

# Efficacy and safety of electromagnetic navigation bronchoscopy with or without radial endobronchial ultrasound for peripheral lung lesions

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## ABSTRACT

**Background and Objectives:** Electromagnetic navigation bronchoscopy (ENB) is a promising new technology to increase the diagnostic yield of peripheral lung and mediastinal lesions. Conventional flexible bronchoscopy has a limited yield in peripheral pulmonary lesions, even in experienced hands. Radial endobronchial ultrasound (r-EBUS) with its real-time imaging capability can help to diagnose peripheral pulmonary lesions. In the present study, we aimed to investigate the diagnostic yield and safety of ENB with or without r-EBUS for peripheral lung lesions. **Materials and Methods:** This study was conducted in a tertiary medical center, and 56 consecutive patients who were thought to be the best candidates for bronchoscopic biopsies at a multidisciplinary meeting were enrolled. ENB was performed under conscious sedation by using an electromagnetic tracking system with multiplanar reconstruction of previously acquired computed tomography (CT) data. Sampling was performed by biopsy forceps, endobronchial brush, and bronchoalveolar lavage. **Results:** Fifty-six patients (50 men and 6 women; mean age, 60 ± 9 years) were studied. While an electromagnetic navigation system was used in all patients, r-EBUS was used in 26 of 56 patients. The median diameter of the lesions was 30 mm (interquartile range: 23-44 mm). Mean distance of the lesions from the pleura was 14.9 ± 14.6 mm. Mean procedure time was 20 ± 11.5 min. Mean registration error was 5.8 ± 1.5 mm. Mean navigation error was 1.2 ± 0.5 mm. The diagnostic yield of the procedure was 71.4% for peripheral lesions (non-small cell lung cancer = 23, small cell lung cancer = 3, benign diseases = 14). Pneumothorax occurred in only 1 patient (1.7%). **Conclusion:** ENB with or without r-EBUS is a safe, efficient, and easily applied method for sampling of peripheral lung lesions, with high diagnostic yield independent of lesion size and location.

**Key words:** Diagnostic yield, electromagnetic navigation bronchoscopy (ENB), peripheral lung lesion, transbronchial biopsy

## INTRODUCTION

Flexible bronchoscopy has been used primarily for the sampling of lesions in the tracheobronchial tract.<sup>[1]</sup>

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**How to cite this article:** Ozgul G, Cetinkaya E, Ozgul MA, Abul Y, Gencoglu A, Kamiloglu E, *et al.* Efficacy and safety of electromagnetic navigation bronchoscopy with or without radial endobronchial ultrasound for peripheral lung lesions. *Endosc Ultrasound* 2016;5:189-95.

### Access this article online

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DOI:

10.4103/2303-9027.183979

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**Received:** 2015-03-25; **Accepted:** 2015-05-04

Diagnostic yield from flexible bronchoscopy in the absence of visible endobronchial abnormality varies, ranging 20-84% for malignant parenchymal lesions and 35-56% for benign lesions.<sup>[2-6]</sup> The diagnostic yield of bronchoscopy is particularly low in lesions  $\leq 2$  cm that are located in the outer third of the lung,<sup>[2,4]</sup> while computed tomography (CT)-guided transthoracic needle aspiration (TTNA) biopsy may provide more accurate diagnosis of the peripheral lung lesions. However, high risk of pneumothorax, ranging 23%-44%, is the limitation of TTNA biopsy.<sup>[7-10]</sup> In addition to TTNA biopsy, surgical biopsy via video-assisted thoracoscopic surgery (VATS) and thoracotomy are other invasive techniques for the diagnosis of the peripheral lung lesions. Thus, alternative diagnostic approaches are necessary in this situation. We therefore used the combination of electromagnetic navigation bronchoscopy (ENB) and radial endobronchial ultrasound (r-EBUS) with the assumption that this approach would increase the diagnostic yield for peripheral lung lesions while decreasing the complication rate.

## MATERIALS AND METHODS

### *Patients*

This study conforms to the principles outlined in the Declaration of Helsinki. The local Ethics Committee approved the study. Fifty-six patients who were admitted to the Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital, the largest tertiary interventional pulmonology center in Turkey, were included in the study. Subjects who were candidates for nonemergency bronchoscopy and aged over 18 years with peripheral lung lesions or solitary pulmonary nodules without any visible endobronchial lesion by bronchoscopy, were included. The present study excluded any subject who could not tolerate conscious sedation or a flexible bronchoscopy procedure. All the patients were discussed in a multidisciplinary meeting, where a thoracic surgeon, an interventional pulmonologist, and an interventional radiologist were available, and the bronchoscopic approach was decided as a safer option over surgical biopsy or computed tomography (CT)-guided TTNA due to underlying comorbidities, poor pulmonary function tests, or severe bullous changes on CT scan.

### *Bronchoscopy*

Flexible bronchoscopy (BF-XP 160, Olympus, Tokyo, Japan) was performed with topical anesthesia and

intravenous (IV) sedation. Topical anesthesia was achieved by applying two puffs of 10% lidocaine to the oropharyngeal mucosa of each spontaneously breathing patient. The patients were premedicated with IV midazolam 2-5 mg. Patient monitoring consisted of continuous finger pulse oximetry and electrocardiography.

### *Electromagnetic navigation procedure*

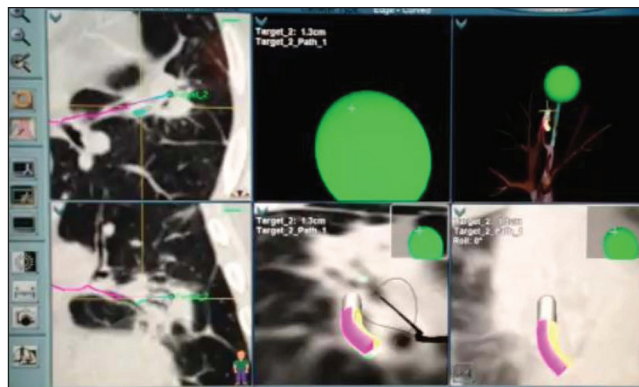
An ENB system (superDimension/Bronchus, superDimension, Inc., Minnesota, Plymouth, MN, USA) was used for all procedures. The system is composed of the following four components:

1. Electromagnetic localization board: This board is 1 cm in thickness with the dimension of  $47 \times 56$  cm<sup>2</sup>, radiating low-frequency electromagnetic waves. The board is located under the bronchoscopy table mattress.
2. Sensor probe: It can navigate the bronchial tree and has eight easily movable navigated pathway mechanisms. The sensor probe is 1 mm in diameter and 8 mm in length and is connected to a flexible metal cable. This constitutes the main assembly of the device (locatable guide).
3. EWC (Extended working channel): A sensor probe or flexible forceps or brush is deployed to the target lesion through this EWC, which is 130 mm in length and 1.9 mm in diameter.
4. The computer software and monitor: This system enables the bronchoscopist to view the reconstructed three-dimensional CT scans of the object's anatomy into multiplanar, including coronal, sagittal, and axial, views together with superimposed graphic information depicting the position of the sensor probe—allowing the bronchoscopist real-time navigation to biopsy endobronchially invisible lesions through the EWC.<sup>[11-13]</sup>

All patients had multislice CT scans of the chest done, with a slice thickness of 1 mm and interval of 0.8 mm. The digitized information from each patient's CT scan was imported into the electromagnetic navigation system in which multislice views of the chest and virtual bronchoscopy images were reconstructed. The target points, which are anatomic landmarks, including the main carina, right and left upper lobe carina, middle lobe carina, and left lower lobe carina, were identified and thus radiological mapping was completed; these data points were then loaded to the electromagnetic navigation system. The navigation error is the closest distance between the sensor probe and the lesion center.

The patients were placed on supine position on the localization board. Three reference electrodes were placed on the anterior chest. The anatomic landmarks, such as carina of the lobes in both right and left lung, are touched with the sensor probe during bronchoscopic examination called endobronchial mapping. When these points were touched with the sensor, they were simultaneously recorded by the navigation system. The system software correlated data obtained during radiological mapping with data obtained during real-time bronchoscopy mapping, providing a registration error. Afterward, flexible bronchoscopy was done with the sensor on its tip pointed toward the target [Figure 1]. When the sensor probe was in relation to the nearest part of the target lesion, the EWC was mechanically locked. Transbronchial forceps biopsy, brushing, and bronchoalveolar lavage were performed in all subjects. Rapid onsite cytopathologic examination was not available for any of the patients. All patients had chest x-rays done after the procedure to rule out pneumothorax.

If the ENB-guided biopsy provided a definitive histopathologic diagnosis, this was marked as diagnostic success by ENB. If the result of the ENB-guided biopsy was nondiagnostic, then other procedures, such as CT-guided TTNA biopsy or surgery, were performed to achieve a definitive diagnosis. If both procedures failed to reveal a definitive diagnosis, these cases were also considered as diagnostic success for ENB. However, if an ENB-guided biopsy provided a negative diagnosis and the subjects were unable or unwilling to undertake further diagnostic testing, clinical and radiologic follow-up was used to observe stability (range 6-24 months). If the lesions remained stable radiologically, then the negative result of ENB-guided biopsy was marked as



**Figure 1.** Real-time navigation screen arrangement

a diagnostic success. Diagnosis made by TTNA biopsy or by surgery other than the ENB-guided biopsy was considered to be ENB failure.

#### *Combined electromagnetic navigation bronchoscopy and electromagnetic navigation bronchoscopy*

r-EBUS was used to confirm the target lesion location after the lesion was navigated by ENB in 26 of 56 patients (UM-BS20-26R, 20 MHz, Olympus, Tokyo, Japan). Once the lesion was located by ENB, the sensor probe was withdrawn and the r-EBUS probe (outer diameter 2.0 mm, length 850 mm) was inserted through the EWC. Normal air-filled alveolar tissue typically produces a “snowstorm-like” appearance. However, solid lesions are seen as darker and more homogeneous [Figure 2]. When such images were captured, the probe was considered to be located within or adjacent to the target lesion. The probe was then removed and biopsies were performed with disposable forceps. However, if no acceptable EBUS image was obtained, renavigation with ENB and subsequent reconfirmation with EBUS was attempted before biopsies were taken.

#### *Specimens*

Transbronchial biopsy specimens were collected into a formalin-filled cup for permanent surgical pathologic examination, while material obtained by brush and bronchoalveolar lavage were split for cytologic and microbiologic examinations.

#### *Statistical analysis*

The statistical analysis was made with the use of a commercially available statistical package, SPSS for Windows, Version 15.0 (IBM SPSS for Windows,



**Figure 2.** A pulmonary nodule seen on r-EBUS image in the center (a) and normal appearance of lung parenchyma around the nodule seen as “snowstorm” (b)

Version 15.0). Continuous variables were expressed as mean  $\pm$  standard deviation, while categorical variables were expressed as ratios. Categorical and discrete variables were compared using the chi-square ( $\chi^2$ ) test. Diagnostic yield (%) =  $100 \times$  ENB-guided biopsy-diagnosed cases/total number of patients with completed procedures. Pearson correlation analysis was made to investigate the possible association between diagnosis and size or location of peripheral lesions. For statistical tests of association,  $P < 0.05$  was considered significant.

## RESULTS

ENB was performed in 56 patients (50 men and 6 women; mean age  $60 \pm 9.6$  years; range 41-79 years). The median diameter of the lesions was 30 mm (interquartile range: 23-44 mm). Mean distance of the lesions from pleural surface was  $14.9 \pm 14.6$  mm. Mean procedure time was  $20 \pm 11.5$  min. Mean registration error was  $5.8 \pm 1.5$  mm. Mean navigation error was  $1.2 \pm 0.5$  mm. Number of forceps biopsy was  $4 \pm 1$ .

Localization of lesions included the right upper lobe ( $N = 21$ ; 37.5%), left upper lobe ( $N = 16$ ; 28.6%), right lower lobe ( $N = 9$ ; 16.1%), left lower lobe ( $N = 8$ ; 14.3%), and right middle lobe ( $N = 2$ ; 3.6%). Definitive diagnosis of the cases by ENB-guided biopsy included lung cancer ( $N = 26$ ), pneumonia ( $N = 2$ ), hamartoma ( $N = 1$ ), and other benign diseases ( $N = 11$ ). Of the 16 ENB-guided biopsy negative cases, all underwent further diagnostic testing and were found to be malignant: 14 cases with CT-guided TTNA biopsy and 2 cases with surgery [Table 1].

The diagnostic yield of ENB-guided biopsy was increased as the lesion size increased but it did not reach a statistically significant level ( $P = 0.065$ ) [Table 2]. When the lesions were analyzed by lobar distribution, there was a trend of the highest ENB yield in lesions being located in the right middle lobe (100%) and the lowest yield in the left upper lobe (56.2%), but because of the small sample size, this did not reach statistical significance ( $P = 0.59$ ) [Table 3].

The diagnostic yield in the ENB-only group was 71.42%. The sensitivity, specificity, positive predictive value, and negative predictive value for malignant diseases were 62%, 100%, 100%, and 47%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value for benign disease were

**Table 1. Final diagnosis of all cases by ENB and by other procedures**

Procedure	Diagnosis	Number of patients
ENB	Malignancies	26
	NSCLC	23
	SCLC	3
	Benign diseases	14
	Pneumonia	2
	Hamartoma	1
	Others	11
TTNA	Malignancies	14
	NSCLC	13
	SCLC	1
Surgery	Malignancies	2

ENB: Electromagnetic navigational bronchoscopy, TTNA: Transthoracic needle aspiration, NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer

**Table 2. Diagnostic yield by size of the peripheral lesions\***

Lesion size	Diagnosis/total	Diagnostic yield (%)
0-20 mm	5/9	55.5
20-40 mm	21/31	67.7
>40 mm	14/16	87.5
Total	40/56	71.4

\* $P = 0.065$

**Table 3. Diagnostic yield by the lobar distribution of the peripheral lesions**

Lobar distribution	Diagnosis/total	Diagnostic yield (%)
Left upper lobe	9/16	56.2
Right lower lobe	6/9	66.6
Left lower lobe	6/8	75
Right upper lobe	17/21	80.9
Right middle lobe	2/2	100
Total	40/56	71.4

100%, 62%, 47%, and 100%, respectively. In the group where ENB and r-EBUS were used, with 26 of the 56 (46.4%) patients, the diagnostic yield was 73.07%. The analysis of patients who had a positive diagnostic yield compared to a negative diagnostic yield showed no significant differences in registration error or navigation error. However, 11 of the 14 cases whose navigation error was below 5 mm had positive definitive diagnosis by ENB with the diagnostic yield of 78.5%. Pneumothorax occurred in only 1 (1.7%) of the patients, who was treated with tube thoracostomy.

## DISCUSSION

There is an increasing need for minimally invasive diagnostic procedures that would provide higher diagnostic yield for peripheral lung lesions. In addition, the patients in whom the conventional bronchoscopy



is nondiagnostic are usually referred for more invasive procedures, such as CT-guided TTNA biopsy or surgical biopsy. Both of these procedures are associated with higher costs and greater risk of complications.<sup>[14-16]</sup>

Identification of peripheral lung lesions using less invasive methods will decrease the necessity of surgical resection.

In a retrospective analysis, Hoffmann and Dienemann<sup>[17]</sup> reported that approximately 50% of the parenchymal lesions were benign. Radke *et al.*<sup>[18]</sup> showed that the number of benign lesions observed in screening programs exceeded 90%. ENB is a novel technique to help the diagnosis of endobronchially invisible lesions. In general, the diagnostic yield of ENB-guided biopsy of peripheral lung lesions has not exceeded 76% (range 62-76%) in the literature.<sup>[11,19-22]</sup> In a comparison study of r-EBUS and ENB, it has been shown that the two procedures used in combination provided a higher diagnostic yield in the sampling of peripheral lung lesions; 69% in only r-EBUS, 59% in only ENB sampling, and 88% in the combination of two procedures.<sup>[23]</sup> The present study has shown minimal increase in the diagnostic yield of peripheral lung lesions when r-EBUS was combined with ENB. The diagnostic accuracy in the only-ENB group was 71.4%, while it was 73% in the combined group. It is likely that due to a small sample size, this increase in diagnostic yield is not statistically significant.

In the present study, the diagnostic yield from ENB was independent of lesion size, lesion location, and technical issues, including registration or navigation error, similar to previously reported studies.<sup>[11,12,21,24]</sup> However, navigation error was shown to affect the diagnostic yield in one study by Makris *et al.* at the point of  $\leq 4$  mm. The overall diagnostic yield was 62.5% and increased to 77.2% if the navigation error was  $\leq 4$  mm.<sup>[19]</sup> Our study showed that the diagnostic yield increased from 71.4% to 78.5% if the navigation error was  $< 5$  mm, but this was not statistically significant. On the other hand, although diagnostic yield was independent of the size of the peripheral lesion in our study, the tendency was observed that diagnostic yield by ENB increased as the size of peripheral lesions increased, which was not statistically significant. In addition, although the diagnostic yield of the present study was independent of lobar distribution, the right middle lobe had a better yield compared to the other lobes. The highest

diagnostic yield and lowest diagnostic yield of the present study were in the right middle lobe (100%) and left upper lobe (56.2%), respectively. The higher yield in the right middle lobe and lower yield of the upper lobes may be attributed to the tendency for sharper angles in the upper lobes in the bronchial tree, making it a challenge to navigate even with a steerable sensor probe. On the other hand, navigation in the lower lobes is also affected by the movement of the diaphragm during respiration, leading to errors.<sup>[22]</sup>

The diagnostic yield of ENB is influenced by several factors. CT-to-body divergence is a more important factor than the size or location of the lesion. The divergence between the data obtained preoperatively by CT and data obtained during bronchoscopy, called CT-to-body divergence, provides a measure of the accuracy of ENB.

Rapid onsite cytological evaluation (ROSE) with ENB has been previously used in a limited number of studies.<sup>[20,25-28]</sup> It was proposed that studies using ENB combined with general anesthesia or ROSE had significantly better yields, which was strongly expected but is yet to be proven.<sup>[29]</sup> Moreover, the exact effect of ROSE on the performance of ENB bronchoscopy has not been assessed in large randomized clinical trials. The effect of general anesthesia was evaluated in two trials, without sufficient statistical power to reach a significant conclusion<sup>[12,23,29]</sup>

The pneumothorax incidence rate of the ENB procedure (1.7%) was similar to the previously published reports in the present study, suggesting the safety of ENB for peripheral lung lesions.<sup>[21,24,26]</sup>

ENB, positron emission tomography (PET)/CT, and rapid onsite cytopathologic examination are efficient and reliable methods when combined for the diagnosis of peripheral lung lesions. This combination prevents insufficient sampling of peripheral lung lesions. Lamprecht *et al.* showed that the diagnostic yield of this combination of methods was 76.9% in peripheral lung lesions.<sup>[20]</sup>

Eberhardt *et al.* compared forceps biopsy using the suction catheter with ENB-guided biopsy of peripheral lung lesion and found an improved diagnostic yield with forceps biopsy.<sup>[21]</sup> The diagnostic yield of peripheral lung lesion sampling by needle aspiration rather than by transbronchial biopsy was also supported in the study by Reichenberg *et al.*<sup>[30]</sup>

ENB has also been used in studies for treatment of lung cancer. The CyberKnife Robotic Radiosurgery System (Accuracy Inc, Sunnyvale, CA, USA) stereotactic body radiosurgery has been considered as a curative option for medically inoperable Stage I lung cancer patients who have severe chronic obstructive lung disease or advanced cardiovascular diseases. ENB provides a safer method for placement of fiducial markers in or near the intraparenchymal tumors. Schroeder *et al.* showed that 52 consecutive inoperable patients with isolated lung tumors underwent fiducial placement using ENB without any migration.<sup>[31]</sup>

ENB can also be used in some inoperable lung tumor patients in such a manner that chemotherapy, endoluminal high-dose brachytherapy, or local radiotherapy can be directed into the peripheral lung lesions.<sup>[32]</sup> Becker *et al.* applied this endoluminal brachytherapy technique with a palliative intent in a feasibility study, and observed a complete remission in 5 out of 9 patients treated. Becker *et al.* have achieved complete remission in all 8 patients treated with curative intent to date.<sup>[33]</sup>

The present study has a higher number of patients than the other studies summarized in Table 4 and has similar and confirmatory diagnostic yield compared to the literature. However, there are some limitations. It is likely that because of the small size of comparison

groups, comparing ENB alone and r-EBUS with ENB, there was no statistical significance in terms of diagnostic yield as opposed to other studies. The second limitation is that we did not have a separate, third group with r-EBUS to compare this modality alone to ENB and ENB plus r-EBUS. The third limitation is that the present study is not a prospective randomized controlled trial for the combinative model of EBUS with ENB for the peripheral lung lesions, leading to the low yield in the EBUS combinative model. Finally, the present study had a variable follow up period for cases of negative biopsy with ENB guidance at first attempt that we considered ENB as successful even though a minimum of a 6-months follow up may not be enough to determine if the lesion is benign or stable.

## CONCLUSION

In conclusion, ENB with or without r-EBUS is a safe, efficient, and easily applied method for sampling of peripheral lung lesions with high diagnostic yield independent of lesion size, lesion lobar location, and registration or navigation error.

### *Financial support and sponsorship*

Nil.

### *Conflicts of interest*

There are no conflicts of interest.

**Table 4. ENB studies for the diagnosis of peripheral lung lesions**

Author, year	Study population/ patients diagnosed by EMN	Diagnostic yield (%)
Becker <i>et al.</i> , 2005 <sup>[22]</sup>	18/30	60
Hautman <i>et al.</i> , 2005 <sup>[34]</sup>	11/16	69
Gildea <i>et al.</i> , 2006 <sup>[11]</sup>	32/56	57
Schwartz <i>et al.</i> , 2006 <sup>[24]</sup>	9/13	69
Makris <i>et al.</i> , 2007 <sup>[19]</sup>	25/40	63
Eberhardt <i>et al.</i> , 2007 <sup>[12]</sup>	52/93	56
Eberhardt <i>et al.</i> , 2007 <sup>[23]</sup>	23/39	59
Eberhardt <i>et al.</i> , 2007 <sup>[23]</sup>	35/40	88
Wilson <i>et al.</i> , 2007 <sup>[25]</sup>	151/271	56
Bertoletti <i>et al.</i> , 2009 <sup>[35]</sup>	33/54	61
Lamprecht <i>et al.</i> , 2009 <sup>[20]</sup>	10/13	77
Eberhardt <i>et al.</i> , 2010 <sup>[21]</sup>	38/55	69
Seijo <i>et al.</i> , 2010 <sup>[26]</sup>	34/51	67
Mahajan, 2011 <sup>[36]</sup>	24/49	49
Lamprecht <i>et al.</i> , 2012 <sup>[27]</sup>	94/112	84
Pearlstein <i>et al.</i> , 2012 <sup>[28]</sup>	67/101	66
Karnak <i>et al.</i> , 2013 <sup>[37]</sup>	32/35	91
Loo <i>et al.</i> , 2014	46/49	94

ENB: Electromagnetic navigational bronchoscopy; EMN: Electromagnetic navigation

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