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Diagnostic yield of radial endobronchial ultrasound procedure with or without fluoroscopy guidance in peripheral pulmonary lesions

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Abstract

Peripheral pulmonary lesions (PPLs) are challenging to diagnose due to their location beyond segmental bronchi. Radial endobronchial ultrasound (rEBUS) has emerged as a promising tool, but the utility of fluoroscopy guidance remains unclear. This study aimed to compare the diagnostic yield and safety of rEBUS-guided bronchoscopic procedures with or without fluoroscopy in PPLs. This single-center prospective randomized controlled study involved 42 adult patients with PPLs, divided into two groups: rEBUS and rEBUS-F (rEBUS with fluoroscopy). Patients underwent routine bronchoscopy to rule out endobronchial abnormalities, followed by rEBUS-guided transbronchial biopsy with or without fluoroscopy guidance. Diagnostic yield, complications, and predictors of diagnostic success were evaluated. The overall diagnostic yield of rEBUS-guided bronchoscopic procedures was 59.5%, with comparable yields in the rEBUS (59.1%) and rEBUS-F (60%) arms. Positive bronchus sign [adjusted odds ratio (OR): 4.92, 95% confidence interval (CI): 1.43-16.93, p=0.011] and concentric image on rEBUS (adjusted OR: 3.83, 95% CI: 1.13-12.99, p=0.031) were identified as significant predictors of diagnostic success. The overall complication rate was 14.3%, including bleeding (4.8%), desaturation (7.1%), and fever (2.4%), with no instances of pneumothorax or life-threatening complications. Omitting fluoroscopy during rEBUS procedures for PPLs may preserve diagnostic performance while reducing radiation exposure and procedural costs. Larger multicenter studies are needed to confirm these exploratory findings.

Key words: peripheral pulmonary lesions, radial endobronchial ultrasound, fluoroscopy, CT bronchus sign, transbronchial biopsy.

Introduction

Peripheral pulmonary lesions (PPLs) are defined as focal radiographic opacities in the outer one-third of the lung that are challenging to diagnose due to their location beyond the segmental bronchi [1]. Early detection is crucial, as the National Lung Screening Trial has demonstrated a 20% reduction in lung-cancer-specific mortality with timely diagnosis [2]. Traditional bronchoscopy has shown limited diagnostic accuracy, particularly for small lesions (<2 cm), with yields as low as 14% [3]. CT-guided transthoracic needle aspiration offers an alternative, with diagnostic yields over 50%, but carries high risks of pneumothorax (45%) and false negative results (30%) [4]. These limitations highlight the need for more effective and safer diagnostic approaches.

Radial endobronchial ultrasound (rEBUS) has emerged as a promising tool for the diagnosis of PPLs, with diagnostic yields ranging from 72% to 82.5% [5]. rEBUS allows real-time ultrasound guidance during bronchoscopy, enabling more accurate sampling of PPLs. In contrast, conventional transbronchial lung biopsy (TBLB) under fluoroscopic guidance has yielded variable diagnostic results, ranging from 14% to 75% [6].

This study aimed to compare the diagnostic yield of rEBUS-guided bronchoscopic procedures with or without fluoroscopy in PPLs. The primary objective was to determine whether the use of fluoroscopy improves the diagnostic yield of rEBUS-guided procedures. The secondary objective was to assess complications of these procedures.

Materials and Methods

This single-centre prospective randomized controlled study was conducted at Department of Pulmonary Medicine (Superspeciality-DM), SCB Medical College and Hospital, India, from June, 2023 to August, 2024. For this study with two arms and a parallel design, α was set at 0.08 to provide 80% power to detect equivalence between the groups. Using an online tool (Cleveland Clinic sample size calculator), total sample size was calculated to be 42 with 22 participants in one group and 20 patients in the other. Patients were selected based on specific criteria, including age over 18 years, lesions in the outer 1/3rd of the lung field as appeared on CT scan. Patients with pure ground glass lesions, intraluminal lesions and nodules on bronchoscopic examination, bleeding diathesis, refractory hypoxia, hemodynamic instability, known active pulmonary tuberculosis under treatment, recent acute coronary syndrome (within 4 weeks) and pregnancy were excluded.

CT Thorax was performed with a routine non-contrast CT scan (1.2 -1.5 mm section thickness) followed by a contrast-enhanced scan. PPLs were defined as focal radiological opacities in the outer one-third of the lung field that are bronchoscopically invisible. CT findings were recorded including the type, number, and size of PPL, associated abnormalities, and presence of positive bronchus sign. Lesions were classified as solid, sub-solid, or mixed ground glass based on CT attenuation. The size of each lesion was measured as the largest diameter on cross-sectional images. Patients meeting inclusion criteria were randomized into two arms: rEBUS (radial endobronchial ultrasound) or rEBUS-F (radial endobronchial ultrasound with fluoroscopy) based on a random sequence generated prior to the commencement of the study using Random Allocation Software version 1.0.0 with a block size of 4. Demographic characteristics, clinical findings, and investigations, including blood tests and radiological exams, were collected using a pre-structured proforma.

The bronchoscopy procedure involved inserting a Fujifilm EB-530S bronchoscope (outer diameter 4.9 mm and working channel diameter 2 mm) through the nostril or mouth, with 2 mL aliquots of 1% lignocaine solution delivered through the bronchoscope using the "spray-as-you-go" technique. rEBUS was performed using a 20-MHz endoscopic radial ultrasonic probe (Fujifilm PB2020-M) with a guide sheath (Olympus SG-200C, 1.95mm). The probe was advanced into the segmental bronchus to localize the peripheral pulmonary lesion, and the target site was located using typical rEBUS images. The probe's position was classified as "within" (concentric), "adjacent" (eccentric), or "distant" (invisible) [7]. After localization, cytology brush (BC-204D-2010, Olympus, OD 1.4 mm) and small biopsy forceps (FB-433D, Olympus, OD 1.5 mm and a cup opening size- 4.0 mm) were inserted sequentially via the guide sheath to obtain cytology and transbronchial biopsy samples. Five brushings were performed with 10 strokes per brushing, and at least 5 biopsies were taken. In the rEBUS-F group, C-arm fluoroscopy was used to confirm the location of the lesion and biopsy forceps before performing TBLB, ensuring precise placement and synchronous movement of the lesion and forceps. TBLB specimens were sent for histopathological examination in 10% formalin and for CBNAAT testing in saline for Mycobacterium tuberculosis detection. Cytology brush was smeared on glass slides, fixed with 95% alcohol, and sent for cytological study along with BAL fluid.

Patients were monitored for peri-procedure complications, including bleeding, arrhythmias, desaturation, pneumothorax, and respiratory failure. Bleeding was graded based on severity as per criteria proposed by Folch et al [8], and desaturation was defined as oxygen saturation <95%. Post-procedure, patients were observed in the ICU for complications, with a chest radiograph done 4 hours after the procedure to rule out pneumothorax, if suspected.

Data of patients were analysed for diagnostic yield, procedural complications, correlation among clinico-radiological, endobronchial ultrasound characteristics and cyto/ pathological or microbiological diagnosis. Diagnostic yield was defined as the proportion of PPLs in which the index tool established a definitive malignant or benign diagnosis that informed treatment decisions. In cases of inconclusive diagnoses, PCNB or surgical biopsy was performed to obtain a definitive diagnosis. In cases with inconclusive or ambiguous histopathology, the final benign or malignant diagnosis was determined by multidisciplinary clinical consensus after at least 12 months of clinico-radiological follow-up. Benignity was defined by lesion stability or regression on serial imaging with clinical improvement. Malignancy was defined by radiologic progression with features suggestive of malignancy, including spiculated margins, mediastinal lymphadenopathy, appearance of metastatic lesions, or high FDG uptake on PET-CT along with clinical deterioration compatible with lung cancer. A lung lesion without a definitive benign or malignant diagnosis after multidisciplinary adjudication was classified as indeterminate.

Statistical analysis of data

All the data were analysed using SPSS version 26 software. Categorical variables were expressed in numbers and percentages and analysed by Pearson chi-square test and Fisher exact test. Continuous variables were expressed as mean and standard deviation and analysed by student ‘t’-test, and/or one-way ANOVA. Descriptive statistics including frequency, distribution, mean and standard deviation were used to describe different characteristics. Correlation between two parameters were seen with Pearson’s and Spearman’s correlation. Univariate and multivariable logistic regression analyses were performed to identify predictors of endosonographic visualization, diagnostic success, and malignancy risk. Predictor variables for the multivariable models assessing endosonographic visualization and malignancy risk were selected based on univariate significance, whereas variables for diagnostic success were selected based on clinical relevance. A ‘P’ value of less than 0.05 was considered as the level of significance for all statistical tests.

Results

Mean age of the study population was 50.69 years, with a male predominance (81.82%). Smoking history was present in 28.57% of patients. The rEBUS and rEBUS-F arms showed similar demographic profiles, with no statistically significant differences. The study population exhibited a significant comorbidity burden (52%) of patients having pre-existing conditions. Average duration of illness was 5.13 ± 7.50 months. PPLs were predominantly found in the left upper lobe (35.71%). The mean lesion size on chest CT scan was 35.95 ± 11.73 mm in the rEBUS arm and 30.37 ± 15.52 mm in the rEBUS-F arm, with an overall mean of 33.81 ± 14.78 mm. The most common margin types were smooth (35.7%) and spiculated (31%). The majority of lesions were pure solid (78.6%) and the rest were sub-solid (21.4%) (Table 1). This study identified three independent predictors of successful visualization on rEBUS: visibility on chest X-ray, solid lesions, and positive bronchus sign (p-values: 0.014, 0.009, and 0.031, respectively) (Table 2).

TBLB was the most effective diagnostic method, yielding definitive results in 59.52% of cases (38.1% malignant, 26.2% benign). Malignant diagnoses included primary lung cancer (30.95%) and metastatic cancer (7.1%), while benign lesions comprised fibrotic lesions (11.9%), granuloma (7.1%), and organizing pneumonia (2.4%). Brush cytology (suggestive in 11.9%) and broncho-alveolar lavage (diagnostic in 2.4%) showed limited utility. Non-diagnostic results accounted for 35.7%, primarily due to normal bronchial tissue, nonspecific inflammation, or unsuccessful biopsy attempts. Among 17 cases with non-diagnostic bronchoscopy, the final diagnosis was established by CT-guided or surgical biopsy in 13 cases and by multidisciplinary consensus during follow-up in 3 cases. One case remained indeterminate, as no definitive diagnosis could be reached by consensus. In final diagnosis, 54.76% of cases were malignant (primarily adenocarcinoma 35.71%), while 42.86% were benign (mainly tuberculosis 16.67% and silicosis:11.90%), with 2.38% cases remaining undiagnosed even after multimodal diagnostic evaluation (Figure 1).

The overall diagnostic yield was 59.5%, with a sensitivity and specificity of 61.0% and 100%, respectively. The positive predictive value (PPV), negative predictive value (NPV), and accuracy were 100%, 5.9%, and 61.9%, respectively. The rEBUS and rEBUS-F arms demonstrated similar diagnostic outcomes without any statistically significant differences (Table 3). This study identified two key predictors of diagnostic success of TBLB- CT bronchus sign and a concentric endosonographic image with adjusted OR of 4.92 (95% CI: 1.43-16.93, p=0.011) and 3.83 (95% CI: 1.13-12.99, p=0.031), respectively. Notably, factors such as X-ray visibility, lesion type, size, location, and final diagnosis did not significantly impact diagnostic yield (Table 4).

Age > 60 years, shorter symptom duration, lesion size exceeding 30 mm, and location in the upper or middle lobe were associated with an increased likelihood of malignancy. These predictors were consistently significant in both univariate and multivariate analyses, with adjusted odds ratios of 2.83, 0.79, 4.17, and 2.15 respectively. Conversely, factors such as gender, smoking status, and chest X-ray visibility did not significantly impact malignancy risk (Table 5).

Overall complication rate was 14.3%. Common complications included bleeding (4.8%), desaturation (7.1%) and fever (2.4%). There were no life-threatening complications or pneumothorax. The complication rates were similar between the two groups (rEBUS: 13.6%, rEBUS-F: 15%, p=1.00), indicating comparable safety profiles.

Discussion

This study evaluated diagnostic yield and complication rates of rEBUS procedures with or without fluoroscopy. Visualization on endobronchial ultrasound is crucial for successful TBLB. Our study identified three independent predictors of successful visualization: visibility on chest X-ray, solid lesions, and positive CT bronchus sign. Minezawa et al. demonstrated a strong correlation between CT bronchus sign and endobronchial ultrasound visualization [9]. When the CT bronchus sign is positive, 70% of lesions yield concentric endosonographic images and 20% yield adjacent images. Conversely, an absent CT bronchus sign reduces successful imaging to 50%. Evison et al. similarly found the bronchus sign to be a significant predictor ($p < 0.0001$, OR 44.8, CI 5.6-354.9) of lesion identification, central probe placement, and accurate diagnosis, irrespective of lesion size, location, or structure [10]. Lesion size (<30 mm vs >30 mm, OR: 1.83, 95% CI: 0.63-5.31, p=0.105) did not significantly impact visualization success in our study. A size >20 mm though had a significant visualization in univariate analysis (p=0.013) but lost significance in multivariate model. This contrasts findings of Hong et al. who reported size >20 mm as an independent predictor of endosonographic visualization (<20 mm vs >20 mm, OR: 2.62, 95% CI: 1.16–5.93, p=0.021) [11]. In our study, the majority of cases had mass lesions (61.9%) which explains this disparity. A subgroup analysis confirmed two independent predictors of visualization on fluoroscopy: solid lesions (adjusted OR=11.54, 95% CI=1.43-92.91, p=0.021) and larger sizes (>20 mm, adjusted OR=0.09, 95% CI=0.01-0.83, p=0.023), with visibility on chest X-ray showing a trend towards significance (adjusted OR=4.17, 95% CI=0.83-20.83, p=0.082).

In this study, TBLB emerged as the most effective bronchoscopic sampling technique, yielding definitive results in 59.52% of cases. In contrast, brush cytology and BAL showed limited diagnostic utility, with only suggestive results in 9.1-15% and 2.4% of cases, respectively. In one of our cases BAL fluid CBNAAT positivity for M. tuberculosis corroborated with granulomatous lesion on TBLB to confirm a diagnosis of TB. While BAL diagnostic yield is lower, it provided valuable microbiological data for infectious disease management according to study by Boonsarngsuk et al. [12]. In the latter study, the overall diagnostic yield of rEBUS-guided bronchoscopy was 80.4% with TBLB showing the highest yield among the 112 specimens: [TBLB (70.5%), brushing cell block (34.8%), brushing smear (62.5%), rinsed brushing fluid (50.0%) and BAL fluid (42.0%) (P<0.001)]. The superiority of TBLB over brush cytology and BAL fluid analysis observed in our study corroborates with Boonsarngsuk et al.'s study. Addition of these ancillary tests to TBLB has been shown to improve overall diagnostic performance [13,14], but this effect was not evident in our study.

TBLB yielded diagnostic results in 59.52% of cases, with malignancy detected in 38.1% (primary lung cancer: 30.95%, metastatic cancer: 7.1%). Diagnostic yield of malignant diseases (69.57%, 16/23) was higher than benign diseases (50%, 9/18) mirroring findings of Minezawa et al. (malignant 78.2% and non-malignant 56.4%) [9]. A meta-analysis by S. Tian et al. also reported higher diagnostic yield of rEBUS in malignant (77.8%) compared to benign (60.8%) PPLs [14]. In the final diagnosis, malignancy (54.76%) was more common than benign diseases (42.86%). Higher proportion of malignancy compared to benign diagnoses was also reported by Hong et al. [15] (61.45% vs 29.33%), Minezawa et al. [9] (73.83% vs 26.17%), Moon et al. [16] (77.72% vs 14.67%). The most common malignancy in our study was adenocarcinoma (seen in 35.71% cases). Predominance of adenocarcinoma was also reported by Minezawa et al. (48.32%) and Ost et al. (38.5%), Moon et al. (64.13%) and Hong et al. (37.56%) [10,15-17]. TBLB yielded benign pathologies in 26.2% cases, of which pulmonary tuberculosis and silicosis were most common (14.29% and 11.90% respectively). Tuberculosis rate was significantly higher than that reported by Minezawa et al. (1.34%) and Hong et al. (7.41%) [10,16]. Ours is a TB endemic region and occupational exposure to silica is also significant which may explain higher incidence of TB and silicosis in our study population.

The overall diagnostic yield of rEBUS was 59.5% (p-values: 0.851-0.781) that tallies with Zhu et al. (64.0%) and Good et al. (55.9%) [18,19]. Tanner et al. in a multicentre prospective randomized trial reported a lower diagnostic yield of 49% [20]. Two meta-analyses demonstrated higher pooled diagnostic yields: 70.6% and 73.4% [15,21]. Most studies included in these meta-analyses are from expert centres and some studies also used advanced navigation tools which might have contributed to higher pooled diagnostic yield. rEBUS and fluoroscopy are new diagnostic modalities in our institution. There is undoubtedly a learning curve for performing effective rEBUS that improves with case experience [22]. Most rEBUS data in papers originate from expert bronchoscopy centres and hence might not reflect "real-world" results. Kurimoto et al [23]. noted a significantly lower yield (40%) for the left upper lobe apico-posterior segment which was the most common location (21.43% cases) of PPL in our study. These factors may explain the lower yield in our study compared to that observed in meta-analyses.

Comparative analyses revealed no statistically significant differences in diagnostic capabilities between two study arms (diagnostic yield- 59.1% in rEBUS arm, 60% in rEBUS-F arm, p= 0.833). No randomized controlled trials have compared diagnostic yield of rEBUS procedures with and without fluoroscopy. Our finding is in accordance with the meta-analysis by S Tian et al. which demonstrated statistical equivalent diagnostic yields rEBUS with and without fluoroscopy (75.5 % vs 71.9 %) [14]. They observed that multimodality approach fails to further improve the diagnostic yield (p=0.718). These findings indicate that rEBUS can be performed in absence of additional fluoroscopy guidance without compromising diagnostic yield.

Sensitivity reached 61% similar to reports by Evison et al. [10] (64%), Hong et al. [15] (67.8%) and Fuso et al. [24] (59%) and higher than Durakovic et al. [25] (49%). Specificity (100%), positive predictive value (100%) and accuracy (64.3%) match that of Hong et al. (100%, 100%, 76.1% respectively) [15]. The lower negative predictive value (5.9%) observed in our study compared to Hong et al. [15] (52%) may be attributed to the high prevalence of malignancy, very low number of true negative and relatively high false negative results within our cohort.

We observed that positive bronchus sign (AOR: 4.92, 95% CI: 1.43-16.93, p=0.011) and concentric image on rEBUS (AOR: 3.83, 95% CI: 1.13-12.99, p=0.031) are significant predictors of diagnostic success. Other variables, including visibility on X-ray, size, density, location of lesion, and final diagnosis, did not significantly impact diagnostic yield. Hong et al. reported that solid lesion (OR, 14.58; 95% CI, 2.64–80.38; P = 0.002) and a concentric endobronchial ultrasound image (OR, 28.50; 95% CI, 6.26–129.85; P < 0.001) were independently associated with diagnostic success in CT bronchus sign negative cases [11]. The same authors in another study evaluating peripheral lesions using rEBUS without fluoroscopy reported that lesions 20 mm, positive bronchus sign in chest CT, a solid lesion, and probe within the lesion (concentric image) were independent factors of diagnostic success. Minezawa et al. and Lee et al. also observed that lesions with positive bronchus sign was associated with a higher diagnostic yield [6,10]. In two different studies, the diagnostic yield of concentric lesions was higher than eccentric (Kurimoto 82% vs 42%; P < 0.0001) [13] or invisible (Yamada 83% vs 61% vs 4%; P < 0.001) lesions [13,26]. Moon et al., Steinfort et al. and Lee et al., reported higher diagnostic accuracy when the probe was positioned within the lesion [16,27,28].

Huang et al. found that lesion size and ultrasound visualization were important factors for the diagnostic yield [22]. The size of the lesion was not a significant predictor of yield in our study, a finding also reported by Yamada et al. and Lin et al. [26,29]. A meta-analysis by Ali et al. reported 4 factors that impact the diagnostic yield of rEBUS: size >20mm, malignant lesion, presence of a positive bronchus sign and concentric endosonographic image [21]. Lobar location of the lesions did not significantly impact the diagnostic yields. Gex et al. reported that the following factors had a higher diagnostic yield: upper or middle lobe lesions in addition to, lesion diameter >2cm, positive bronchus sign [30]. In our study, although upper and middle lobe location were associated with diagnostic success (p=0.023), this significance was lost in logistic regression analysis (Adjusted OR:1.47; CI: 0.51-4.23; P=0.479).

The study identified four significant predictors of malignant lung lesions- age> 60 years, shorter average symptom duration, size>30 mm and upper/middle lobe location. According to Bellier et al., the malignancy risk of solitary pulmonary lesions increases sharply among patients older than 60 years, with an adjusted OR of 2.61 (95% CI: 1.86–3.66) [31]. The larger size of malignant lesions may be due to rapid growth which can also explain shorter duration of symptoms. Swensen et al. reported upper lobe location of solitary pulmonary nodule as an independent risk factor for malignancy [32]. The National Lung Screening Trial data set showed 65.7% of all lung cancers were located in the upper lobe [2]. Furthermore, the result of NELSON trial, the largest European lung cancer CT screening trial, observed that 64.1% of all lung cancers were localized in the upper lobe [33]. Thus, our findings corroborate existing evidence.

Gender and smoking status did not significantly influence diagnosis. This aligns with observations by Zo et al. [34]. It's essential to note that these results from a single centre may not be generalizable due to the limited sample size. We found no significant value of nodule density and margin type on CT scan in predicting the final diagnosis. Although a spiculated margin is associated with the highest risk of malignancy, some benign conditions such as tuberculoma, and progressive massive fibrosis may also have a spiculated margin [35]. Our analysis was likely confounded by predominance of such benign diagnoses (TB- 16.67% and silicosis -11.90%). Malignant lesions were also less common in our study (56.09%) compared to other studies e.g. Minezawa et al. (73.83%), Moon et al. (77.72%) and Tanner et al. (86%) [10,17,21]. These factors might have masked the true predictive value of spiculation.

Overall complication rate in this study was 14.3%. Other studies reported complication rates ranging from 2.0% to 13% [15,11,17,23,36]. Desaturation was the most common complication (7.1%) consistent with Lee et al.'s report (8.1%) [15]. Occurrence of bleeding (grade 1 - 4.8% cases) was similar to that reported by Huang et al. [22] (4.7%) and lower than Jacomelli et al. [36] (9.3%). Pneumothorax rates reported in different studies are- Evison et al. 0.9%; Hong et al. 2.0%; Moon et al. 4.8% [11,16,17], However, no pneumothorax was reported in our study. Incidence of post-procedure fever in our study (2.4%) was lower compared S. Park et al.'s study (5.5%) [37]. A recent meta-analysis of prospective trials by S. Tian et al. reported a pooled overall complication rate of 3.1%. Incidence of moderate and severe bleeding (requiring additional therapeutic interventions) was 1.1% and pooled pneumothorax rate was 0.4% [14]. Though overall complication rate in our study is higher which may be due to the learning curve, we did not find any pneumothorax or bleeding requiring additional therapeutic interventions. Our study reaffirms the safety of radial endobronchial ultrasound guided biopsy, consistent with existing literature.

The strength of the study lies in its novel approach and prospective randomization. However, several limitations should be acknowledged. It was a single-centre pilot study with a small sample size, limiting statistical power and generalizability. The results of the multivariable analyses, although clinically plausible, should be interpreted cautiously, as the small sample size and limited number of outcome events relative to the number of predictor variables increased the risk of model overfitting. Additionally, histopathological confirmation, the diagnostic gold standard, was not available in all cases, and some final diagnoses were based on multidisciplinary consensus after follow-up, introducing a potential risk of misclassification bias, while operator-dependent bias stemming from the procedural learning curve could have influenced the results.

Conclusions

In this single-centre, prospective pilot study, the diagnostic yield of rEBUS-guided biopsy was comparable between procedures performed with and without the use of fluoroscopy (59.1% vs. 60.0%). These preliminary findings suggest that omitting fluoroscopy may not compromise diagnostic performance, while offering potential benefits such as reduced radiation exposure and procedural costs. However, given the limited sample size, these results should be considered exploratory. Larger, adequately powered multicentre studies are required to validate these findings before a change in clinical practice can be recommended.

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Table 1. Study population demographics and lesion characteristics.

VARIABLES	rEBUS arm (n=22)	rEBUS-F arm (n=20)	All patients (n=42)	p-value
AGE	49.86 ±14.10	53.6 ±9.03	50.69±13.72	0.31
GENDER				0.86
MALE, n (%)	18 (81.82)	15 (75)	33 (78.57)	
FEMALE, n (%)	4 (18.18)	5 (25)	9 (21.43)	
SMOKING STATUS				0.38
SMOKER, n (%)	5 (22.73)	7(35)	12 (28.57)	
NEVER SMOKER, n (%)	17 (77.27)	13(65)	30 (71.43)	
AVG. SYMPTOM DURATION IN MONTHS (MEAN ±SD)	7.29 ±9.24	3.48 ±5.09	5.13±7.50	0.11
PPL LOCATION				0.168
UPPER LOBE	15 (68.2%)	9 (45%)	24 (57.1%)	
MIDDLE LOBE/LINGULA	2 (9.1%)	3 (15%)	5 (11.9%)	
LOWER LOBE	5 (22.7%)	8 (40%)	13 (31%)	
NO OF PPL				0.877
SINGLE	15 (68.18%)	15 (75%)	30 (71.43%)	
MULTIPLE	7 (31.82%)	5 (25%)	12 (28.57%)	
MEDIAN (RANGE)	1(1-3)	1(1-3)	1(1-3)	0.955
SIZE OF PPL				
MEAN ±SD	35.95 ±11.73	30.37±15.52	33.81± 14.78	0.099
<20mm	1 (4.55%)	3 (15%)	4 (9.52%)	
20-30 mm	6 (27.27%)	6 (30%)	12 (28.57%)	
>30 mm	15 (68.18%)	11 (55%)	26 (61.9%)	
MARGIN TYPE ON CT SCAN				
SMOOTH	6 (27.3%)	9 (45%)	15 (35.7%)	0.233
SPICULATED	8 (36.4%)	5 (25%)	13 (31%)	0.443
ILL-DEFINED	3 (13.6%)	1 (5%)	4 (9.5%)	0.317
IRREGULAR	2 (9.1%)	4 (20%)	6 (14.3%)	0.233
LOBULATED	3 (13.6%)	1 (5%)	4 (9.5%)	0.317
CT FEATURE				
PURE SOLID	16 (72.7%)	17 (85%)	33 (78.6%)	0.626
SUBSOLID (MIXED GGO)	6 (27.3%)	3 (15%)	9 (21.4%)	
CAVITATION	2 (9.1%)	6 (30%)	8 (19%)	
CALCIFICATION	5 (22.7%)	3 (15%)	8 (19%)	0.923
POSITIVE BRONCHUS SIGN	9 (40.9%)	8 (40%)	17 (40.5%)	0.643
EBUS IMAGE				
ECCENTRIC	7 (31.8%)	9 (45%)	16 (38.1%)	0.383
CONCENTRIC	9 (40.9%)	6 (30%)	15 (35.7%)	0.503
INVISIBLE	6 (27.3%)	5 (25%)	11 (26.2%)	0.869

Table 2. Predictors of visualization on radial EBUS.

CATEGORIES	VARIABLES	VISUALIZATION (n=31)	NON- VISUALIZATION (n=11)	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
				OR (95% CI)	p	ADJUSTED OR (95% CI)	p-value
VISIBILITY ON CHEST X-RAY	VISIBLE	21 (67.7%)	6 (54.5%)	4.67 (1.43-15.23)	0.011	4.51 (1.36-15.01)	0.014
	INVISIBLE	10 (32.3%)	5 (45.5%)				
CT DENSITY	SOLID	23 (74.2%)	10 (90.9%)	5.56 (1.89–16.37)	0.005	5.43 (1.54-19.23)	0.009
	MIXED GGO	8 (25.8%)	1 (9.1%)				
CT BRONCHUS SIGN	POSITIVE	13 (41.9%)	4 (36.4%)	3.45 (1.13-10.53)	0.013	3.39 (1.12-10.27)	0.031
	NEGATIVE	18 (58.1%)	7 (63.6%)				
SIZE (mm)	<30 mm	12 (38.7%)	4 (36.4%)	1.83 (0.63-5.31)	0.105		
	>30 mm	19 (61.3%)	7 (63.6%)				
LOCATION	UL/ML	21 (67.7%)	8 (72.7%)	1.21 (0.44-3.33)	0.494		
	LL	10 (32.3%)	3 (27.3%)				

Variables included in the multivariable model were selected based on univariate significance.

Table 3. Diagnostic performance.

PARAMETERS	rEBUS arm (n=22)	rEBUS-F arm (n=20)	OVERALL (n=42)	p-value*
TRUE POSITIVE	13 (59.1%)	12 (60%)	25 (59.5%)	1.000
TRUE NEGATIVE	0 (0%)	1 (5%)	1 (2.4%)	0.476
FALSE POSITIVE	0 (0%)	0 (0%)	0 (0%)	NA
FALSE NEGATIVE	9 (40.9%)	7 (35%)	16 (38.1%)	0.758
DIAGNOSTIC YIELD	59.1% (13/22)	60% (12/20)	59.5% (25/42)	1.000
SENSITIVITY	59.1% (13/22)	63.2% (12/19)	61.0% (25/41)	1.000
SPECIFICITY	NA	100% (1/1)	100% (1/1)	NA
POSITIVE PREDICTIVE VALUE	100% (13/13)	100% (12/12)	100% (25/25)	NA
NEGATIVE PREDICTIVE VALUE	0% (0/9)	12.5% (1/8)	5.9% (1/17)	1.000
ACCURACY	59.1% (13/22)	65% (13/20)	61.9% (26/42)	0.760

True positive was defined as concordance between the initial bronchoscopic and final diagnoses, while true negative referred to a non-diagnostic bronchoscopy with an indeterminate final diagnosis. False positive was defined as discordance between the initial bronchoscopic and final diagnoses, whereas false negative referred to a non-diagnostic bronchoscopy in lesions subsequently diagnosed on further evaluation. *P values were calculated using Fisher's exact test.

Table 4. Predictors of diagnostic success.

PARAMETER	CATEGORIES	DIAGNOSTIC SUCCESS (n=25)	DIAGNOSTIC FAILURE (n=17)	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
				OR (95% CI)	p- value	ADJUSTED OR (95% CI)	p-value
VISIBILITY ON CHEST X-RAY	VISIBLE	17 (68%)	10 (58.8%)	0.83 (0.33-2.09)	0.796	0.73 (0.26-2.05)	0.554
	INVISIBLE	8 (32%)	7 (41.2%)				
CT DENSITY	SOLID	21 (84%)	12 (70.6%)	1.67 (0.54-5.16)	0.231	1.41 (0.43-4.63)	0.573
	MIXED GGO	4 (16%)	5 (29.4%)				
SIZE (mm)	<20 mm	1 (4%)	3 (17.6%)	1.21 (0.43-3.41)	0.641	2.19 (0.73-6.59)	0.163
	20-30 mm	8 (32%)	4 (23.5%)				
	>30 mm	16 (64%)	10 (58.8%)				
CT BRONCHUS SIGN	POSITIVE	14 (56%)	3 (17.6%)	5.44 (1.63-18.21)	0.004	4.92 (1.43-16.93)	**0.011**
	NEGATIVE	11 (44%)	14 (82.4%)				
EBUS IMAGE	ECCENTRIC	11 (44%)	5 (29.4%)	4.67 (1.43-15.29)	0.011	3.83 (1.13-12.99)	**0.031**
	CONCENTRIC	14 (56%)	1 (5.9%)				
	INVISIBLE	0 (0%)	11 (25%)				
LOCATION	UL, ML	17 (68%)	12 (70.6%)	1.28 (0.49-3.35)	0.623	1.47 (0.51-4.23)	0.479
	LL	8 (32%)	5 (29.4%)				
FINAL DIAGNOSIS	BENIGN	9 (36%)	9 (52.9%)	1.75 (0.63-4.85)	0.281	1.92 (0.63-5.83)	0.246
	MALIGNANT	16 (64%)	7 (47.1%)				

Variables included in the multivariable model were selected based on univariate significance.

Table 5. Predictors of benign and malignant diagnosis.

PARAMETER	CATEGORIES	BENIGN (n=18)	MALIGNANT (n=23)	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
				OR (95% CI)	p-value	ADJUSTED OR (95% CI)	p-value
AGE	<60 YRS	15 (83.3%)	14 (60.9%)	3.11 (1.01-9.59)	0.048	2.83 (1.01-7.93)	0.047
	>60 YRS	3 (16.7%)	9 (39.1%)				
GENDER	MALE	15 (83.3%)	17 (73.9%)	0.75 (0.25-2.23)	0.503		
	FEMALE	3 (16.7%)	6 (26.1%)				
SMOKING STATUS	EVER SMOKER	3 (16.7%)	8 (34.6%)	2.67 (0.76-9.37)	0.201		
	NEVER SMOKER	15 (83.3%)	15 (65.2%)				
AVERAGE SYMPTOMS DURATION	MONTHS (MEAN ±SD)	7.89 ± 6.83	3.01 ± 5.30	0.78 (0.65-0.93)	**0.006**	0.79 (0.65-0.96)	0.016
VISIBILITY ON CHEST X-RAY	VISIBLE	11 (61.1%)	15 (65.2%)	1.14 (0.49-2.65)	0.754		
	INVISIBLE	7 (38.9%)	8 (34.8%)				
DENSITY OF LESION	SOLID	14 (77.8%)	18 (78.3%)	1.01 (0.34-3.01)	0.973		
	MIXED GGO	4 (22.2%)	5 (21.7%)				
SIZE (mm) ON CT	<30 mm	11 (61.1%)	5 (21.7%)	4.67 (1.63-13.39)	**0.004**	4.17 (1.48-11.74)	0.006
	>30 mm	7 (38.9%)	18 (78.3%)				
CT BRONCHUS SIGN	POSITIVE	7 (38.9%)	9 (39.1%)	1.01 (0.43-2.37)	0.985		
	NEGATIVE	11 (61.1%)	14 (60.9%)				
LOCATION	UL/ML	10 (55.6%)	17 (73.9%)	2.38 (1.01-5.61)	0.048	2.15 (1.01-4.59)	0.046
	LL	8 (44.4%)	6 (26.1%)				
MARGIN	SMOOTH	8 (44.4%)	7 (30.4%)	0.58 (0.24-1.39)	0.401		
	SPICULATED	2 (11.1%)	3 (13%)				
	ILL-DEFINED	2 (11.1%)	2 (8.7%)				
	IRREGULAR	5 (27.8%)	8 (34.8%)				
	LOBULATED	1(5.6%)	3 (13%)				

Variables included in the multivariable model were selected based on clinical relevance.

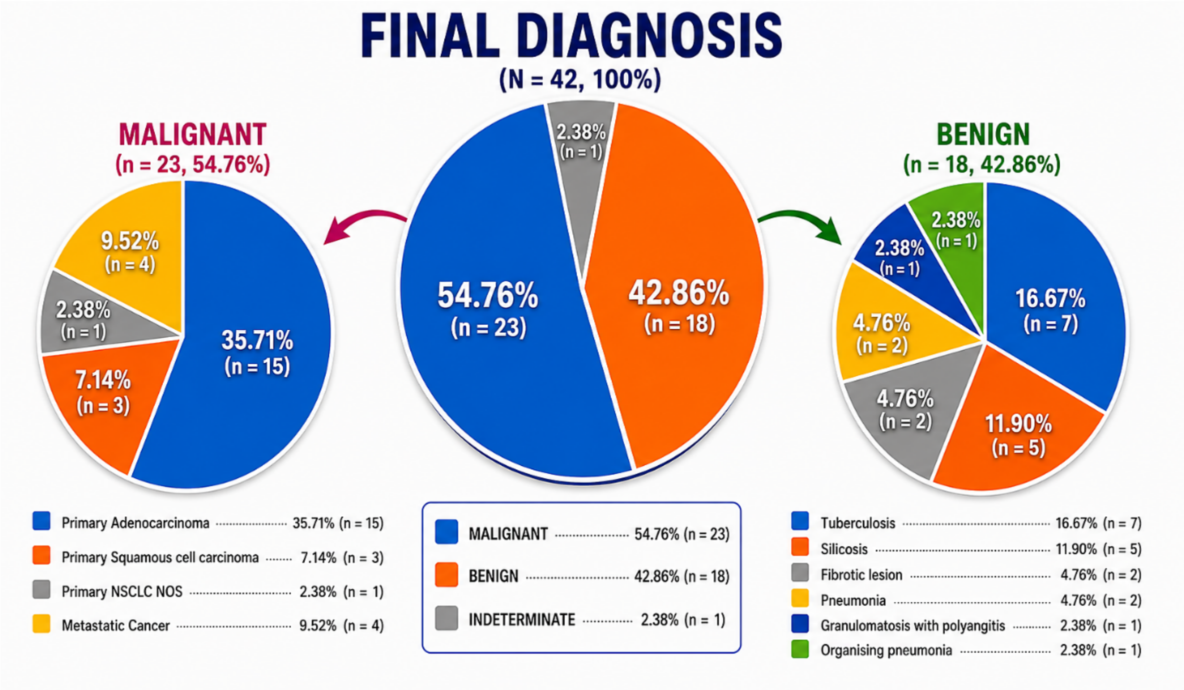

Figure 1. Distribution of final diagnosis. NSCLC NOS, non-small cell lung cancer not otherwise specified.