

## Radial Probe Endobronchial Ultrasound for Peripheral Pulmonary Lesions: Initial Experience in an Indian Tertiary Healthcare Centre

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### ARTICLE INFO

Article type:  
Original Article

Article history:  
Received: 11 Aug 2017  
Revised: 20 Sep 2017  
Accepted: 30 Oct 2017

Keywords:  
Endobronchial Ultrasound  
Lung Biopsy  
Lung Cancer  
Pulmonary Nodule  
Tuberculosis

### ABSTRACT

**Introduction:** Diagnosis of peripheral pulmonary nodules is confusing; therefore, an accurate and safe lung biopsy can prevent unnecessary invasive diagnostic procedures. This study sought to study the diagnostic yield, sensitivity, specificity, and negative and positive predictive values (NPV and PPV) of radial probe endobronchial ultrasound (EBUS)-guided biopsy for peripheral pulmonary lesions.

**Materials & Methods:** Patients referred to the Department of Pulmonary Medicine, AIIMS, Kochi, India, during May 2015-September 2016 for the evaluation of peripheral pulmonary lesions were subjected to radial probe EBUS-guided transbronchial lung biopsy under conscious sedation after reviewing positron emission tomography scan/computed tomography results. The obtained specimens were considered diagnostic when the cytological, histopathological, or microbiological diagnosis was consistent with the clinical presentations.

**Results:** Totally, 14 procedures were performed on 13 patients with the mean lesion size of 30.42 mm. Mean distance between the lesion and pleura was 1.17±0.68 cm, and the diagnostic yield of this technique was 78.57%. Furthermore, the sensitivity, specificity, and NPV were 70% (range: 34.75 to 93.33), 100% (range: 39.76 to 100), and 57.14% (range: 18.41 to 90.10), respectively. This procedure was not associated with any major complications.

**Conclusion:** Radial probe EBUS with satisfactory diagnostic yield and low complication rate is a promising tool for early diagnosis of lung cancer.

► Please cite this paper as:

Nair R A, Haridas N, Ahmed S, Eapen M. Radial Probe Endobronchial Ultrasound for Peripheral Pulmonary Lesions: Initial Experience in an Indian Tertiary Healthcare Centre. J Cardiothorac Med. 2017; 5(4): 213-217.

### Introduction

Peripheral pulmonary lesions are a source of anxiety among patients and diagnostic confusion among clinicians. With the advent of lung cancer screening programs, evaluation of pulmonary lesions is essential to rule out lung malignancies. The computed tomography- (CT) guided and blind transbronchial lung biopsy (TBLB) techniques are

the conventional diagnostic methods with the diagnostic yield of approximately 34-63%, while CT-guided lung biopsy has diagnostic yield of 99% with diverse complications, such as pneumothorax and bleeding (1, 2). The incidence of complications increases along with the lesion depth from the pleural surface. The bronchoscopic techniques

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including electromagnetic navigation, virtual bronchoscopy, and radial probe endobronchial ultrasound (EBUS) improved the diagnostic yield for peripheral pulmonary lesions (3-6).

Data for radial probe ultrasound in Indian subcontinent is limited to few case reports (7). Here, we analyzed the data on our experience with radial probe EBUS-guided biopsy for diagnosis of peripheral pulmonary lesions. This study aimed to evaluate the diagnostic yield, sensitivity, specificity, and negative and positive predictive values (NPV and PPV) of radial probe EBUS-guided biopsy for diagnosis of peripheral pulmonary lesions.

### Study setting

This study was conducted in the Division of Pulmonary Medicine, Amrita Institute of Medical Sciences and Research Center, Amrita Vishwa Vidya Peetham, Kochi, India, from May 2015 to September 2016.

### Materials and Methods

We included all the patients referred to the Department of Pulmonary Medicine, Amrita Institute of Medical Sciences and Research Center, Kochi, India, during May 2015-September 2016 for bronchoscopy for the evaluation of peripheral pulmonary lesions.

The procedures were performed under conscious sedation induced by midazolam and fentanyl. Bronchoscopes of varying sizes were used during the procedures (Olympus CLV 190 series video processor and ultrasound, Japan). Biopsy targets were selected by reviewing the available CT or positron emission tomography/CT images. No additional image guidance software (virtual bronchoscopy and electromagnetic navigation software) was used to assist with procedure planning. Radial probe

EBUS was performed using a 1.4-mm, 20-MHz radial EBUS miniprobe (UM S20-17S; Olympus, Japan). A guide sheath was not used; Biopsies were performed using a 21-gauge transbronchial aspiration needle and a 1.8-mm forceps or a cytology brush.

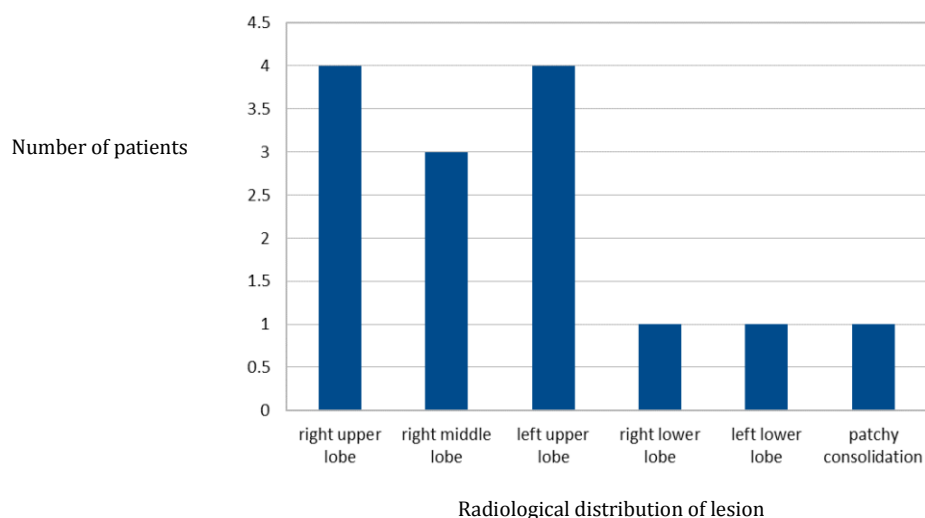
The specimens were considered diagnostic when a cytological, histopathology, or microbiologic diagnosis was consistent with the clinical presentation. Patients in whom the procedures were not diagnostic were referred for surgery when appropriate or were followed up by chest CT scan.

A finding of inflammation was considered diagnostic if the biopsied lesion was resolved on the follow-up CT. If the follow-up imaging was not available or if the lesion was unchanged or enlarged, the finding of inflammation was considered non-diagnostic.

### Results

Fourteen procedures were performed on 13 subjects, seven of whom were males and six were females. The technique was repeated twice for one of the patients; the first procedure was performed for the diagnosis of the lesion and the second one was for ruling out a second primary cancer, which may occur after an initial response to treatment. All the procedures were carried out under local anesthesia and conscious sedation induced by midazolam and fentanyl. Mean age of the study population was 57.78 years (age range: 24 to 73 years) and mean size of the lesions was 30.42 mm.

As demonstrated in Figure 1, most of the lesions are distributed in the upper lobes. According to the radiological imaging, 14 lesions were identified, 10 of which had solid density, two were cavities, one was a partly solid nodule, and one was a nodule with ground-glass opacity.



**Figure 1.** Radiological distribution of lesion

**Table 1.** Diagnosis obtained by radial probe endobronchial ultrasound-guided biopsy

Diagnosis	Number
Non-small cell carcinoma	4
Poorly differentiated carcinoma	1
Atypical cells/malignancy	2
No evidence of granuloma or malignancy	7

All the pulmonary lesions were peripheral with the mean distance of  $1.17 \pm 0.68$  cm from the pleura. The CT-guided biopsy before radial probe EBUS-guided biopsy was recommended to four and the pleura was less than 1 cm.

The CT-guided biopsy was unyielding and two cases experienced pneumothorax as a complication of this procedure. In this study, the mean standardized uptake value (SUV) in PET of the lesion was  $7.71 \pm 4.3$ . On radial probe EBUS, no abnormalities could be detected in two cases. In the patient who had patchy areas of consolidation in CT, endobronchial ultrasound showed three focal areas of consolidation involving the lingula, right middle lobe, and right lower lobe. The radial probe ultrasound showed focal abnormal area in nine cases and circumferential involvement in two cases.

Table 1 shows the diagnosis obtained after radial probe EBUS guided biopsy. Non-small-cell lung cancer was the most common diagnosis. Two patients had atypical cells suggestive of malignancy on histopathology. One patient showed was positive for ROS1 (c-ros oncogene 1) rearrangement when the tissue was subjected to fluorescent in situ hybridization (FISH).

Among the seven cases in whom no evidence of granuloma or malignancy was observed, one patient was subjected to lobectomy, which showed cavity with inflammation, one patient underwent VATS biopsy, which presented no evidence of granuloma or malignancy, and two cases showed resolution of lesion on clinical and radiological follow-up. These four patients were hence taken as true negatives. One patient with negative results on EBUS had PET scan showing an uptake suggestive of malignancy. One patient was lost to follow-up and another patient died on follow-up. These three cases were considered as false negative. Of the two patients in whom no abnormality could be visualized in EBUS, one patient had a high uptake on PET scan and was taken as false negative. The other patient showed no evidence of inflammation or malignancy on VATS biopsy, and thus, was considered true negative.

The diagnostic yield, sensitivity, specificity, negative likelihood ratio, PPV, and NPV of this procedure were 78.57%, 70% (range: 34.75 to 93.33), 100% (range: 39.76 to 100), 0.30 (range: 0.12 to 0.77), 100% (range: 59.04 to 100%), and 57.14% (range: 18.41 to 90.10), respectively. It is worth mentioning that this procedure was not

associated with any major complications.

## Discussion

Lung cancer is the fourth most commonly diagnosed cancer in India with approximately one million new cases annually (8). Solitary pulmonary nodules (SPNs) should be approached with caution. With the advent of lung cancer screening, the clinicians are encountered with pulmonary nodules with undetermined significance. The probability of malignancy in a SPN depends on multiple factors such as nodule size, imaging characteristics, epidemiological risk factors, and growth rate.

Nonsurgical techniques for sampling, including transbronchial and transthoracic needle biopsy methods, are preferred in patients with a nodule that has an intermediate risk of malignancy (5-65%), high-risk patients (more than 65%) without indication for surgery, and those in whom a benign diagnosis is suspected that requires therapy. The conventional bronchoscopy has a sensitivity of 34% (range: 5% to 76%) for lesions smaller than 20 mm and 63% (range: 31% to 82%) for larger ones (1).

In this study, the EBUS-guided biopsy with diagnostic yield of 78.57% revealed no significant complications in the patients with the lesions with mean size of 30.42 mm and mean depth of  $11.7 \pm 6.8$  mm from the pleural surface. Lang et al. conducted a study to evaluate the diagnostic yield of CT-guided biopsy for peripheral pulmonary lesions and revealed that its diagnostic yield was 99.5% and that 31.4% of the patients developed a pneumothorax as a procedure-related complication (9). In the mentioned study, the mean size of the lesion was 34.6 mm and the distance between the lesion and the pleura was not measured.

Another standard technique for the diagnosis of non-endobronchial pulmonary lesions is fluoroscopy-guided TBLB. In the Rittirak et al. study, the diagnostic yield of this procedure was found to be 43.8% and the prevalence of pneumothorax was 1.2% (10). Electromagnetic navigation and virtual bronchoscopy are used for sampling from the peripheral pulmonary lesions. In a study by Eberhardt, the electromagnetic navigation bronchoscopy had a diagnostic yield of 67%, while virtual bronchoscopy-guided biopsy showed a diagnostic yield of 65.4% (4).

According to a study by Shinigawa et al., the diagnostic yield of radial probe EBUS-guided biopsy was lower in comparison to transthoracic needle aspiration and higher in comparison to image-guided bronchoscopy techniques such as fluoroscopic guidance, electromagnetic navigation, and virtual bronchoscopy (11). This method is associated with less complications in comparison

to the other conventional techniques. This procedure has a minimized exposure to radiation compared to the fluoroscopy-guided biopsy. Furthermore, the diagnostic yield of this method was 78.57% for the lesions with the mean size of 30.42 mm.

Regarding the results obtained by Hesla et al., the diagnostic yield was 65% in lesions with a mean size of  $20.4 \pm 6$  mm, while Kokkonouzis et al. revealed the diagnostic yield of 75% for the lesions with the mean size of 30.2 mm (12, 13). In the mentioned study, five subjects had lesions smaller than 20 mm. The diagnostic yield was not studied separately due to small sample size of the study. Paone et al. demonstrated that radial probe EBUS-guided TBLB has a sensitivity of 75% and 71% for detecting lesions smaller than 2 cm and 3 cm, respectively, while these values were 31% and 23%, respectively, for the conventional TBLB (14). In this study, the mean distance between the lesion and the pleura was  $1.17 \pm 0.68$  cm; however, in the study by Hesla et al., the mean distance was  $2.03 \pm 1.91$  cm (12).

According to the literature, the majority of the lesions were found in the upper lobes of both lungs although all the false-negative results were associated with the apical segment of the upper lobe lesions, which might be due to difficult access to the upper areas (12, 14). Inconsistent with that study, Kokkonouzis et al. demonstrated that lower lobe lesions were more prevalent, and the EBUS visualization and diagnostic yield were greater for lower lobe lesions (83.33% and 100%, respectively) (13).

In this study, the average SUV used in PET for the suspicious pulmonary lesions was  $7.71 \pm 4.3$ . Additionally, high FDG uptake reflects the high risk of malignancy and affects the final pathological diagnosis. India is considered as a tuberculosis-endemic country; therefore, these findings were inconsistent with expectation of more number of granulomatous disorders. This inconsistency might be due to the fact that these patients were diagnosed by microbiological techniques, conventional bronchoscopy, and bronchoalveolar lavage rather than EBUS-guided biopsy for a peripheral pulmonary nodule.

The procedure used in this study had diagnostic yield, sensitivity, specificity, negative likelihood ratio, PPV, and NPV of 78.57%, 70% (range: 34.75 to 93.33), 100% (range: 39.76 to 100), 0.30 (range: 0.12 to 0.77), 100% (range: 59.04 to 100%), and 57.14% (range: 18.41 to 90.10), respectively.

In line with our study, Paone et al. compared EBUS-guided biopsy with conventional TBLB and determined that the EBUS-guided TBLB had a sensitivity, specificity, NPV, and PPV of 78.7% (range: 68.4 to 89), 100%, 66.7 (range: 53.3 to

80), and 100, respectively (14). Peschke et al. conducted a study in which radial probe EBUS-guided biopsy was performed under fluoroscopic guidance and the diagnostic yield was 67.2% (15). Recently, Hayama et al. investigated the diagnostic yield of radial probe EBUS with a guide sheath for peripheral cavitory lesions in the lungs, which was 80% (16). According to a meta-analysis by Steinfert et al., EBUS had point specificity and sensitivity of 1.00 (with 95% confidence interval [CI], ranging from 0.99 to 1.00) and 0.73 (with 95% CI, ranging from 0.70 to 0.76), respectively, for the diagnosis of lung cancer with positive and negative likelihood ratios of 26.84 (range: 12.60 to 57.20) and 0.28 (range: 0.23 to 0.36), respectively (17). A recently published case series from India utilized cryobiopsy and fluoroscopic guidance and reported a diagnostic yield of 70.9% (18), which was comparable with the results of this study in terms of diagnostic yield and sensitivity in the absence of any guidance.

### Limitations of the Study

The small sample size is the limitation of this study, which did not allow a detailed analysis on the differences of diagnostic yields and sensitivities based on size of the lesion, EBUS findings, and presence of bronchus sign on CT scan.

### Conclusion

Radial probe EBUS-guided transbronchial biopsy has a satisfactory diagnostic yield with low complication rates for peripheral pulmonary lesions. It could be considered as a promising tool for the early diagnosis of lung cancer. Further studies are recommended to evaluate the efficacy and cost-effectiveness of this instrument in the developing countries like India.

### Acknowledgments

None.

### Conflicts of Interest

The authors declare no conflict of interest.

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