Original Article

Radial endobronchial ultrasound for the diagnosis of bronchoscopically invisible lesions: First case series from India

Kedar Ravi Hibare, Rajiv Goyal, Chetan Nemani, Rao Avinash, Bajpai Ram[1], Batra Ullas

Rajiv Gandhi Cancer Institute and Research Center, New Delhi, [1]Nayati Healthcare and Research Center, Mathura, Uttar Pradesh, India

ABSTRACT

Background: A peripheral, bronchoscopically invisible pulmonary lesion is a diagnostic challenge. Transthoracic needle aspiration has long been the investigation of choice but runs the risk of pneumothorax (up to 44%). Newer technologies like radial endobronchial ultrasound (R-EBUS) offer a safer approach. We present our results of R-EBUS in the diagnosis of bronchoscopically invisible lesions. This is the first large case series from India. **Aims:** (1) To determine the yield of R-EBUS for the diagnosis of bronchoscopically invisible lesions. (2) To compare the yields of forceps versus cryobiopsies in the diagnosis of these lesions. **Setting:** Tertiary care cancer center. **Design:** Prospective study. **Methods:** Consecutive patients presenting between January and October 2015 with bronchoscopically invisible peripheral pulmonary lesions were included. R-EBUS was used to localize and sample the lesion and the yields were analyzed. Yields of cryo and forceps biopsy were compared where both methods had been used. Data were analyzed using SPSS version 22. **Results:** A definite diagnosis obtained in 67.3% (37/55) patients with no major complications. No significant difference was found in yield between: (1) small (<3 cm) and large (>3 cm) lesions: (46.2% versus 78.6%, $P = 0.38$). (2) central and adjacent lesions: 61.5% versus 70%. (3) forceps and cryobiopsy ($n = 28$, 75% versus 67.9% $P = 0.562$). **Conclusions:** R-EBUS is a safe procedure in our setting and its yield is comparable to that reported in literature. The yield of central and adjacent lesions and forceps or cryobiopsy appears similar. Further refinements in the technique could improve yield.

KEY WORDS: Bronchoscopically invisible lesion, peripheral pulmonary lesion, radial endobronchial ultrasound

Address for correspondence: Dr. Kedar Ravi Hibare, 203, Sri Paduka, 1st L Mn, 1st Blk, N'bhavi – 2nd Stg, Bengaluru - 560 072 Karnataka, India.
E-mail: kedarhibare@gmail.com

INTRODUCTION

Most patients presenting with solitary pulmonary nodule (SPN) or peripheral pulmonary lesion (PPL) need an accurate diagnosis. By definition, SPN is a lesion <3 cm in size, not associated with atelectasis or adenopathy and surrounded by normal lung parenchyma. Larger lesions >3 cm are called pulmonary masses. Both types of lesions may be bronchoscopically invisible making the diagnosis more challenging. Traditionally, the approach to diagnose a PPL or SPN would be either by a percutaneous transthoracic needle aspiration or biopsy under ultrasound or computed tomography scan (CT) guidance or a bronchoscopic transbronchial biopsy under fluoroscopic guidance. The first technique suffers from a high rate of complications-namely pneumothorax (up to 44%)[1,2] while the second has a low yield, especially for smaller lesions.[3]

With the advent of newer technologies, accessing smaller lesions with greater accuracy and safety has become

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.197100

How to cite this article: Hibare KR, Goyal R, Nemani C, Avinash R, Ram B, Ullas B. Radial endobronchial ultrasound for the diagnosis of bronchoscopically invisible lesions: First case series from India. Lung India 2017;34:43-6.

possible. Radial endobronchial ultrasound (R-EBUS) is one such modality to obtain biopsies from PPLs. A guide sheath can be used as a conduit to access the PPL after localizing it with R-EBUS probe and biopsies taken via forceps inserted through it.[4] In addition, fluoroscopic guidance may also be used during the procedure to ensure greater accuracy.[5] In an attempt to get more representative tissue, some workers have successfully obtained cryobiopsies from such peripheral lung lesions.[6]

In this study, we present our initial experience with use of R-EBUS for bronchoscopically invisible PPLs/masses.

METHODS

This was a retrospective observational study conducted at Rajiv Gandhi Cancer Hospital and Research Institute, a tertiary care cancer referral center between January 2015 and October 2015. The study protocol was approved by the ethics committee of the institute. Written informed consent was obtained from all patients.

Inclusion and exclusion criteria

All patients requiring R-EBUS for diagnosis of a PPL were eligible for inclusion in the study. We defined PPLs as any lesion, which was bronchoscopically invisible and needed guidance for obtaining a tissue biopsy irrespective of its size. Patients with an endobronchial growth, pure ground-glass lesions, or those with contraindications for bronchoscopy and transbronchial biopsies were excluded from the study. Patients in whom the lesion could not be localized by R-EBUS within 20 min of the start of the procedure were also excluded from the study.

Methodology

The central airways were first assessed bronchoscopically (BF type 1T 150 bronchovideoscope ED 6.0 ID 2.8, Olympus Medical Systems, India). If an endobronchial tumor growth was visible, the patient was excluded from the study. Based on the CT of the thorax, an R-EBUS probe (UM-S20-17S; Olympus, Tokyo, Japan) sometimes with a flexible guide sheath was advanced through the working channel of the bronchoscope, into the suspected bronchial segments to detect the PPL. Additional fluoroscopy was used, if considered necessary, to ensure that the lesion was accessed with confidence. Once the lesion was detected by R-EBUS probe (as evidenced by a change in ultrasound characteristics), the length inside the bronchoscope and the position of the probe in relation to the lesion was noted. This navigation technique has already been described in other studies.[4,7,8] Lesions, when visible on ultrasound all around the probe, were classified as central, whereas those in which the image was only partially present was called adjacent. The mini probe was removed while the guide sheath remained in position as a conduit for the forceps.

All patients randomly had up to 3–6 transbronchial biopsies of their lung lesion through each modality with forceps and/or with the cryoprobe. For the forceps biopsy, a commercially available reusable forceps (fenestrated forceps with needle needing 2 mm working channel, FB-34C-1 Olympus) was used through the guide sheath. When guide sheath was not used a larger forceps (Radial Jaw 4 Pulmonary Biopsy Forceps, pulmonary standard capacity needle 1.8 mm jaw OD, 100 cm length and 2 mm working channel; Boston Scientific, Natick, MA, USA) was used for biopsy. The correct position of the guide sheath was reconfirmed at the end of the three biopsies by R-EBUS and/or fluoroscopy to exclude misplacement. If the larger forceps was used for biopsy, each attempt at biopsy was preceded by localization of lesion by R-EBUS and/or fluoroscopy to confirm accuracy.

Cryobiopsy was obtained with a flexible cryoprobe (90 cm in length, 1.9 mm in diameter, ERBE, Medizintechnik GmbH, Tu¨bingen, Germany), which was passed through the working channel of the bronchoscope into the bronchial subsegment leading to the lesion. Guide-sheath technique was not used when cryobiopsies were performed. After placement, which was on occasion confirmed with fluoroscopy, the tip was cooled for 4 s and immediately thereafter the probe was retracted with the bronchoscope *en bloc*. The frozen biopsy was thawed in normal saline and fixed in formalin. As with the forceps, after each cryobiopsy, the lesion was reconfirmed by R-EBUS probe and fluoroscopy if required. About six biopsies, i.e., three each with the forceps and the cryoprobe, were obtained prior to the termination of the procedure. Bronchial lavage was taken in each case for microbiology and or cytology.

Data were anlayzed using SPSS, version 22, Armonk NV, USA.

RESULTS

During the study period, a total of 64 cases were studied in which R-EBUS was performed either independently or in conjunction with CP-EBUS. In 9 (14%) cases, the lesion was not accessible within 20 min and hence they were excluded from the study. In the remaining 55 patients, included in the final analysis a total of 58 procedures were performed, i.e., in 3 patients the procedure had to be repeated before histopathologic results were obtained.

Of the 55 cases, 37 (67%) were male with mean age of 61.8 ± 7.2 years and 18 (33%) were female with a mean age of 59.3 ± 11.2 years. Right upper lobe lesions (n = 16, 29.1%) were the most common followed by left upper lobe (n = 11, 20.0%). On R-EBUS, 70.9% lesions were central while the rest were adjacent to the probe. 50.9% lesions in the study were >3 cm in size while true SPNs defined as ≤3 cm were 24%. Since many patients had

their scans performed at other centers, exact data on size were missing for 14 patients. Fluoroscopy (n = 7, 13%) and guide sheath (n = 11, 20%) were used at physician discretion to localize lesions during procedures.

Histopathologic confirmation, which was the primary objective of the study was obtained in 37 (67.3%) of the lesions [Table 1]. When microbiological data was included, the overall yield in the study was 70.9%. For lesions >3 cm the yield was 78.6% while for those <3 cm it was 46.2% (P = 0.38). The yield for centrally located lesions was 61.5% while that for an adjacent lesion on R-EBUS was 70%.

Both cryo and forceps biopsies were performed in 28 cases. The yield by forceps was obtained in 21 (75%) and for cryobiopsies was 19 (67.9%); however, the difference was not statistically significant (P = 0.562) [Table 2]. The forceps and cryobiopsies were both positive in 17 (60.7%) cases in the study. In 2 patients cryobiopsy yielded histopathology confirmation where forceps biopsies were negative, while in 4 cases where forceps yielded the result, cryobiopsies being negative. Notably on visual inspection the size of all cryobiopsies was larger than that of forceps biopsies; however, no morphometric analysis of biopsy samples was done.

Moderate bleeding (>30 ml)[9] was noted in two patients; hemostasis was achieved subsequently. One patient desaturated during the procedure and recovered after the procedure was stopped temporarily.

DISCUSSION

In this study, R-EBUS was used to sample bronchoscopically invisible lung lesions in 55 cases, and we achieved a yield of 67% where the lesion could be located. This is comparable to early studies published in literature where yields between 53% and 80% have been reported with the use of R-EBUS.[4,7,8,10-21] The reasons for the variable yields in these studies range from number of patients with smaller lesions, operator's expertise in performing R-EBUS, and the use of guide sheath. Also additional equipment, like a thin bronchoscope and navigation have been used, in some studies, for more accurate localization. Importantly,

Table 1: Comparison of yield with varying factors

HPE	HPE + microbiology of BAL	*P*
37 (67.3%)	39 (70.9%)	
Size of lesion ≤3 cm	**Size of lesion >3 cm**	
46.2%	78.6%	0.38
Central lesion	**Adjacent lesion**	
61.5%	70%	0.726

BAL: Bronchoalveolar lavage, HPE: Histopathological examination

Table 2: Forceps versus cryobiopsy yields

	n=28 (%)	*P*
Forceps	21 (75)	0.562
Cryobiopsy	19 (67.9)	

17 (60.7%) both forceps biopsy and cryobiopsy were positive

there is hardly any data from the Indian subcontinent on the use of R-EBUS. Recently, a case report on R-EBUS was published from India describing its utility.[22] However, to our knowledge, this is the first case series on R-EBUS from India.

Our study looked at the yield for all lesions that were "bronchoscopically invisible." In this study, 50.9% lesions were >3 cm and 24% were <3 cm in size. As mentioned earlier many patients had CT scans done from other centers where either the size of the lesion was not stated or mapping the path to the lesion was difficult as thin section protocols were unavailable. Our yield was higher for patients with larger lesions (78.6%), which is similar to the yield reported in literature. The yield however for the smaller lesions was lower at 46.2% though it compares with the other reports in the literature.[3,23] We did not use the guide sheath and fluoroscopy consistently in all the patients. The yield might have been better if we had combined R-EBUS with a guide sheath, a thin bronchoscope, and fluoroscopy in all cases.

As mentioned earlier, in 9 (14%) cases the lesion could not be located by R-EBUS. A thin section HRCT scan (or a virtual navigation modality) would help in better judgment of mapping the path to the lesion. In our study, we had no access to any navigational modality and due to resource constraints; we did not repeat CT scans for patients who already had this investigation done from another center before seeking our consultation. Many therefore had conventional CT scans, which could provide only limited help in mapping a path to the lesion. In the literature, some workers have shown excellent results by combining navigation through virtual bronchoscopy or electromagnetic navigation with R-EBUS.[18,24,25]

We also did not perform a transbronchial needle aspiration or collect samples of the guide sheath washings after completing the procedure. Both these techniques have also shown by various workers to improve yield.[13,26-28] However, this technology has yet to be introduced in India.

The R-EBUS image obtained after localization of the lesion can be of two different types depending on whether the probe is at the center of the lesion or adjacent to it. Many researchers have found that the yield in the central lesion is better than with adjacent lesions.[29] In our series, out of a total of 49 cases, 39 were central while 10 showed an adjacent type image on R-EBUS. However, the yields from these were almost similar at 61.5% for central and 70% for the adjacent type of lesions. This lack of difference in yield for these two types of lesions in our series could be due to the relatively small number of "adjacent" lesions in our study.

Cryobiopsies from PPLs have been found to be safe and feasible by Schuhmann *et al*. in a series of about forty patients.[6] Theoretically, because cryobiopsies are larger than conventional forceps biopsy specimens and also pick

up a spherical core of tissue surrounding the probe, the yield should be higher. We were able to study this in 28 of our cases where both cryobiopsies and conventional forceps biopsies were obtained. However, the difference in yield was not statistically significant. This finding is similar to the results of Schuhmann *et al*. who also failed to show any difference in yield despite using a prototype 1.4 mm thin cryoprobe. It is possible that a thinner cryoprobe, which could be passed through the working channel of a thin bronchoscope, through a guide sheath, with additional fluoroscopic guidance, could enhance yield.

Finally, the R-EBUS procedure is safe as we found no significant complication except bleeding in a few patients, which was easily controlled with simple measures.

CONCLUSIONS

Yields with R-EBUS of bronchoscopically invisible lesions, obtained with currently available equipment, at our center are modest and comparable to those reported in literature. Furthermore, the current study found no additional yield with the use of cryoprobe biopsy.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Gupta S, Krishnamurthy S, Broemeling LD, Morello FA Jr., Wallace MJ, Ahrar K, *et al*. Small (</=2-cm) subpleural pulmonary lesions: short- versus long-needle-path CT-guided biopsy – comparison of diagnostic yields and complications. Radiology 2005;234:631-7.
2. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Ann Intern Med 2011;155:137-44.
3. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed.: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143 5 Suppl: e142S-65S.
4. Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, *et al*. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 2004;126:959-65.
5. Casutt A, Prella M, Beigelman-Aubry C, Fitting JW, Nicod L, Koutsokera A, *et al*. Fluoroscopic-guided radial endobronchial ultrasound without guide sheath for peripheral pulmonary lesions: A safe and efficient combination. Arch Bronconeumol 2015;51:338-43.
6. Schuhmann M, Bostanci K, Bugalho A, Warth A, Schnabel PA, Herth FJ, *et al*. Endobronchial ultrasound-guided cryobiopsies in peripheral pulmonary lesions: a feasibility study. Eur Respir J 2014;43:233-9.
7. Yamada N, Yamazaki K, Kurimoto N, Asahina H, Kikuchi E, Shinagawa N, *et al*. Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest 2007;132:603-8.
8. Yoshikawa M, Sukoh N, Yamazaki K, Kanazawa K, Fukumoto S, Harada M, *et al*. Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without x-ray fluoroscopy. Chest 2007;131:1788-93.
9. Herth FJ, Becker HD, Ernst A. Aspirin does not increase bleeding complications after transbronchial biopsy 2002;122:1461-4.
10. Herth FJ, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. Eur Respir J 2002;20:972-4.
11. Kikuchi E, Yamazaki K, Sukoh N, Kikuchi J, Asahina H, Imura M, *et al*. Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. Eur Respir J 2004;24:533-7.
12. Herth FJ, Eberhardt R, Becker HD, Ernst A. Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. Chest 2006;129:147-50.
13. Asahina H, Yamazaki K, Onodera Y, Kikuchi E, Shinagawa N, Asano F, *et al*. Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. Chest 2005;128:1761-5.
14. Shirakawa T, Imamura F, Hamamoto J, Honda I, Fukushima K, Sugimoto M, *et al*. Usefulness of endobronchial ultrasonography for transbronchial lung biopsies of peripheral lung lesions. Respiration 2004;71:260-8.
15. Paone G, Nicastri E, Lucantoni G, Dello Iacono R, Battistoni P, D'Angeli AL, *et al*. Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest 2005;128:3551-7.
16. Yang MC, Liu WT, Wang CH, Lin HC, Chen HC, Chou CL, *et al*. Diagnostic value of endobronchial ultrasound-guided transbronchial lung biopsy in peripheral lung cancers. J Formos Med Assoc 2004;103:124-9.
17. Dooms CA, Verbeken EK, Becker HD, Demedts MG, Vansteenkiste JF. Endobronchial ultrasonography in bronchoscopic occult pulmonary lesions. J Thorac Oncol 2007;2:121-4.
18. Asano F, Matsuno Y, Tsuzuku A, Anzai M, Shinagawa N, Yamazaki K, *et al*. Diagnosis of peripheral pulmonary lesions using a bronchoscope insertion guidance system combined with endobronchial ultrasonography with a guide sheath. Lung Cancer 2008;60:366-73.
19. Chao TY, Lie CH, Chung YH, Wang JL, Wang YH, Lin MC. Differentiating peripheral pulmonary lesions based on images of endobronchial ultrasonography. Chest 2006;130:1191-7.
20. Chung YH, Lie CH, Chao TY, Wang YH, Lin AS, Wang JL, *et al*. Endobronchial ultrasonography with distance for peripheral pulmonary lesions. Respir Med 2007;101:738-45.
21. Fielding DI, Robinson PJ, Kurimoto N. Biopsy site selection for endobronchial ultrasound guide-sheath transbronchial biopsy of peripheral lung lesions. Intern Med J 2008;38:77-84.
22. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Use of radial probe endobronchial ultrasound for the diagnosis of peripheral pulmonary lesion: First report from India. Lung India 2016;33:212-5.
23. Steinfort DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. Eur Respir J 2011;37:902-10.
24. Eberhardt R, Morgan RK, Ernst A, Beyer T, Herth FJ. Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. Respiration 2010;79:54-60.
25. Eberhardt R, Anantham D, Herth F, Feller-Kopman D, Ernst A. Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions. Chest 2007;131:1800-5.
26. Reichenberger F, Weber J, Tamm M, Bolliger CT, Dalquen P, Perruchoud AP, *et al*. The value of transbronchial needle aspiration in the diagnosis of peripheral pulmonary lesions. Chest 1999;116:704-8.
27. Peschke A, Wiedemann B, Höffken G, Koschel D. Forceps biopsy and suction catheter for sampling in pulmonary nodules and infiltrates. Eur Respir J 2012;39:1432-6.
28. Zaric B, Stojsic V, Carapic V, Kovacevic T, Stojanovic G, Panjkovic M, *et al*. Radial endobronchial ultrasound (EBUS) guided suction catheter-biopsy in histological diagnosis of peripheral pulmonary lesions. J Cancer 2016;7:7-13.
29. Chen A, Chenna P, Loiselle A, Massoni J, Mayse M, Misselhorn D. Radial probe endobronchial ultrasound for peripheral pulmonary lesions. A 5-year institutional experience. Ann Am Thorac Soc 2014;11:578-82.