Comparison of diagnostic yield and safety profile of radial endobronchial ultrasound-guided bronchoscopic lung biopsy with computed tomography-guided percutaneous needle biopsy in evaluation of peripheral pulmonary lesions: A randomized controlled trial

Ayush Gupta, Jagdish Chander Suri, Dipak Bhattacharya, Manas Kamal Sen, Shibdas Chakrabarti, Abhijeet Singh, Tulsi Adhikari

Department of Pulmonary, Critical Care and Sleep Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, National Institute of Medical Statistics, Indian Council of Medical Research, New Delhi, India

ABSTRACT

Background: Peripheral pulmonary lesions (PPLs) pose a diagnostic challenge, and the optimal investigation in many such cases remains unclear. Computed tomography (CT)-guided percutaneous needle biopsy (CT-PNB) has been the modality of choice for such lesions with a high diagnostic accuracy but with high rates of pneumothorax. Endobronchial ultrasound (EBUS) with a radial probe is an alternate diagnostic modality with increased diagnostic yield of bronchoscopy in the evaluation of PPL. We conducted a randomized controlled trial comparing the diagnostic accuracy and complication rates of radial EBUS with CT-guided lung biopsy for the evaluation of PPL. Methods: Fifty patients with PPL surrounded by lung parenchyma on all sides were randomly assigned to either radial EBUS or CT-PNB group (25 each). Results: Both groups had similar clinicoradiologic characteristics. The diagnostic accuracy of radial EBUS was comparable to CT-PNB with no statistically significant difference (72 vs. 84%; P = 0.306). However, the yield was significantly lower in right upper lobe lesions (20% vs. 83.3%; P = 0.03). CT-PNB group had significantly higher pneumothorax rates than radial EBUS (20% vs. 0%; P = 0.03). The lesions that were more than 2 cm, those with ultrasound feature of continuous hyperechoic margin around the lesion (P = 0.007), and the position of the ultrasound probe within the lesion (P < 0.001) were associated with a higher diagnostic yield with radial EBUS. Conclusion: Our findings suggest that radial EBUS is a safer investigation than CT-PNB with a comparable diagnostic accuracy for PPL not abutting the chest wall (CTRI/2017/02/007762).

KEY WORDS: Bronchoscopy, computed tomography, peripheral pulmonary lesions, radial endobronchial ultrasound

INTRODUCTION

Flexible bronchoscopy (FB) has a variable and often poor success rate in sampling pulmonary lesions which are not visible endoscopically. Such focal radiological opacities without endobronchial extension are referred to as peripheral pulmonary lesions (PPLs).

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are abutting the chest wall can easily be sampled using ultrasound-guided transthoracic needle biopsy in real time, without any radiation exposure and without significant risk of pneumothorax. However, those PPLs which are surrounded by normal lung parenchyma and without evidence of endobronchial extension on computed tomography (CT) are difficult to access bronchoscopically as well as under ultrasound guidance. Traditionally, CT-guided percutaneous needle biopsy (CT-PNB) or fluoroscopy-guided bronchoscopic lung biopsy (BLB) has been used to diagnose such lesions. While the yield of fluoroscopy-guided BLB has been reported to be very low (<40% for nodules <2.5 cm), CT-PNB has a variable diagnostic yield (74%–96%) but is associated with a high risk of pneumothorax (15%–44%).

Endobronchial ultrasound (EBUS) with the help of a radial probe is an alternate modality that has increased the diagnostic yield of FB in the evaluation of PPL. Studies have reported a 53%–80% diagnostic accuracy which depends on several factors including lesion characteristics and operator experience. However, the two most promising advantages of radial EBUS over CT-PNB are its safety profile and absence of radiation exposure.

The present study was done because, in a significant proportion of patients with PPL surrounded by lung parenchyma, the optimal investigation remains unclear. There are limited data directly comparing radial EBUS-guided lung biopsy with CT-PNB for evaluation of such lesions. There is a need to define the clinical and radiological characteristics of PPL that would clearly favor one investigation over the other. We conducted this study to compare the diagnostic accuracy and complication rates of EBUS-BLB with that of CT-PNB for the evaluation of PPL selected randomly for each procedure and also looked for lesion characteristics that would help in selecting the correct procedure.

**METHODS**

We conducted a randomized controlled trial at a tertiary hospital of a medical college after obtaining the institutional review board approval and a written, informed consent from the patients. The trial was registered with Clinical Trials Registry-India (CTRI/2017/02/007762), and the study details can be accessed at ctri.nic.in. We have adhered to the CONSORT guidelines for optimal reporting of parallel group randomized trials.

**Inclusion criteria and exclusion criteria**

Consecutive patients referred to our department for the evaluation of PPL were considered for inclusion in the study. A CT scan was done, and patients having PPL with surrounding lung parenchyma on all sides and without the evidence of endobronchial extension were randomized to either radial EBUS-guided biopsy or CT-PNB (25 patients in each group). Lesions <1 cm and those abutting the chest wall or with endobronchial extension were excluded from the study.

The primary outcomes were diagnostic accuracy and the rate of pneumothorax in the two groups. Sample size was determined for an effect size of 15% for rate of pneumothorax between two groups with a power of 80% and an alpha error of 5% and was calculated to be 25 for each group. Randomization to either procedure was performed using a computer-based random sequence generator by an independent person of our department not involved in the study. The allocation was done by the same person, using sequentially numbered sealed, opaque envelopes which were handed over to the included patients in the order of their recruitment into the study by the investigators. Both patients and the investigators were unblinded to the randomization outcome. In the event of a nondiagnostic procedure, patients who had undergone radial EBUS were then subjected to CT-PNB and vice versa. If no diagnosis could be made even after the patient having undergone both the procedures, the next course of action was determined in the departmental meeting comprising of two pulmonologists, one radiologist, and one thoracic surgeon. A final diagnosis was made based on histopathology findings which were considered as gold standard.

**Procedure**

**Radial endobronchial ultrasound-guided bronchoscopic lung biopsy**

FB was performed using a video bronchoscope (BF-1TQ180, distal end outer diameter 6.3 mm; working channel inner diameter 2.8 mm, Olympus, Tokyo, Japan), with a 20-MHz radial EBUS probe (UM-S20-20R; Olympus, Tokyo, Japan), guide sheath (K-203; minimum working channel required 2.6 mm; Olympus, Tokyo, Japan), and a bronchoscopic forceps (FB 231D, single use, oval fenestrated cup without needle, Olympus, Tokyo, Japan). Radial probe EBUS has a scanning view of 360 degrees and a tissue penetration of 4–5 cm providing good quality images. The bronchoscope was first positioned at the opening of the suspected segment with the lesion based on the CT findings. The guide sheath was advanced through the working channel of the bronchoscope, and after positioning in the desired segment, the radial EBUS probe was inserted through the guide sheath. The ultrasound probe was actuated and the lesion was localized on the ultrasound image. The position of the probe at the proximal end of the sheath was marked, and the length of the probe was measured after removing it from the sheath. The biopsy forceps were marked at the same distance using the rubber stopper and were then inserted through the guide sheath till the mark so as to reach the suspected lesion. This navigation technique has already been described in other studies. A total of five biopsies were taken from the same site.

**Computed tomography-guided percutaneous biopsy**

CT scan of the chest was performed using a 6-slice CT scanner (Siemens Healthcare, Germany) to localize the...
lesion, and the site was marked on the skin. The exact depth of the lesion and the needle trajectory required to reach the lesion were determined using CT images. The skin and the soft tissue were infiltrated with 2% lignocaine, and an 18-gauge lumbar puncture needle (used as a coaxial needle) was inserted through the chest wall till the periphery of the lesion, confirmed by a repeat CT. Five core biopsies were obtained using a 20-gauge core biopsy gun (Bard Max-Core Disposable Core Biopsy Instrument, MC 2016, USA) passed through the 18-gauge needle by coaxial technique.

Statistical analysis
Sensitivity, specificity, diagnostic accuracy, and complication rates of each procedure were determined according to standard definitions and compared using Fisher’s exact test. Clinically, significant difference in diagnostic accuracy and the rate of pneumothorax between the two groups was predefined at 15%. Continuous variables are expressed as mean ± 2 standard deviation, with comparison performed using an unpaired t-test. The impact of lesion size, lobar location, distance of the lesion from chest wall/hilum, and ultrasound characteristics on the diagnostic yield was evaluated as an exploratory subgroup analysis. The analysis was performed using the SPSS (Statistical Package for the Social Sciences) software (IBM Corp., Released 2013; IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA).

RESULTS

From December 22, 2014, to May 31, 2016, 96 patients were referred to our department for the evaluation of PPL. Of these, 46 patients were excluded from the study [Figure 1]. Thirty-two of them had PPL abutting the chest wall with no intervening lung parenchyma, and they successfully underwent ultrasound-guided transthoracic trucut biopsy. Six patients had evidence of intraluminal lesion on CT scan with bronchus cutoff sign which was confirmed on bronchoscopy, and a bronchial biopsy was taken from the endoluminal mass lesion. Seven patients had associated cervical lymphadenopathy, and a diagnosis was made by excision biopsy of the lymph node. All these patients were successfully diagnosed with a single procedure. One patient was excluded in view of poor general condition with hypotension and was unfit to undergo bronchoscopy. The remaining fifty patients were included in the study and were randomized to either radial EBUS or CT-PNB group according to the computer-generated randomization model. Overall, the two groups were evenly matched in terms of demographic, clinical, and radiological characteristics of the lesions [Tables 1 and 2]. The majority of tumors in both groups were adenocarcinoma (80%), and overall, there was no relationship between the histopathology and the type of procedure [Table 2].

The diagnostic accuracy of radial EBUS-guided biopsy was 72% (18/25) as compared to 84% (21/25) in the CT-guided biopsy group. The difference in the diagnostic accuracy was less than the predetermined value of 15% and was not statistically significant ($P = 0.306$). The diagnostic yield of the right upper lobe (RUL) lesions was significantly lower (20%) in the radial EBUS group as compared to CT-PNB group (83.3%) [Table 3]. Seven patients in radial EBUS group required CT-PNB and four patients in CT-PNB

| Table 1: Demographic and the clinical characteristics of patients in radial endobronchial ultrasound and computed tomography-guided percutaneous needle biopsy group |
|-----------------|-----------------|-----------------|
|                  | Radial EBUS     | CT-PNB          | $P$ value |
| Participants     | 25              | 25              | 0.739     |
| Males/females    | 21/4            | 20/5            | 0.713     |
| Hemoptysis (%)   | 7 (28)          | 4 (16)          | 0.306     |
| Chest pain (%)   | 11 (44)         | 10 (40)         | 0.774     |
| Current/past smokers (%) | 15 (60) | 17 (68) | 0.469 |

| Table 2: Radiological characteristics and histopathological diagnosis of patients in radial endobronchial ultrasound and computed tomography-guided percutaneous needle biopsy group |
|-----------------|-----------------|-----------------|
|                  | Radial EBUS     | CT-PNB          | $P$ value |
| Participants     | 25              | 25              | 0.67      |
| Size of lesion (cm), mean±2 SD | 2.80±0.9 | 2.9±0.7 | 0.545 |
| Distance from hilum (cm), mean±2 SD | 3.9±1.1 | 3.7±1.2 | 0.750 |
| Lobar position, n (%) | 0.924 |
| Lower lobes      | 12 (48)         | 12 (48)         | 0.924     |
| Right upper lobe | 5 (20)          | 6 (24)          |           |
| Left upper lobe  | 8 (32)          | 7 (28)          |           |
| Histopathological diagnosis, n (%) | 0.804 |
| Adenocarcinoma   | 18 (72)         | 17 (68)         |           |
| Squamous cell carcinoma | 5 (20) | 5 (20) | 0.669 |
| Undifferentiated nonsmall cell carcinoma | 1 (4) | 2 (8) | 0.701 |
| Tuberculosis     | 1 (4)           | 1 (4)           | 0.861     |

EBUS: Endobronchial ultrasound, CT-PNB: Computed tomography-guided percutaneous needle biopsy, SD: Standard deviation
group required radial EBUS for diagnosis. We could make a diagnosis in all the 50 patients (22 with radial EBUS and 28 with CT-PNB), and none of them required a surgical biopsy.

In the radial EBUS group, smaller PPL (<2 cm) could not be localized. The distance of the lesion from the chest wall or hilum had no effect on the diagnostic outcome. The ultrasound features such as continuous hyperechoic margin around the lesion and the presence of probe within the lesion were associated with significantly higher diagnostic yield with radial EBUS than when the probe was found on the side of the lesion. In 7 out of 25 patients with negative results on radial EBUS-guided biopsy, 4 patients had PPL in RUL (2 each on the apical and posterior segments of RUL), 1 in the left upper lobe (apicoposterior segment), 1 in the right lower lobe (superior segment), and 1 in the left lower lobe (segmental). Of these, 3 lesions in the RUL and 1 in the left upper lobe could not be localized with radial EBUS as the probe could not be negotiated into the target segments. Of the remaining three lesions, which could be visualized using radial EBUS but were still nondiagnostic on biopsy, the ultrasound probe was adjacent to the lesion in all of them ($P = 0.01$) [Table 4].

In the CT-PNB group, the only feature predictive of a positive yield was the successful entry of the biopsy needle into the lesion. In 4 out of 25 cases with negative results, the needle could not be inserted in 2 of them due to the overlying scapula and in the other 2 cases due to the occurrence of pneumothorax. The sensitivity of radial EBUS was 72% and of CT-PNB was 84% whereas the specificity of both the procedures was 100%. Radial EBUS was found to be very safe with no episode of pneumothorax, massive hemoptysis, and no patient requiring postprocedure hospital admission. Twenty-four percent patients experienced intrabronchial bleeding which was easily controlled with local instillation of adrenaline and/or iced saline. Mild hemoptysis was more common in the radial EBUS group but was self-limiting ($P < 0.001$). In the CT-PNB group, significantly higher rate of pneumothorax (20% vs. 0%; $P = 0.03$) was observed which was greater than the predetermined difference of 15%. All five patients who developed pneumothorax were hospitalized (three had Intercostal drainage tube (ICD) insertion and two received supplemental oxygen) [Table 5].

The biopsy material obtained by either of the procedures (5 biopsies) was sufficient for further immunohistochemistry and molecular studies.

The representative radial EBUS images are shown [Figures 2-6].

**DISCUSSION**

We found the diagnostic accuracy of radial EBUS to be comparable with CT-guided biopsy for PPL with a significantly lower risk of pneumothorax. Specific radiological features such as RUL and smaller lesions were associated with a lower yield of radial EBUS while ultrasound features of continuous hyperechoic margin and ability to localize the probe within the lesion predicted a higher yield.

The diagnostic accuracy of radial EBUS in our study was comparable to that in the previously published studies and meta-analysis. The diagnostic outcomes of CT-guided biopsy varied across published studies due to heterogeneity in the study design, inclusion criteria, size, and nature of peripheral lesions sampled. However, it has been generally found to be higher in malignant (90%) than benign (80%) lesions. The diagnostic accuracy in our study for CT-PNB was higher than that published in literature as most of our patients had malignancy. The poor diagnostic yield of radial EBUS for the RUL lesions was in concordance with previous studies. We did not find radial EBUS to be useful for...
RUL lesions; however, a number of such lesions were very small to give any definite opinion. Similar to our findings, the poor diagnostic yield of radial EBUS for lesions smaller than 2 cm was also observed in other studies.[11,21,22]

The major advantage of radial EBUS was its excellent safety profile with no patient experiencing pneumothorax or requiring hospitalization postprocedure in our study. The absence of pneumothorax in the radial EBUS group indicates that the pleura was not included in the biopsy when the lesion was localized with the ultrasound probe. All the patients who had pneumothorax belonged to CT-PNB group. The rates of pneumothorax with two procedures observed in our study were comparable to the published studies.[4,6,12]

Our findings add to the existing data and suggest that radial EBUS has a lower diagnostic yield for the RUL and lesions <2 cm. Because of its comparable diagnostic accuracy and low complication rates, it should be preferred over CT-PNB for all other PPLs not abutting the chest wall. Our study also highlights the importance of proper localization of lesion with probe well within it as this was associated with a higher diagnostic yield. These findings suggest that when the probe was in the center of the lesion, there was a transmural invasion of the bronchus by the tumor than when it was adjacent to the lesion. In the latter case, forceps opened and closed outside the lesion

Table 5: Comparison of complications between two groups

|                          | Radial-EBUS, n (%) | CT-PNB, n (%) | P value | Risk difference (95% CI) |
|--------------------------|--------------------|---------------|---------|--------------------------|
| Pneumothorax             | 0                  | 5 (20)        | 0.03    | −0.20 (−0.37 to −0.03)   |
| Bleeding                 | 6 (24)             | 4 (16)        | 0.476   | 0.08 (−0.14 to 0.30)     |
| Hemoptysis               | 6 (24)             | 0             | <0.001  | 0.24 (0.07 to 0.41)      |
| Chest pain               | 3 (12)             | 6 (24)        | 0.184   | −0.12 (−0.33 to 0.09)    |
| Hospitalization          | 0                  | 5 (20)        | 0.03    | −0.20 (−0.37 to −0.03)   |

CI: Confidence interval, EBUS: Endobronchial ultrasound, CT-PNB: Computed tomography-guided percutaneous needle biopsy

Figure 2: Radial endobronchial ultrasound image of normal peripheral air-filled lung – typically described as snowstorm-like appearance without margins

Figure 3: Radial endobronchial ultrasound image showing ultrasound probe in the center of the lesion with continuous hyperechoic margin and heterogeneous internal echoes (adenocarcinoma in this case)

Figure 4: Radial endobronchial ultrasound image showing hyperechoic dots suggestive of air bronchograms (tuberculosis in this case)

Figure 5: Radial endobronchial ultrasound image showing lesion with heterogeneous internal echoes but without continuous hyperechoic margin (squamous cell carcinoma)
resulting in a negative biopsy. Hence, the bronchoscopist must ensure that the ultrasound probe is located well within the PPL by scanning multiple segments before taking a biopsy.

**Strengths and limitations**

Our study had several strengths. It was a randomized controlled comparative trial using a computer-generated randomization model, thus eliminating any kind of selection bias. We carefully excluded PPL abutting the chest wall (USG-guided transthoracic biopsy) and those with endobronchial extension (bronchoscopic biopsy). We included only those PPLs surrounded by lung parenchyma on all sides in which the decision to perform either radial EBUS or CT-PNB as the first investigation is often intuitive. The other major strength of our study is the similar clinicoradiologic features of lesions in both the groups, thus taking away any advantage for a particular group for the diagnostic outcome. Our results will help the clinicians in appropriate decision-making while evaluating the PPL.

We recognize certain limitations in our study. The number of patients with RUL lesions was small in our study, and the low diagnostic yield of radial EBUS in these patients needs to be confirmed in larger trials with more number of such cases. Ours being a tertiary care referral department, the majority of PPLs in our study were of malignant etiology; therefore, differences in ultrasound features between benign and malignant lesions could not be determined. The presence of a continuous hyperechoic margin due to compression of surrounding lung and heterogeneous echoes on ultrasound has been linked to malignant etiology. We noticed these features in the majority of our patients. All the procedures were performed by the same group of clinicians at a single center, and the generalization of our results to other patient cohorts with PPL with different clinicoradiologic characteristics may not be applicable and would also depend on the level of expertise and competence of the treating physician in radial EBUS and CT-guided biopsies. We did not use ultrathin bronchoscope, fluoroscopy, electromagnetic navigation bronchoscopy, or virtual bronchoscopy with radial EBUS, all of which could have further improved the diagnostic accuracy of radial EBUS-guided biopsy by helping to localize smaller lesions. These techniques may be appropriate for selected patients though the selection criteria remain unclear. We did not combine biopsy with other modalities such as bronchial aspirate and brush cytology in the radial EBUS group, which could have further increased the diagnostic yield. Further studies will be more effective if performed as multicenter trials to confirm replication of similar results.

**CONCLUSION**

Radial EBUS-guided BLB is an extremely safe procedure with an acceptable diagnostic accuracy in the evaluation of PPL not abutting the chest wall. The high rate of pneumothorax with CT-PNB precludes its acceptance as the investigation of choice. Specific radiological features such as RUL and smaller lesions are associated with a lower yield of radial EBUS while ultrasound features of continuous hyperechoic margin and ability to localize the probe within the lesion predict a higher yield. Both the procedures are complimentary to each other and their judicious use is essential to achieve a high diagnostic accuracy with minimal complications. Lack of operator experience and limited availability of radial EBUS are the major obstacles which we need to overcome in future.

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**Conflicts of interest**

There are no conflicts of interest.

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