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Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions

D. Makris*, A. Scherpereel*, S. Leroy*, B. Bouchindhomme#, J-B. Faivre¶, J. Remy¶, P. Ramon* and C-H. Marquette*

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

The study was conducted in a tertiary medical centre on 40 consecutive patients considered unsuitable for straightforward surgery or computed tomography (CT)-guided transthoracic needle aspiration biopsy, due to comorbidities. The lung lesion diameter was mean±SEM 23.5±1.5 mm and the depth from the 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 a bronchoscope. Information obtained during bronchoscopy was superimposed on previously acquired CT data. Divergence between CT data and data obtained during bronchoscopy was calculated by the system's software as a measure of navigational accuracy.

All but one of the target lesions was reached and the overall diagnostic yield was 62.5% (25–40). Diagnostic yield was significantly affected by CT-to-body divergence; yield was 77.2% when estimated divergence was ⩽4 mm. Three pneumothoraces occurred and chest drainage was required in one case.

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

KEYWORDS: **Bronchoscopy, computed tomography, pulmonary nodule, three-dimensional imaging**

Lung cancer is still a leading cause of cancer mortality with an overall 5-yr survival of <20% in Europe and in the USA [1]. The main reason of low survival rates and treatment failure is late diagnosis of extensive disease. The stage of disease at diagnosis still 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 computed tomography (CT) screening programmes [3, 4]. Nonetheless, this diagnostic advance will not be applicable if current management cannot overcome two related problems. First, the high proportion of false-positive CT findings may reach 70% [5] and thus, histological confirmation is essential for diagnosis. Secondly, 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, current nonsurgical techniques available to diagnose small peripheral lung lesions (SPLL) are limited either by low accuracy [8–11] or by potential complications [12–15]. The diagnostic yield of bronchoscopy for such lesions may be <30% [10, 16, 17]. However, although TTNA

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AFFILIATIONS
*Clinic of Respiratory Disease, Depts of #Anatomopathology, and ¶Radiology, Albert Calmette Hospital, CHRU, Lille, France.

CORRESPONDENCE
C-H. Marquette
Clinic of Respiratory Disease
Albert Calmette Hospital
Centre Hospitalier Régional
University of Lille
59037 Lille
France
Fax: 33 320445611
E-mail: c-marquette@chru-lille.fr

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may reach a diagnostic yield of 82–96% [12, 13], it is associated with increased pneumothorax rates ranging 23–44% [18, 19]. Furthermore, the high diagnostic yield of this method derives from selected populations that fulfil, in advance, the clinical and radiological criteria to undergo TTNA.

Novel methods aiming to improve the yield of bronchoscopy in pulmonary nodules have attracted clinical interest [20–22]. Electromagnetic guided bronchosopy (EGB) can guide the biopsy of endobronchially invisible peripheral lesions. However, previous clinical studies either included small populations, in which 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 EGB biopsy of SPLL, for patients in which conventional bronchoscopy was not diagnostic and who were not eligible for straightforward curative surgery due to comorbitities.

METHODS

Patients

The study had a prospective open-label design. Consecutive sampling was used to recruit patients who attended outpatient clinics in the Albert Calmette University Hospital (Lille, France) between October 2005 and September 2006 and who met the following criteria: 1) peripheral pulmonary lesion (solid or fatty solid nodule located beyond the visible range of flexible bronchoscopy) detected by chest radiography and CT; 2) suspicion of cancer by CT morphology or positive positron emission tomography (PET) scan; 3) nondiagnostic conventional bronchoscopy; 4) absence of other metastatic lesions accessible for biopsy; 5) negative TTNA or contraindication for TTNA (severe pulmonary impairment, bleeding diathesis, lesions not accessible by TTNA as judged by a radiologist panel); 6) contraindication for straightforward curative surgery; or 7) if associated mediastinal lymph node transbronchial needle aspiration (TBNA) was negative or in case that lymph nodes were difficult to reach with TBNA. All cases presented were discussed in a weekly multidisciplinary meeting in the authors' tertiary hospital where it was judged that, due to important comorbidities, they required treatment other than the typical surgical approach, considering the benefit–risk ratio for each individual case. The discussion of each case in this meeting was part of the inclusion process. Exclusion criteria for the present study included: 1) contraindication to short-acting anaesthetic agents; 2) bleeding diathesis; 3) presence of concomitant endobronchial lesion; 4) a pacemaker/defibrillator; or 5) a diagnosis by other means (sputum cytology, microbiology).

Follow-up included clinical assessment and erect postero-anterior chest radiographs immediately after biopsy, within 24 h and within 15 days for the evaluation of potential complications. Informed consent was obtained from all patients before conventional and EGB 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: 1) slice thickness 2–3.5 mm; 2) slice interval (with overlap of 1 mm) 1–2.5 mm; 3) image size 512x512 pixels; and 4) dicom format. If thoracic CT performed during the initial diagnostic work-up did not fulfill the above criteria a new CT was performed.

EGB

The electromagnetic navigation system (superDimension/Bronchus, Hertzliya, Israel) and navigation procedures are described in detail in the supplementary data. Briefly, the system uses a sensor probe that picks up the electromagnetic field generated by a localisation system (a processor, 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 and superimposed upon previously acquired CT images. This image-guided localisation device aimed at guiding transbronchial biopsies in desired predetermined targets within the bronchial tree. Initially, the digitised information from each patient's CT scan was imported into the electromagnetic navigation system where 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 to the actual anatomy. When these points were touched with the sensor, they were simultaneously recorded by the navigation system (registration).

The system software had the ability to correlate pre-operative CT data and actual position, to display the estimated actual location of the target on screen and to provide a navigation scheme with which to approach the lesion. In addition, the system could calculate the divergence between data obtained pre-operatively 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 anaesthesia and was carried out by two experienced bronchoscopists, C-H. Marquette and P. Ramon (see supplementary data). Navigation aimed to closely approach the target lesion (distance between sensor tip and lesion centre $\leqslant$15 mm). Nine attempts for biopsy were scheduled for each lesion and, every three attempts, the forceps were withdrawn and the position of the sensor probe in relation to the target lesion was checked.

Statistical analysis

The primary efficacy end-point was whether the EGB biopsy resulted in the diagnosis of lung cancer or 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 in diagnosis of lung cancer or lung pathology, the cases were considered as nondiagnosed 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 with completed procedures.

The yield of EGB was examined by lesion characteristics, CT-to-body divergence and bronchoscopy operator. The learning curve regarding the use of this technique was assessed by 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±SEM values for continuous data or as percentage for categorical data. Comparisons between groups of categorical data were performed using Fisher's exact and Chi-squared goodness of fit tests.

RESULTS

A total of 40 patients were enrolled in the study. Patients were aged 60±2.5 yrs and 30 out of 40 (75%) were male. A group of 12 patients had primarily severe cardiovascular problems, four had severe renal impairment (haemodialysis), 10 had severe obstruction (forced expiratory volume in one second 30.3±2.1% of predicted values), three had undergone lobectomy and the remaining eleven had mixed comorbidities (cardiovascular disease, diabetes, chronic obstructive pulmonary disease (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 size of 23.5±2 mm (range 8–49; table 1). In total, 25 lesions were classified as T1 and 15 as T2 according to tumour, node, metastasis 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 centre (or perimeter) of the target lesion before each attempt for biopsy was 8.7±0.8 mm (or -3.8±1 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-yr-old patient.

EBG produced a diagnosis in 25 (62.5%) out of 40 cases. In 20 cases, the biopsies obtained showed cancer (10 adenocarcinoma and 10 squamous cell cancer) and in five cases biopsies demonstrated a benign disease/condition (two with tuberculosis, one sandblasting silicose, one noncaseating granuloma and one hamartoma) confirmed by surgery (n=3), 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). A group of 13 EGB nondiagnostic cases were malignant (nine with lung adenocarcinoma, two metastatic adenocarcinoma and 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 finally diagnosed by open lung biopsy (n=8), mediastinoscopy (n=2) or TTNA (n=3). One patient with nondiagnostic biopsy did not complete the follow-up procedure and final diagnosis was not available. Biopsy was not feasible in the case of a 15 mm diameter peripheral nodule located in the apical segment of left lower lobe; the closest distance to target reached was 26 mm. PET was negative and CT showed regression of the lesion at 14 months follow-up.

TABLE 1 Patient characteristics

	n	Mean±SEM
Age yrs	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.

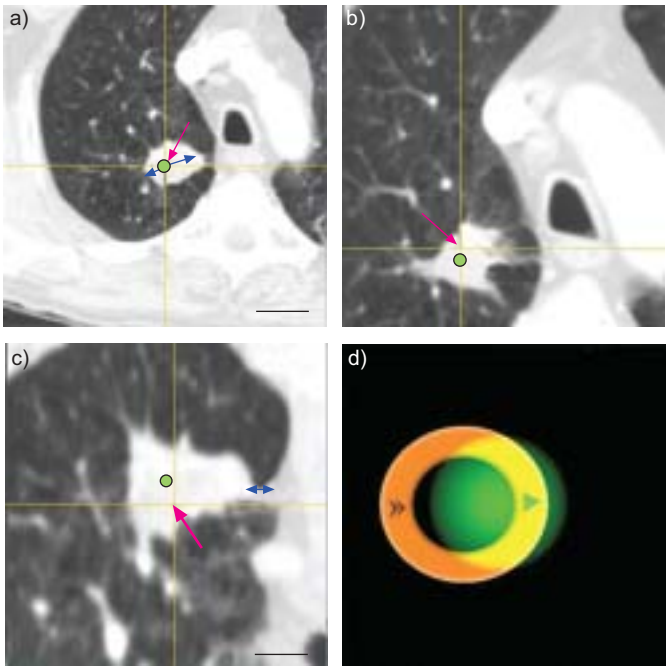

FIGURE 1. a) Computed tomography (CT) image of a nodule (green circle) of 28 mm in diameter (blue arrow) in the posterior segment of the right upper lobe, taken with the patient in a supine position. Scale bar=2 cm. b) Enlarged image of a). c) CT taken with the patient in an upright position, the nodule is 6 mm (blue arrow) from the chest wall. Scale bar=1 cm. d) The distance from the tip of the sensor probe to the target is 8 mm. In total seven biopsies were performed, out of which six contained normal lung parenchyma and one was positive for squamous cell carcinoma. Pink arrows represent the tip of the sensor probe.

The diagnostic yield of EGB for different influencing factors is shown in table 2. The yield was significantly greater when the CT-to-body divergence was ⩽4 mm (77.2 *versus* 44.4%; p=0.03). The yield for T1 and T2 lesions was 56 and 73.3%, respectively; 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 and 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).

TABLE 2 Diagnostic yield by lesion type, size, volume, location, computed tomography (CT)-to-body divergence and operator

Factors	n	Yield %
T1 lesion	25	56
T2 lesion	15	73.3
Size	4	75
⩽10 mm		
>10 mm ⩽20 mm	16	43.7
>20 mm ⩽30 mm	7	71.4
>30 mm	13	76.9
Volume	21	57.1
⩽1 cm^3		
>1 cm^3	19	68.4
Right or left upper lobe	27	66.5
All other lobes	13	53.8
Depth from visceral pleura	23	60.8
⩽14 mm		
>14 mm	17	64.7
CT-to-body divergence	22	77.2#
⩽4 mm		
>4 mm	18	44.4
Minimum distance from target	18	66.5
⩽8 mm		
>8 mm	22	59
Operator A	26	73
First 13 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.

In every lesion, 8.5±0.7 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 unrecognisable material and were judged as improper for evaluation. No significant differences were found between EGB diagnosed and EGB nondiagnosed cases in terms of number of biopsies attempted, specimens obtained and specimens analysed.

A 58-yr-old smoker with severe COPD presented with pneumothorax requiring chest drainage 5 h after bronchoscopy, while another two patients experienced small asymptomatic spontaneously resolved pneumothoraces immediately after procedure. No late adverse events were reported.

DISCUSSION

The current study is the first prospective study to demonstrate that electromagnetic navigation during flexible bronchoscopy increases the reliability of bronchoscopy for SPLL diagnosis without additional fluoroscopic assistance [22–24]. 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 ⩽4 mm, the diagnostic yield reached 77.2%. This is superior to the yield of conventional bronchoscopic techniques for SPLL reported in most studies [8–11].

The yield of flexible bronchoscopy in nodular lung lesions ranges between 19 and 62% because it is greatly affected by both lesion size and location [7, 8, 11, 25, 26]. Thus, in the study of BAAKLINI *et al*. [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 the sensitivity of bronchoscopy [27]. However, fluoroscopy causes radiation exposure [28] and the yield is still affected by lesion characteristics [8, 9, 29]. Alternative techniques, such as endobronchial ultrasound or CT-fluoroscopy, may significantly improve the diagnostic yield of conventional bronchoscopy [15, 21] but there are also drawbacks to these methods. Endobronchial ultrasound is costly, requires regular probe replacement and includes difficulty in selecting the bronchial branch of interest thus producing a lower yield in apical-posterior lobes. Conversely, radiation exposure for both staff and patients restricts the efficient application of CT-fluoroscopy [15]. Therefore, electromagnetic navigation for bronchoscopy guidance may be valuable in the diagnosis of SPLL when conventional bronchoscopy fails.

In the present study, the authors 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 the limitations that exist in the diagnosis and treatment of pulmonary nodules in medically nonoperable patients. Surgery is associated with a 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 that can be substantial in patients with an already compromised respiratory or low performance status. Consequently, both diagnostic and treatment decisions for medically nonoperable 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, histopathological confirmation of malignancy is essential prior to the initiation of these alternative treatments. In the present study, EGB successfully established a diagnosis in the majority of patients in this population. Moreover, in agreement with the results of earlier studies [22–24] 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 nonoperable patients.

The effect of electromagnetic navigational accuracy on SPLL biopsy results has not been evaluated until now. Although GILDEA *et al.* [24] recently reported an excellent yield of EGB in the diagnosis of parenchymal and mediastinal lung lesions, additional fluoroscopic guidance was used systematically before biopsy. In this respect, the present study is the first to evaluate the accuracy of this technique in SPLL diagnosis

without the help of additional fluoroscopic guidance. Moreover, it demonstrates a relationship between a measure of the navigational accuracy and biopsy results. The current findings suggest that the diagnostic yield of EGB may be affected by CT-to-body divergence rather than the size or location of the lesion. The EGB yield was found to be significantly lower when CT-to-body divergence was >4 mm.

CT-to-body divergence is unavoidable as EBG is not a real-time navigational system and this may be one of its current drawbacks. EBG yield is based on the reconstructed positioning as generated by the computerised system from the three-dimensional CT data and the registration process. Therefore, the bronchial relationships of a nodule may differ from fibreoptic 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 with ultra-fast temporal resolution and/or respiratory gating.

In the present study, despite efforts to approach the target as closely as possible, the mean distance achieved from the centre of the target was 8.7 mm. This is most likely to be due to the progressive narrowing and branching of the bronchial tree. Although this difference did not significantly affect the results, it remains to be seen whether further improvements in equipment and software can overcome problems related to the architecture of the bronchial tree and further ameliorate the yield of EBG.

In the present study, no significant learning curve related to the technique was observed; the diagnostic accuracy during the first sessions of EBG was not significantly lower than that achieved during last session. EGB is not a cumbersome technique. Providing a previous experience in flexible bronchoscopy, EGB can be easily learnt.

As a large bronchoscope is needed for EBG, and the technique involves more manipulations than conventional bronchoscopy, the current patients underwent this procedure under anaesthesia in order to increase their comfort. Hence, the present results are not likely to be affected by cough or body movement. In addition, it is questionable whether respiration-induced movement significantly affects the yield of EGB [22–24]. The present findings indirectly suggest that the opposite is the case. 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 study, 8.5 ± 0.7 biopsies were attempted per lesion which is greater than that reported in most studies. On the one hand this may have contributed to the high accuracy rate of this study but, on the other hand, makes a comparison with other studies difficult. However, a large number of biopsies were attempted because sampling issues may have a major role in the misdiagnosis in lung lesions cases [33]. In the current study not all the samples obtained were adequate for analysis by the pathology department. Specimens obtained by flexible bronchoscopy forceps may be of small size, damaged or contain crush artefacts and thus, may be of low quality and consequently offer limited interpretation [34]. Moreover, random problems that may occur during specimen delivery or conservation are not unlikely in clinical practice. These type of drawbacks underline the fact that, despite all the 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 biopsy is negative or nondiagnostic, using all available diagnostic methods.

The pneumothorax rate in the current study (three out of 40) was similar to that reported in a previous study (two out of 60) [24], although additional fluoroscopic guidance was not used during bronchoscopy and, in addition, a large number of biopsies were performed per lesion. Two patients experienced asymptomatic pneumothoraces immediately after procedure and a third patient presented with symptomatic pneumothorax a few hours later. In this respect, attention should be paid to the occurrence of adverse events in the 24 hours following the 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 the present study is superior to rates reported in most previous studies 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 a substantial contribution in the early diagnosis and treatment of lung cancer, particularly in patients considered medically inoperable. However, the 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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