Electromagnetic navigation bronchoscopy (ENB): Increasing diagnostic yield

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Summary
Objectives: To determine factors associated with diagnostic yield of ENB.
Methods: In 112 consecutive patients referred to our department between March 2010 and December 2010 the diagnostic work-up for solitary pulmonary lesions included a FDG-PET-CT scan, and ENB in combination with ROSE. The final diagnosis was confirmed by histopathological evaluation of specimen obtained either by ENB, or if ENB was not diagnostic by CT-guided fine needle aspiration or surgery.
Results: Thirty-seven (33%) subjects were female, mean age was 66.7 (±1.04) years. The mean diameter of lesions was 27 mm (range: 6–46 mm). In 83.9% the combination of PET-CT, ENB, and ROSE established a correct diagnosis, as defined by the definite histopathological result. 15.2% (17/112) of lesions were benign, and 84.8% (95/112) were malignant. For 112 procedures we observed a steep learning curve with a diagnostic yield of 80% and 87.5% for the first 30 and last 30 procedures, respectively. The diagnostic yield in lesions ≤20 mm and >20 mm in diameter was 75.6% and 89.6% (p = 0.06), respectively. No significant difference in diagnostic yield was seen depending on lung function, and the localization of the lesions. Two cases (1.8%) of pneumothorax were seen during and up to 24 h after bronchoscopy, none of them required a chest tube.
Conclusion: Diagnostic yield increased with experience but was independent from the size of the lesion, the localization in the lungs, and lung function. The diagnostic yield of ENB can be as high as for CT-guided transthoracic biopsies but carries a significantly lower complication rate.
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Abbreviations: ENB, Electromagnetic navigation bronchoscopy; ROSE, Rapid on-site cytopathologic examination; PET/CT, Positron-emission computed tomography.
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Introduction

Data from the National Lung Screening Trial suggest a 20% reduction in lung cancer mortality (and a 7% reduction in all-cause mortality) when low-dose CT instead of chest-x-ray is used for lung cancer screening. However, the incidence of solitary pulmonary lesions increases with utilization of more sensitive diagnostic methods. In high-risk populations, screening for lung cancer with low-dose CT has shown an incidence of suspicious lung nodules of 2.2%. Thus the clinical management of pulmonary nodules will gain much greater attention in the near future.

Sensitivity of conventional bronchoscopy for the diagnosis of peripheral lung lesions <2 cm and >2 cm was reported to be about 33% and 62%, respectively. For lesions with a diameter of less than 2 cm located in the periphery of the lung, the diagnostic yield decreases to 14%. Fluoroscopic guidance, endobronchial ultrasound (EBUS) or electromagnetic navigation bronchoscopy (ENB) can help to improve sensitivity. In peripheral lung lesions electromagnetic navigation bronchoscopy has been shown to increase diagnostic yield up to the range of 59–74%. Inadequate specimen collection is another factor limiting the yield of bronchoscopy. For transbronchial needle aspirates (TBNA), rapid on-site examination has been reported to be highly useful, accurate and cost-effective. In non-small cell lung cancer the maximum standardized uptake value (SUV) of pulmonary nodules on positron-emission tomography has shown to be a predictor of stage and tumor characteristics. Therefore the use of PET/CT in the diagnostic approach to peripheral lung lesions helps to plan diagnostic (and therapeutic) procedures.

In this prospective, single-center study PET/CT was performed prior to ENB and ROSE was used to overcome the limitation of inadequate specimen collection. We hypothesized that this combined approach to pulmonary lesions can exceed previously reported diagnostic yield of ENB. By now this is the largest series of patients undergoing ENB in combination with adjunct ROSE and preceding PET-CT.

Methods

This is a single-center, prospective, observational study to evaluate the diagnostic yield of ENB in combination with PET/CT and ROSE and to determine factors associated with diagnostic yield.

Clinical setting

The data were recorded at the Department of Pulmonary Medicine, Paracelsus Medical University, Salzburg, Austria. This is a tertiary care unit performing more than 600 bronchoscopies per year. The majority of these procedures are performed in subjects referred for suspected lung cancer. In our clinical setting rapid on-site cytopathologic examination (ROSE) and PET-CT are part of the routine diagnostic work-up.

Study population

One hundred and twelve consecutive patients were enrolled between March 2010 and December 2010. All subjects were candidates for nonemergency bronchoscopy of a solitary pulmonary lesion. All presented with lesions usually difficult to reach by conventional bronchoscopy: located in the peripheral third of the chest, endobronchially invisible, and/or too small to be visible on chest radiograph or fluoroscopy. The work has been approved by the ethical committee and all subjects provided informed consent.

FDG-PET-CT

Prior to electromagnetic navigation bronchoscopy subjects had an integrated fluorodeoxyglucose-positron-emission-computed tomography (FDG-PET-CT). The CT scans of the chest were configured with slices of 1 mm thickness at 0.8 mm intervals. For each patient the maximum standard uptake value (maxSUV) of the lesion was recorded. A SUV >3 was assumed to be suggestive for malignancy.

Electromagnetic navigation bronchoscopy

PET-CT data were used to generate a three-dimensional CT roadmap by the inReach system version 5.3 (superDimension). The software version used did not have the automatic registration or airway synchronization modalities and worked with four viewing panes during the navigation procedure.

The electromagnetic navigation system is an image-guided localization device that assists the endobronchial accessories (forceps, needle, and brush) in reaching the endobronchially invisible peripheral lung lesions. Details of the equipment and configuration have already been described. All procedures were done in rigid bronchoscopic intubation technique and general anesthesia using an Olympus 1T160, 2.8 mm working channel, adult therapeutic bronroscope. No additional guidance technique (e.g. fluoroscopic guidance) was used. Navigation to the lesion was assumed successful when the distance from the tip of the locatable guide to the center of the lesion was ≤10 mm. Three bronchoscopists at the same level of bronchoscopy training started to use ENB and performed the studied 112 procedures (30–40 procedures each).

Rapid on-site cytopathologic evaluation (ROSE)

Bronchoscopy was done in combination with rapid on-site cytopathologic examination which is routinely available at our institution. ROSE is facilitated by immediate smearing of the specimens onto slides, drying and fixation. An experienced cytopathologist evaluated specimens sampled by variable biopsy techniques (forceps biopsy with imprint cytology, TBNA and brush with smears). The Papanicolaou (Pap) test grading system (I–V) was used to describe findings of the cytopathologic examination. For confirmation of final diagnosis a histopathological examination was performed in all cases, further immuno-histological evaluation was performed if appropriate.

Statistical analysis

The parametric t-test was used to evaluate the impact of lesion size on the diagnostic yield of electromagnetic
navigation bronchoscopy. All statistical analyses were done with SAS 8.2 (SAS Institute Inc, Cary, NC, USA).

**Results**

Electromagnetic navigation bronchoscopy was performed in 112 patients. 37 (33%) were female, the mean age was 66.7 (range: 32–87) years. 66% (74/112) of subjects presented with impaired lung function (FEV1 < 80% predicted), the mean FEV1% predicted was 69% (range: 26–144%). Characteristics of pulmonary lesions are summarized in Table 1.

The mean Standard Uptake Value (SUV) recorded by PET-CT was 6.7, and was significantly higher in malignant lesions than in benign lesions (7.4 vs 2.9, p < 0.001). The positive predictive value of a suspicious PET-CT scan for a diagnosis of malignancy was 93.3%.

All bronchoscopic procedures were done in general anesthesia. Mean duration of general anesthesia including total bronchoscopic procedure time was 45.0 (±2.0) and 45.4 (±2.8) minutes for lesions >20 mm and lesions ≤20 mm in diameter, respectively.

A flow diagram of the diagnostic work-up of pulmonary lesions is shown in Fig. 1. Overall, in 83.9% the combination of PET-CT, ENB, and ROSE established a correct diagnosis, as defined by the definite histopathological result. 15.2% (17/112) of lesions were benign, and 84.8% (95/112) were malignant. The number of biopsies taken to establish the diagnosis ranged from 1 to 9 (median of 6 biopsies).

The diagnostic yield of ENB in lesions ≤20 mm and >20 mm in diameter was 75.6% and 89.6%, respectively (p = 0.06). No significant difference in diagnostic yield was seen depending on the localization — lower lobes vs upper lobes — of the lesions, see Table 2.

The diagnostic yield of ENB was found to be independent from lung function (FEV1% predicted). Among 38 subjects with normal lung function (FEV1 ≥ 80% predicted) the diagnostic yield was 78.9% (30/38), among 30 subjects with severe to very severe airways obstruction (FEV1 ≤ 50% predicted) the diagnostic yield was 93.3% (28/30). The mean FEV1% predicted was 67.7% and 75.6% for subjects with reachable and unreachable pulmonary lesions, respectively (p = 0.127).

Diagnostic yield of ENB increased with the number of performed procedures. For the observed 112 ENB procedures, the average diagnostic yield was 80% and 87.5% (p = 0.724) for the first 30 and the last 30 procedures, respectively (see Fig. 2). In parallel to this increasing diagnostic yield the mean diameter of lesions decreased from 30.4 mm to 25.3 mm.

When navigation to the lesion was successful (distance from the tip of the locatable guide to the center of the lesion ≤10 mm), sensitivity and specificity of rapid on-site cytopathologic examination (ROSE) for a diagnosis of malignancy was 92.6% and 100%, respectively.

In 11 cases (9.8%) navigation was not successful (distance from the tip of the locatable guide to the center of the lesion >10 mm), in 7 (6.2%) cases navigation seemed to be successful but collected specimen/ROSE were not diagnostic. Altogether, in 16% (18/112) of lesions were benign, and 84.8% (95/112) were malignant. The number of biopsies taken to establish the diagnosis ranged from 1 to 9 (median of 6 biopsies).

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In this series of 112 consecutive patients with solitary pulmonary lesions the combination of PET-CT, electromagnetic navigation bronchoscopy, and rapid on-site cytopathologic examination established a diagnosis in 84%.

This is significantly better than the diagnostic yield of 53% that was shown for the combination of flexible standard bronchoscopy with the use of uniplanar fluoroscopy and PET scanning (in lesions less than 3 cm in size).15 It has been shown that ENB is a safe procedure and can increase the diagnostic yield of bronchoscopy up to approximately 70%.6–9,16 In the presence of a bronchus sign on CT imaging ENB has recently been shown to be diagnostic in 79%.17 The diagnostic yield observed in our large series of patients is even higher and close to the diagnostic yield that is reported for transthoracic CT-guided (92%)9 or surgical (nearly 100%)18 biopsies. In contrast to these more invasive procedures with several risks,19,20 bronchoscopy has less risks and is usually more comfortable.21

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**Table 1** Characteristics of solitary pulmonary lesions (n = 112).

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Mean</td>
<td>27.1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>6–46</td>
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</table>

**Localization**

<table>
<thead>
<tr>
<th>Localization</th>
<th></th>
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<tbody>
<tr>
<td>Right lung</td>
<td>69 (61.6%)</td>
<td></td>
</tr>
<tr>
<td>Left lung</td>
<td>43 (38.4%)</td>
<td></td>
</tr>
<tr>
<td>Upper lobe</td>
<td>57 (50.9%)</td>
<td></td>
</tr>
<tr>
<td>Lower lobe</td>
<td>41 (36.6%)</td>
<td></td>
</tr>
<tr>
<td>Middle lobe</td>
<td>14 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

**Dignity & final diagnosis**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th></th>
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<tbody>
<tr>
<td>Malignant lesions</td>
<td>95 (84.8%)</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>81 (72.3%)</td>
<td></td>
</tr>
<tr>
<td>BALT lymphoma</td>
<td>1 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Metastases</td>
<td>13 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>Benign lesions</td>
<td>17 (15.2%)</td>
<td></td>
</tr>
<tr>
<td>Tuberculoma</td>
<td>4 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Hamartoma</td>
<td>2 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Vasculitic granuloma</td>
<td>1 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>(Polyarteritis nodosa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>2 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Epithelioid granuloma (Sarcoidosis)</td>
<td>2 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Mycetoma</td>
<td>3 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Necrotizing granuloma</td>
<td>1 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>(Rheumatoid arthritis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>2 (1.8%)</td>
<td></td>
</tr>
</tbody>
</table>
In this series of patients two cases (1.8%) of pneumothorax were seen during and up to 24 h after bronchoscopy. Previous studies on ENB reported an incidence of pneumothorax between none and 8%.6–9 This is remarkably lower than the pneumothorax rate reported for CT-guided coaxial cutting needle biopsies (23%).19 A recent study on 102 cases of CT-guided tru-cut transthoracic biopsies (TTB) revealed a rate of pneumothorax of 15.7%, more than half of them (8.8%) required a chest tube.22 When lesion size was less than 2 cm or emphysematous changes were present the rate of pneumothorax increased up to 30% and 28%, respectively.

The issue of this complication is highly important, since the majority of subjects with pulmonary lesions presents with impaired lung function — in our study the mean FEV₁% predicted was 69%.

Besides the greater risk of pneumothorax and bleeding, transthoracic needle biopsy using intermittent CT-guidance also causes additional radiation exposure for both, the patient and the operator.

We observed a very satisfactory diagnostic yield right from the beginning. The diagnostic yield increased on average from 80% to 87.5% after about 30–40 ENB procedures for each bronchoscopist. Even though inclusion criteria remained unchanged, the average diameter of the lesions slightly decreased over time. We observed a trend towards referral of smaller lesions and we suppose this is due to both, increasing lung cancer screening efforts and increasing awareness (among our referring physicians) that innovative and promising bronchoscopy tools are available (at our institution).

**Advantages of the combined approach to pulmonary lesions**

ENB uses anatomical data and CT scans convertible into multiplanar images with three-dimensional virtual bronchoscopy reconstruction. In addition to this PET-CT provides information on tissue activity and is a discriminator of disease load.23 There is evidence that the maximum standard uptake value (maxSuv) on PET-CT is an independent predictor of stage and tumor characteristics in non-small lung cancer. The integrated PET-CT has been shown to improve the diagnostic accuracy of the staging of non-small-cell lung cancer.24 While PET-CT adds valuable information to the staging process, it does not provide a definite tissue diagnosis. Therefore, tissue sampling is still required to confirm the suspected malignancy.25 For tissue sampling rapid on-site cytopathologic examination is useful and cost-effective. ROSE has been shown to improve
Figure 2  Diagnostic yield by number of performed ENB procedures (learning curve) for three bronchoscopists; left, individual learning curves; right, average learning curve.

diagnostic efficacy independent of the localisation and histology of the lesion and experience of the operator. Previous studies have indicated that diagnostic yield can be improved when ENB is performed in combination with ROSE. While ENB helps to reach SPN’s, rapid on-site cytopathologic examination ensures that the collected specimen are diagnostic. Therefore, the combination of ENB and ROSE helps to overcome the limitation of inadequate specimen collection. On the one hand, on-site determination of cytologic adequacy helps to allow termination of the bronchoscopy to minimize the risk of potential complications, and on the other hand, it dictates the need for additional collection of specimen to improve the diagnostic yield. Especially in the latter case the use of ROSE may slightly prolong bronchoscopy and time of anesthesia.

ENB (in combination with PET-CT and ROSE) is an expensive procedure and has not yet established a clear place in routine practice. However, there are several indications and subsets of patients in which this procedure appears to be a specifically reasonable work-up: (1) a medically inoperable patient requiring tissue confirmation of malignancy prior to the initiation of radiotherapy with curative intent. (2) A patient with a pulmonary lesion suspicious for a specific benign disease, especially if accompanied by negative or inconclusive PET finding. (3) And last but not least a patient preferring confirmation of malignancy prior to the initiation of more invasive procedures such as lobectomy. In our study population 24.1% were inoperable due to severely impaired lung function and/or significant comorbid disease. For another 10.7% a specific benign disease was considered possible.

A limitation of this study is that it is using data from one single-center. In addition to this, bronchoscopy in general anesthesia is likely to improve diagnostic yield compared to bronchoscopy in conscious sedation. Diagnostic yield was higher in lesions >20 mm compared to lesions ≤20 mm, but this difference did not reach the level of statistical significance (p = 0.06). However, statistical significance might have been reached in a larger cohort of patients.

Conclusions

Diagnostic yield was found independent from the size of the lesion, the localisation in the lungs, and lung function, but the yield increased with experience. In combination with helpful information from PET-CT and ROSE a diagnostic yield of about 80% is within reach right from the beginning. With increasing experience diagnostic yield of ENB can be as high as for CT-guided transthoracic biopsies. However, the complication rate (1.8% pneumothorax rate for ENB in this study) is significantly lower than the one associated with CT-guided transthoracic biopsies. In the face of an increasing number of detected pulmonary lesions, ENB can be a reasonable work-up in defined subsets of patients.

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Conflict of interest statement

The authors have no conflict of interest.

References


