics was shown in Table 1; There were no significant differences were seen between the two groups ($p$ >0.05).

### CT characteristics of the Lesions

The presence or absence of the CT bronchus sign (i.e., the finding of a bronchus leading directly to a PPL) (Fig. 1A, B and C) based on the HRCT findings. The most biopsied area in the EBUS-GS-VBN group was in the right upper lobe [9 cases (34.62%)], followed by the left upper lobe [6 cases (23.08%)] and right lower lobe [6 cases (23.08%)], left lower lobe were 4 cases(15.38%), only 1 patient underwent biopsy of right middle lobe lesions [3.85%]. In the radial EBUS group, the most frequency of biopsy lobe is the right upper lobe [20 cases (28.57%)]and right lower lobe [18 cases (25.71%)] followed by left upper lobe [15 cases (21.43%)], right middle and left lower are [9 cases(12.86%)] and [8 cases (11.43%)] respectively (Table 2). Both of the two groups, there were no cases had lesions of <10 mm. In EBUS-GS-VBN group, the maximal number of patients with lesions diameter 10-30 mm [14 cases (53.84%)], followed by 30-50mm [9 cases (34.62%) and over 50 mm [3 cases (11.54%)]. In the EBUS group, the maximal number of patients with lesion diameter between 30-50 mm [34 cases (48.57%)], followed by lesions diameter 10-30 mm [21 cases (30.00%)], and > 50 mm [15 cases (21.43%)] (Table 2). The imaging malignant manifestations of CT such as lobulaton sign, spiculation sign, vocule sign, pleural indentation and obstructive pneumonia do not overlap with the diagnostic yield both of the two groups. Similarly lesions with Bronchus sign on CT images dose not influence the diagnostic yield either.

### Ultrasonic image and procedure characteristics

According to probe positions, the EBUS group was classified into three sub-groups: [1] “within” (the probe was located within PPL); [2] “adjacent to” (the probe was located adjacent to PPL); and [3] “outside” (the probe was located outside PPL) (Fig. 2D,E and F). The times of biopsy tissue obtained successfully in each PLLs of EBUS-GS-VBN group were much more than EBUS group (9.04±1.9 vs 4.64±0.68, $p$< 0.001). Although the searching lesion time of EBUS-GS-VBN was shorter than EBUS group (1.47±0.49 min vs 2.12±1.36min, $p$<0.001), mean procedure time of EBUS-GS-VBN was extended, compared with EBUS group( 24.07±5.53 min vs 17.41± 4.38min, $p$<0.001) (Table 3). Both of the two groups, the maximal number of ultrasonic image diameter was 10-20 mm [13 cases (50.00%) and 31 cases (44.29%)], followed by 20-30mm [9 cases (34.62%) and 30 cases (42.86%)]. There was no case of < 10 mm in EBUS group, while 3 cases in EBUS-GS-VBN group (11.54%). Among most cases of the two group, the margins of ultrasound images were clear (88.46% vs 71.34%), and densities were homogeneous (73.08% vs 72.86%).

### Biopsy accuracy

Pathological examination was performed after the biopsy in EBUS-GS-VBN and EBUS groups. If tumors were found in biopsy tissues, they were considered to be diagnosed certainly. If the benign pathological manifestations such as granuloma or chronic inflammation or organizing pneumonia were found in the tissues, they were classified as confirmed cases or non-confirmed pathologies according to whether the lesions are absorbed after corresponding treatment. Surgical biopsy is strongly recommended if the patient is highly suspicious of cancer. If the patient refuses the operation, we will follow-up closely. When the lesion enlarges, we will suggest the patient to perform a second biopsy. The overall diagnosis rate of the EBUS-GS-VBN group was 92.31%, which was similar as the EBUS group 88.57% ($p$=0.594, Table 4). In general, the diagnosis rate of malignant diseases of two group were similar (84.62% vs 95.35%, $p$=0.227), while the diagnosis rate of benign diseases of two group were 100% vs 84% ($p$=0.278). Among the two groups of confirmed malignant tumor cases, adenocarcinoma is the most common type [9 cases (34.62%) *vs* 28 cases (40.00%)], followed by squamous in EBUS group (6 cases). There were fewer cases of small cell lung cancer or neuroendocrine neoplasm in both groups (1case vs 2 cases) (Table 4). Finally, the misdiagnosed cases were 2 in EBUS-GS-VBN group (7.69%), while it was 8 cases in EBUS group (11.43%). There was no significant difference in the diagnostic yield between the groups in the subgroup analysis (Table 5,6). In order to develop more precise treatment for patients, each patient diagnosed with non-small cell lung cancer underwent genetic testing. In the EBUS-GS-VBN group, we did genetic testing in 6 NSCLC patients among them (75%). In the EBUS group, 24 patients underwent EGFR testing (70.58%). Diagnosis was confirmed in 2 case of the EBUS-GS-VBN group with CT-TTNA biopsy. Few patients with malignant tumors in EBUS group undergo surgical operations to further clarify the pathological pattern (2 cases). It is worth noting that two patients in EBUS group have not yet been diagnosed.

### Complications

There were no severe complications in either group. The most common postoperative complications of the both groups were intrapulmonary hemorrhage, and the EBUS-GS-VBN group was associated with less risk than the EBUS group [21 cases (80.7%) vs 70 cases (100%), $p$=0.001]. Other complications such as bloody phlegm, chest pain, pneumothorax, fever and chest pain were very few in two groups. Pulmonary infection was not found in both of the groups. Only one patient suffered pneumothorax in EBUS group. And All patients with pneumothorax were improved after oxygen inhalation and bed rest without closed drainage. There was no difference in the rate of those complications between the two groups.

### Medical cost and CT times

There was significant difference between the two groups of the average cost of patients. In the EBUS-GS-VBN group was 6315±1817 RMB, while the average cost of patients in the EBUS group was 3128±1086 RMB ($p$=0.001). In addition, the number of chest CT examinations in the past three months was also different between the two groups ($p$=0.001). 65.38% patients in EBUS-GS-VBN group received three or more CT examinations, while the most patients in EBUS group received two chest CT examinations (65.71%).

## Discussion

Traditional diagnostic methods of pulmonary peripheral lesions are transbronchial lung biopsy or transthoracic needle aspiration biopsy. However, due to the lack of precise guidance, it is inevitable to suffer lower diagnostic accuracy rate and more complications compared with those in guidance under visual conditions. It has been reported that the diagnostic yield for small peripheral pulmonary lesions by transbronchial biopsy ranges widely from 53 to 75% [5, 6, 7]. The low accuracy of biopsy was mainly due to that the operator could not confirm the lesions under bronchoscope during operation. As an epoch-making innovative technology, ultrasonic miniprobe has greatly improved the efficiency of diagnostic bronchoscopy for PPLs. Systematic reviews on radial EBUS for PPLs have reported an overall diagnostic yield varying from 35–80% [8]. With additional of a GS, the diagnostic yields range from 64.4–81.9% [9]. Virtual bronchoscopic navigation (VBN), which is an advanced bronchoscopy technology combining virtual navigation technology, bronchoscopy technology and three-dimensional CT imaging technology, can shorten the examination time to a great extent and improve the biopsy yields due to precise localization and practical inspecting path mode. VBN does not require disposable position sensor used for ENB, but sometimes, there is a necessity for X-ray fluoroscopy to confirm arrival of the biopsy instrument at the indicated site due to the lack of several real-time sensor- dependent location tracking instruction [10]. In general, it has been widely accepted that VBN increases the diagnostic yield and shortens the examination time [11]. But in this study, we found that there were no significant differences of the diagnostic yield between the two groups.

According to our study, we analyzed the baseline data of the two groups patients and found there was no difference between the two groups in the size, distribution of the lesions, and the most of imaging characteristics of various malignant lesions. However, in the EBUS group, the ratio of patients with obstructive pneumonia was slightly higher (11.53% vs 34.29%, $p$ = 0.028). During the operation, there was no significant difference between the location of the probe and the lesions ($p$ = 0.295). The searching lesion time of EBUS-GS-VBN was shorter than that in EBUS group(1.47 ± 0.49 min vs 2.12 ± 1.36 min, $p$ < 0.001), but the mean procedure time of EBUS-GS-VBN was longer than that in EBUS group( 24.07 ± 5.53 min vs 17.41 ± 4.38 min, $p$ < 0.001).The size of ultrasound image of EBUS-GS-VBN was less than that in EBUS group($p$ = 0.032). Several previous literatures reported that compared with conventional radial EBUS, EBUS-GS-VBN shared more obvious advantages in detecting small lesions, reducing misdiagnosis rate. The characteristics of ultrasound image such as location of EBUS probe, size, margin, and even density did not influence the diagnostic yield.

It has been reported that the VBN group had significantly higher yield than non-VBN group (80.4% vs. 67.0%; $p$ = 0.032) and procedure duration was shorter [4]. But in our study, the total diagnostic rate of the EBUS-GS-VBN group was 92.31%, which was similar as that of the EBUS group (88.57%). There was no significant difference in the diagnostic yield between both ($p$ = 0.594). No matter benign or malignant disease, significant differences were not presented in the diagnosis yield between the two groups. It seems that EBUS-GS-VBN group has a higher diagnostic accuracy for benign diseases theoretically, but the statistical results show that there was no significant difference between the two groups. In both of the two, adenocarcinoma was the majority disease established through follow-up diagnosis in light of biopsy, and pulmonary tuberculosis was one of the most common benign diseases. The misdiagnosed rate of two groups were 7.69% vs.11.43% ($p$ = 0.594). Additionally, as for those bearing malignant lesions, the two groups were liable to catch equal specimens in quality for following genetic sequencing (75% vs 70.58%, $p$ = 0.128), facilitating precise detection and treatment.

The following factors do not significantly affect the diagnostic yield between the two groups: location of EBUS probe [odds ratio (OR) = 0.833, 95% CI (0.146–4.572)], ultrasound image size, margin [OR = 0.913, 95%CI (0.155–5.383)], and ultrasound image density [OR = 0.809, 95% CI (0.136–4.79)]. Interestingly, our results are not consistent with previous reports.

What should also be taken into account is the underlying complications of two detection approaches. In our study, patients with post-operative complications comprised 80.7% and 100% in the EBUS-GS-VBN group and EBUS group, respectively. For intrapulmonary hemorrhage, EBUS group

was significantly higher (100% vs 80.7%, $p = 0.001$), others complications such as bloody phlegm, chest pain, fever and pneumothorax have no statistical difference. Patients in both groups did not suffer pulmonary infections.

In this study, we also pay more attention on the economic toxicity of medical treatment. Schroeder and his colleague reported that the diagnosis and treatment of cancer places patients at risk for serious financial consequences, which are detrimental to overall health and wellbeing [13]. For most Chinese patients, it is indeed very important to find an economic and accurate way to examine the peripheral lung lesions. Throughout our analysis, we thought that EBUS is recommended for peripheral lung disease. Although VBN are quite useful, they are just available in top hospitals. In view of the current per-capita economic level and medical insurance policy of nation, the use of VBN for ordinary patients will increase a great financial burden, and in turn increase the subtle contradiction in doctor-patient relationship. The average cost of EBUS-GS-VBN group was 6315 ± 1817 RMB, while it was 3128 ± 1086 RMB in the EBUS group ($p = 0.001$). To sum up, EBUS have the potential to be an economic and efficient diagnostic method for patients with limited economic conditions in PPLs detection.

However, this clinical study also bears several limitations. Firstly, as a retrospective, non-randomized, single-institution study with a small sample size., our study contains selection bias which may affect the results. Secondly, since the detecting procedures were not performed by the identical operator, it remained unclear whether the results can be generalized to other institutions. Finally, the number of enrolled patients was relatively small, which cannot facilitate further study to expose the differences of the two approaches in real world. Due to these limitations, we intended to launch prospective randomized controlled studies, further validating the outcome which we have concluded in this study. All in all, this research highlights a safer, more precise and economical biopsy method using EBUS-GS-VBN when performing TBLB for peripheral lung lesions, compared with conventional ultrasound probe plus with thin bronchoscopy. Taken the perspective of health economic into account, our work shared the opinion that EBUS-GS-VBN is optimal method in detecting PPLs for national conditions.

## Conclusions

In this study, we observed the EBUS-GS-VBN for diagnosing PLHs based on our clinical experience. Our results indicate that EBUS-GS-VBN is a safe and effective combined procedure for diagnosis of PLHs. Further multicenter prospective studies are recommended in the future.

## Abbreviations

EBUS
endobronchial ultrasonography;
EBUS-GS
endobronchial ultrasonography using a guide sheath;
GS
guide sheath
NSCLC
non-small cell lung cancer
PPL
peripheral pulmonary lesions
TBLB
transbronchial lung biopsy
VBN
virtual bronchoscopic navigation

## Declarations

### Ethics approval and consent to participate

Review List of the Ethics Committee of the First Affiliated Hospital of the Forth Military Medical University (No. KY20182044-C-1)

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.


### Funding

This work was supported by Key Special Funds of the Ministry of Science and Technology Foundation (No. 2017YFC0112700).


### Authors' contributions

Selection of the cases: Shuo-yao Qu; Interventional procedure: Yan Zhang；Data statistics: Zhang Yong; Cases follow up: Ning Chang and Ming-Ming Wang; Conception and experiment design: Xin-Yu Ti and Jian Zhang


### Acknowledgements

Not applicable



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## Tables

Please see the supplementary files section to view the tables.

## Figures

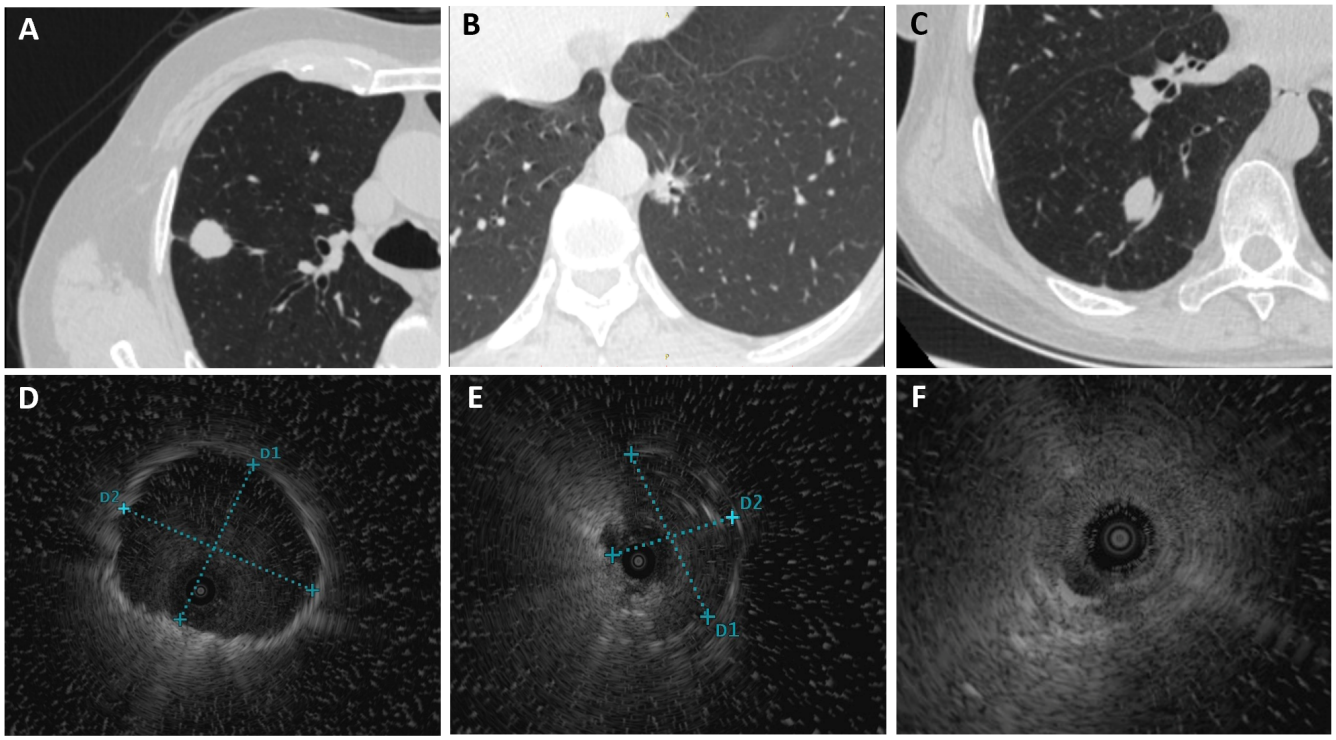


**Figure 1**

EBUS image according to the relationship between the peripheral lung lesion structures and the bronchus (A, B) A chest CT image revealing a bronchus leading directly to a PPL (CT bronchus sign positive). (C) A chest CT image revealing a bronchus that does not lead directly to a PPL (CT bronchus sign-negative). (D)The EBUS probe is located within a PPL.(E) The EBUS probe is located adjacent to a PPL.(F) The EBUS probe is located outside a PPL.

## Supplementary Files

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- Table3.docx
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