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**TITLE: Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions**

Authors : Demosthenes MAKRIS [1]
Arnaud SCHERPEREEL[1]
Sylvie LEROY[1]
Brigitte BOUCHINDHOMME [2]
Jean-Baptiste FAIVRE [3]
Jacques REMY[3]
Philippe RAMON [1]
Charles-Hugo MARQUETTE [1]

1. Clinique des Maladies Respiratoires, CHRU, Lille
2. Département d'Anatomopathologie, CHRU, Lille
3. Département de Radiologie, CHRU, Lille

CORRESPONDANCE :

Charles-Hugo MARQUETTE
Clinique des Maladies Respiratoires
Hôpital Albert Calmette
Centre Hospitalier Régional Universitaire de Lille
59037 Lille cedex
mail: c-marquette@chru-lille.fr

**Running title:** Electromagnetic guided lung biopsy.

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**ABSTRACT**

**Objectives**: This study evaluated prospectively the diagnostic yield and safety of electromagnetic navigation guided bronchoscopy biopsy, for small peripheral lung lesions in patients where standard techniques were non-diagnostic.

**Subjects and Methods:** The study was conducted in a tertiary medical centre on 40 consecutive patients considered unsuitable for straightforward surgery or CT-guided transthoracic needle aspiration biopsy due to co-morbidities. Lung lesions mean(SE) diameter was 23.5(1.5)mm and depth from visceral-costal pleura was 14.9(2)mm. Navigation was facilitated by an electromagnetic tracking system which could detect a position sensor incorporated into a flexible catheter advanced through bronchoscope. Information obtained during bronchoscopy was superimposed on previously aquired CT-data. Divergence between CT-data and data obtained during bronchoscopy (divergence) was calculated by system's software as a measure of navigational accuracy.

**Results:** All target lesions but one was reached and the overall diagnostic yield was 62.5%(25/40). Diagnostic yield was significantly affected by CT-to-body divergence ($p=0.03$); yield was 77.2% when estimated divergence was ≤4mm. Three pneumothoraces occurred and chest drainage was required in one case.

**Conclusion:** Electromagnetic navigation guided bronchoscopy has the potential to improve the diagnostic yield of transbronchial biopsies without additional fluoroscopic guidance and may be useful in early diagnosis of lung cancer, particularly in non-operable patients.

**Key words:** pulmonary nodule; bronchoscopy; CT; three-dimensional imaging. **Word count**: 200.

## INTRODUCTION

Lung cancer is still a leading cause of cancer mortality with an overall 5-year survival of less than 20% in Europe and in USA(1). The main reason of low survival rates and treatment failure is late diagnosis of extensive disease. The stage of disease at diagnosis yet represents one of the most powerful determinants of outcome in lung cancer (2). In this respect, a number of studies have suggested that small lung cancers which are potentially resectable, can be identified using CT screening programs (3)(4). Nonetheless, this diagnostic advance will not be applicable if current management will not overcome two related problems. First, the high proportion of false-positive CT findings may reach 70%(5) and thus, histologic confirmation is essential for diagnosis. Second, a significant proportion of early-stage lung cancer patients may be medically inoperable due to comorbid medical illness or poor pulmonary function (6). Therefore, a diagnostic procedure, less invasive than surgery such as transthoracic needle aspiration biopsy (TTNA) or bronchoscopy, is warranted to provide definitive diagnosis and to offer the prospect of cure in medically inoperable patients by the application of local treatment, such as radiation (7).

However, the current non surgical techniques available to diagnose small peripheral lung lesions (SPLL) are limited either by low accuracy (8)(9)(10)(11) or, by potential complications (12)(13(14)(15). The diagnostic yield of bronchoscopy for such lesions may be lower than 30% (10)(16)(17). On the other hand although TTNA may reach a diagnostic yield of 82 to 96% (12)(13),it is associated with increased pneumothorax rates that range from 23 to 44% (18)(19). Furthermore, the high diagnostic yield of this method derives from selected populations that fulfilled in advance clinical and radiologic criteria to undergo TTNA.

Novel methods aiming to improve the yield of bronchoscopy in pulmonary nodules attract clinical interest (20)(21)(22). Electromagnetic navigation during bronchosopy (EGB) can guide the biopsy of endobronchially invisible peripheral lesions. However, previous clinical studies either included small populations and the lesions were too inhomogeneous to draw definitive conclusions regarding yield and safety of the method (22)(23) or used additional fluoroscopic guidance for diagnosis (24). The purpose of the present study was to provide basic data about the diagnostic yield and the incidence of complications with respect to electromagnetic guided bronchoscopy biopsy of SPLL, for patients in which conventional bronchoscopy was not diagnostic and patients were not eligible for straightforward curative surgery due to comorbitities.

## METHODS

### Patients

This investigation was a prospective open-label case series study. Consecutive sampling was used to recruit patients who attended outpatient clinics in Albert Calmette University Hospital between October 2005 and September 2006 and met the following criteria: a/ peripheral pulmonary lesion (solid or fatty solid nodule located beyond the visible range of flexible bronchoscopy) detected by chest radiography and CT, b/ suspicion for cancer by CT morphology or positive Positron Emission Tomography scan, c/ non diagnostic conventional bronchoscopy, d/ absence of other metastatic lesions accessible for biopsy, e/ negative TTNA or contraindication for TTNA (severe pulmonary impairment, bleeding diathesis, lesions not accessible by TTNA as judged by radiologist pannel), f/ contraindication for straightforward curative surgery or g/ if

associated mediastinal lymph node transbronchial needle aspiration (TBNA) was negative or in case that lymph nodes were difficult to reach TBNA. All cases presented here, were discussed in a weekly multidisciplinary meeting in this tertiary hospital and judged initially that should have other than surgical approach due to important co-morbidities, considering the benefit/risk ratio for each individual case. Discussion of each case in this meeting was part of the inclusion process. Contraindication to short acting anesthetic agents, bleeding diathesis, presence of concomitant endobronchial lesion or, of a pacemaker/defibrillator or, a diagnosis by other means (sputum cytology, microbiology) was exclusion criteria in this study.

Follow-up included clinical assessment and erect postero-anterior chest radiographs immediately after biopsy, within 24 hours and within 15 days for the evaluation of potential complications. Informed consent was obtained from all patients before conventional and electromagnetic guided bronchoscopy according to ethical principles and permission of the institutional review board.

**CT**

All patients underwent thoracic CT examinations prior to the bronchoscopy procedures. Recommended technical thoracic CT criteria for navigation software were: slice thickness 2-3.5 mm, slice interval (with overlap of 1mm) 1-2.5 mm, image size 512x512 pixels and dicom format. If thoracic CT performed during the initial diagnostic work up did not fulfill the above criteria a new CT was performed (See protocol in data supplement).

**Electromagnetic navigation bronchoscopy**

The electromagnetic navigation system (superDimension/Bronchus; Hertzliya, Israel) and navigation procedures are described in detail in data supplement. Briefly, the

system uses a sensor probe that picks up the electromagnetic field generated by a Localization system (a processor, an amplifier and a location board). When the sensor was placed within the electromagnetic field, its position and orientation could be identified and this information was displayed on a monitor in superimposed upon previously acquired CT images. This image-guided localization device aimed in guiding transbronchial biopsies in desired predetermined targets within the bronchial tree, in this study. Initially, the digitized information from patient's CT scan was imported into the electromagnetic navigation system and axial, coronal, and sagittal views of the chest and virtual endoscopy images were reconstructed. Consequently, anatomic landmarks -typically major bronchial tree bifurcations- were identified as coordinates on the corresponding CT as well as on the virtual bronchoscopy image (planning). The same identifiable landmarks were then used during real time bronchoscopy in order to relate the CT data and the actual anatomy. When these points were touched with the sensor, they were simultaneously recorded by the navigation system (registration).

The system's software had the ability to correlate pre-operative CT data and actual position, to display target's estimated actual location on screen and to provide a navigation scheme to approach the lesion. In addition, the system could calculate the divergence between data obtained preoperatively by CT and data obtained during bronchoscopy (CT-to-body divergence), providing a measure of accuracy of electromagnetic navigation.

Flexible bronchoscopy (Pentax; Tokyo, Japan) was performed under general anesthesia and was carried out by two experienced bronchoscopists, CHM and PR (see data supplement). Navigation aimed to approach closely the target lesion (distance between sensor tip and lesion center at least less than 15 mm). Nine attempts for biopsy were

scheduled for each lesion and every three attempts, forceps were withdrawn and the position of the sensor probe in relation of the target lesion was checked.

**Statistical analysis**

The primary efficacy endpoint was, whether or not the EGB biopsy resulted to the diagnosis of lung cancer or of another lung pathology. Patients underwent additional diagnostic procedures (TTNA, surgery) or clinical and thoracic imaging follow up, if EGB biopsy was inconclusive. When these additional procedures resulted to diagnosis of lung cancer or of lung pathology, the cases were considered as non-diagnosed by EGB. The following formula was used to compute yield of EGB biopsy:

Diagnostic yield (%) = 100 x EGB biopsy diagnosed cases / total number of patients completed procedures.

The yield of EGB was examined by lesion characteristics, CT-to-body divergence and bronchoscopy operator. The presence of learning curve regarding the use of this technique was assessed comparing the diagnostic yield achieved in the first sessions with the yield achieved in the last sessions, for each operator separately. Results are presented as mean (SE) values for continuous data or as percentage for categorical data. Comparisons between groups on categorical data were done using Fisher's exact and chi-square goodness of fit tests. The statistical package SPSS 13.0 (Chicago.IL; USA) was used for the entire analysis.

**RESULTS**

Forty patients were enrolled in the study. Patients were of mean(SE) 60(2.5) years age; thirty out of 40 (75%) were male. Twelve patients had primarily severe cardiovascular

problems, four had severe renal impairment (hemodialysis), ten had severe obstruction [mean (SE) FEV1%pred 30.3(2.1)], three had undergone lobectomy and the remaining eleven had mixed co-morbidities (cardiovascular disease, diabetes, COPD, hepatic failure, obesity). In nine patients, thoracic CT performed during the initial diagnostic work up did not fulfill technical criteria for navigation software and a new CT was performed.

The lesions had a mean (SE) size of 23.5 (2), (min-max 8-49) mm. Twenty-five lesions were classified as T1 and fifteen as T2 according to TNM staging. The accuracy of the navigation process, as expressed by the average of CT-to-body divergence was 4 (0.15) mm while the distance between sensor probe and center [or perimeter] of target lesion before each attempt for biopsy was 8.7 (0.8) [or -3.8 (1) respectively] mm. Figure 1 shows the three-dimensional CT scan data appearance of a nodule with 28 mm diameter demonstrating navigational information for direction - distance in a 64 years-old patient.

EBG resulted in obtaining diagnosis in 25 out of 40 cases (62.5%). In twenty cases obtained biopsies showed cancer (ten adenocarcinoma, ten squamous cell cancer) and in five cases biopsies showed benign disease/condition (two tuberculosis, one sandblasting silicose, one non-caseating granuloma, one hamartoma) confirmed by surgery (n=3) or, TTNA (n=1) or, clinical/CT examination at 14 months follow up. In the remaining 15 cases EGB biopsy was either not diagnostic (n=14) or not feasible (n=1). Thirteen EGB non diagnostic cases were malignant (nine lung adenocarcinoma, two metastatic adenocarcinoma, two squamous cell cancer) and corresponded to exo-bronchial (n=4), small (<12 mm) (n=2) extremely peripheral lesions (n=3); for four cases no obvious explanation could be found. These cases were diagnosed finally by open lung biopsy (n=8), or mediastinoscopy (n=2), or TTNA (n=3). One patient with

non-diagnostic biopsy did not complete follow up procedure and final diagnosis was not available. Biopsy was not feasible in a case of a 15 mm diameter peripheral nodule located in the apical segment of left lower lobe; closest distance from target reached was 26 mm. PET was negative and CT showed regression of the lesion at 14 months follow up.

The diagnostic yield of EGB for different influencing factors is shown in Table 2. The yield was significantly greater when CT-to-body divergence was less or equal to 4 mm (77.2% versus 44.4%; p= 0.03). The yield for T1 lesions was 56% while it was 73.3% for T2 lesions; however, no statistical difference was noted between them. In addition, no significant learning curve was observed in these series of patients (Table 2). The sensitivity, negative predictive value of EBG for malignancy were 57% and 25% respectively, assuming that the case which remained without diagnosis and the case where biopsy was not feasible were not benign (or 60.6% and 35% respectively, assuming the two cases were benign).

In every lesion, 8.5 (0.7) mean (SE) biopsies were attempted and 6.7 (0.4) specimens per lesion were obtained. Among specimens obtained on site, 2 (0.5) specimens per lesion [or 29(1)% of specimens obtained] corresponded to clots, unidentifiable cellular casts or non recognisable material and were judged as improper for evaluation. No significant differences were found between EGB diagnosed and EGB non-diagnosed cases in terms of number of biopsies attempted, specimens obtained and specimens analysed.

A 58 years-old smoker with severe COPD presented pneumothorax requiring chest drainage five hours after bronchoscopy while another two patients experienced immediately after procedure small asymptomatic spontaneously resolved pneumothoraces. No late adverse events were reported.

## DISCUSSION

This is the first prospective study which demonstrates that electromagnetic navigation during flexible bronchoscopy increases the reliability of bronchoscopy for SPLL diagnosis without additional fluoroscopic assistance (22)(23)(24). The overall diagnostic yield of EGB for SPLL in this consecutive series of patients where standard diagnostic techniques failed in establishing diagnosis was 62.5%. Notably, when CT-to-body divergence – a measure of data registration accuracy - was less or equal to 4 mm, the diagnostic yield reached 77.2%. This is superior to the yield of conventional bronchoscopic techniques for SPLL reported in most studies (8)(9)(10)(11).

The yield of flexible bronchoscopy in lung nodular lesions ranges between 19-62% because it is greatly affected by lesion size and location (7)(8)(11)(25)(26). Thus, in Baaklini's study (10) the yield for lesions < 2 cm which were located in the peripheral third of the lung, was 14%. Fluoroscopic guidance has been used to increase sensitivity of bronchoscopy (27). However, fluoroscopy causes radiation exposure (28) and yield is still affected by lesion characteristics (8)(9)(29). Alternative techniques, such as endobronchial ultrasound or CT-fluoroscopy, may improve significantly the diagnostic yield of conventional bronchoscopy (15)(21) but there are also drawbacks in these methods. Endobronchial ultrasound is costly, requires regular probe replacement and includes difficulty in selecting the bronchial branch of interest presenting lower yield in apical–posterior lobes. On the other hand, radiation exposure for stuff and patients restrict efficient application of CT-fluoroscopy (15). In this ground, electromagnetic

navigation for bronchoscopy guidance may be considered in the diagnosis of SPLL where conventional bronchoscopy fails.

In the present investigation, we evaluated the efficacy of EBG in a population of subjects who had arrived in a diagnostic cul-de-sac. These patients were not good candidates for surgery and previous diagnostic procedures –including bronchoscopy, TBNA or TTNA- had not been diagnostic. This population is illustrative of limitations that exist in diagnosis and treatment of pulmonary nodules in medically non-operable patients. Surgery is associated with high incidence of postoperative mortality and morbidity in these patients (30)(31). Despite the progress that has been made surgical interventions may not be appropriate for every patient with radiographic evidence of early stage lung cancer. In addition, other diagnostic procedures such as TTNA carry a risk of complications which can be substantial in patients with an already compromised respiratory or low performance status. Consequently, both diagnostic and treatment decisions for medically non-operable patients with lung nodules are not straightforward. However, the prospect of therapy should be given to these patients. Advances in radiation oncology, and locally ablative techniques have resulted in improved survival with a significant decrease in post-procedure mortality and morbidity (7)(32). On this basis, histopathologic confirmation of malignancy is essential prior to the initiation of these alternative treatments. In the present study, EGB established successfully the diagnosis in the majority of patients in this population. Moreover, in agreement with the results of earlier studies (22)(23)(24) serious complications did not occur. Thus, EGB can be a valuable diagnostic tool in the investigation of pulmonary nodules and may offer an alternative to surgical treatment in medically non-operable patients.

The effect of electromagnetic navigational accuracy on SPLL biopsy results has not been evaluated until now. Although Gildea et al(24) reported recently an excellent yield of EGB in the diagnosis of parenchymal and mediastinal lung lesions, additional fluoroscopic guidance was systematically used before biopsy. In this respect, the present is the first investigation which evaluates the accuracy of the technique in SPLL diagnosis without the help of additional fluoroscopic guidance. Moreover, it demonstrates a relation between a measure of the navigational accuracy and biopsy results. Our findings suggest that the diagnostic yield of EGB may be affected by CT-to-body divergence rather than size or location of the lesion. We found that EGB yield was significantly lower when CT-to-body divergence was more than 4 mm.

CT-to-body divergence is unavoidable since EBG is not a real time navigational system and might be one of its drawbacks for the time being. EBG yield is based on the reconstructed positioning as generated by the computerized system from the three-dimensional CT data and the registration process. Therefore, the bronchial relationships of a nodule may differ from fiberoptic endoscopy to CT acquisition and concurrent reformations. In addition, the differences in pulmonary volumes between endobronchial navigation and CT acquisition may result in variation in bronchial lengths and obliquities. However, these differences could be obviated in the near future with the application of CT of ultra fast temporal resolution and/or respiratory gating.

In this investigation, despite our efforts to approach target as close as possible, the mean distance achieved was 8.7 mm. This is most likely due to progressively narrowing and branching nature of the bronchial tree. Although this difference did not affect significantly our results it remains to be seen whether further improvements in equipments and software can achieve to overcome obstacles arising due to the architecture of bronchial tree and to ameliorate further the yield of EBG.

In the present study a significant learning curve related to the technique was not observed. The diagnostic accuracy during first sessions of EBG was not significantly lower compared to that achieved during last sessions. EGB is not a cumbersome technique. Providing a previous experience in flexible bronchoscopy, EGB can be easily learned.

To increase the comfort of these patients during procedure since a large bronchoscope is needed and more manipulations than conventional bronchoscopy are necessary, patients underwent the procedure under anaesthesia in this investigation. Hence, our results are not likely to be affected by cough or body movement. In addition, it is questionable whether respiration-induced movement affects significantly the yield of EGB (22)(23)(24). Our findings suggested indirectly rather the opposite. Since respiration-induced movement is larger in the caudal and peripheral parts of lungs than in the apical and central parts, a lower diagnostic yield would be expected in apical-central lesions. However, no significant association between the diagnostic yield of the technique and location of the lesion was observed.

In the present investigation, 8.5(0.7) mean(SE) biopsies per lesion were attempted which is greater than that reported in most of papers. This may have contributed to the high accuracy rate of this study but on the other hand makes difficult the comparison with other historical studies. However, we attempted many biopsies because sampling issues may have a major role in the misdiagnosis in lung lesions cases (33). In this study not all obtained samples were identified as proper for analysis in the pathology department permitting diagnosis. Specimens obtained by flexible bronchoscopy forceps may be of small size, damaged, containing crush artefacts and thus, they may be of low quality and consequently of limited interpretation (34). Moreover, problems that may occur by random during specimen delivery or conservation are not unlikely in clinical

practice. This type of drawbacks underline the fact that, beside all sophisticated advances in endoscopical tissue sampling, the yield of a diagnostic method can be still affected by other confounding factors and the negative predictive value for malignancy may be low (35). Thus, the clinician must always continue to pursue a diagnosis if an EGB guided biopsy is negative or non-diagnostic using all available diagnostic methods.

In this investigation, pneumothorax rate (3/40) was similar to that reported in a previous study (2/60) (24) although we did not use additional fluoroscopic guidance during bronchoscopy and in addition, a large number of biopsies per lesion were performed. However, while two patients experienced asymptomatic pneumothoraces immediately after procedure a third one presented symptomatic pneumothorax few hours later. In this respect, attention should be paid for occurrence of adverse events during the 24hours following procedure.

In summary, electromagnetic navigation bronchoscopy without additional fluoroscopic guidance is a safe and efficient technique for the diagnosis of peripheral pulmonary nodules. The overall diagnostic yield found in this study is superior to rates reported in most studies previously performed for small peripheral pulmonary nodules with bronchoscopy. In contrast to fluoroscopy, this technique is not associated with radiation exposure. Furthermore, this technique has the potential of substantial contribution in the early diagnosis and treatment of lung cancer, particularly in patients considered medically non operable. However, integrated navigation sensor and software improvements are necessary in order to improve navigational accuracy before the method is widely applied in clinical practice.

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**Table 1** Characteristics of all 40 patients participated in the study.

| | **n** | **mean** | **SE** |
|---|---|---|---|
| age | 40 | 60 | 2.5 |
| lesion size (mm) | 40 | 23.5 | 1.5 |
| lesion volume ($cm^3$) | 40 | 3.1 | 1.2 |
| lesion depth from visceral costal pleura (mm) | 40 | 14.9 | 2 |
| lesion depth from visceral diaphragmatic pleura(mm)* | 12 | 97 | 6 |
| *TNM staging* | | | |
| T1 size (mm) | 25 | 17 | 1 |
| T2 size (mm) | 15 | 37 | 2 |

*only for lower lobe nodules

**Table 2.** Diagnostic yield by lesion type, size, volume, location, CT-to-body divergence and operator.

| Factors | n | Yield % |
|---|---|---|
| T1 lesion | 25 | 56 |
| T2 lesion | 15 | 73.3 |
| size ≤ 10 mm | 4 | 75 |
| size > 10 mm ≤ 20 mm | 16 | 43.7 |
| size > 20 mm ≤ 30 mm | 7 | 71.4 |
| size >30 mm | 13 | 76.9 |
| volume ≤1cm$^3$ | 21 | 57.1 |
| volume >1cm$^3$ | 19 | 68.4 |
| right or left upper lobe | 27 | 66.5 |
| all other lobes | 13 | 53.8 |
| depth from visceral pleura ≤ 14 mm | 23 | 60.8 |
| depth from visceral pleura > 14 mm | 17 | 64.7 |
| CT-to-body divergence ≤ 4 mm | 22 | 77.2* |
| CT-to-body divergence > 4 mm | 18 | 44.4 |
| minimum distance from target reached ≤ 8 mm | 18 | 66.5 |
| minimum distance from target reached > 8 mm | 22 | 59 |
| operator A | 26 | 73 |
| first13 sessions - last 13 sessions | | 76.9 - 69.2 |
| operator B | 14 | 42.8 |
| first 7 sessions - last 7 sessions | | 42.8 - 42.8 |

*difference according to CT-to-body divergence, p= 0.03.

**Figure legend**

**Figure 1**

Nodule (target), 28 mm diameter, in the posterior segment of the right upper lobe, 6 mm away from the chest wall (left). The distance of the tip of the sensor probe to the target is 8 mm (right). Seven biopsies were performed, out of which six contained normal lung parenchyma and one was positive for squamous cell carcinoma.