Interventional Pulmonology

Respiration

Respiration 2009;78:293–300
DOI: 10.1159/000226128

Received: October 20, 2008
Accepted after revision: March 16, 2009
Published online: June 23, 2009

Accuracy and Feasibility of Electromagnetic Navigated Bronchoscopy under Nitrous Oxide Sedation for Pulmonary Peripheral Opacities: An Outpatient Study

Laurent Bertoletti[a, e] Aurélie Robert[b] Michèle Cottier[c]
Marie Laure Chambonniere[d] Jean-Michel Vergnon[a, e]

Departments of [a]Chest Diseases and Thoracic Oncology, [b]Radiology, [c]Cytology, and [d]Pathology, Hôpital Nord, University Hospital of St Etienne and Université Jean Monnet, and [e]French-Speaking Group of Thoracic Endoscopy (GELF), Saint-Etienne, France

Key Words
Bronchoscopy · Electromagnetic navigated bronchoscopy · Lung cancer · Solitary pulmonary nodule

Abstract
Background: Recent studies have described the promising method of electromagnetic navigated bronchoscopy (ENB) for diagnosis of peripheral solitary nodules. However, they require general anaesthesia or intravenous sedation. We wanted to know if ENB could be applied more easily in outpatients. ***Objectives:*** We prospectively evaluated the accuracy and the feasibility of ENB under local anaesthesia and nitrous oxide/oxygen inhalation as unique sedation in outpatients. ***Methods:*** After mapping time, the bronchoscopic procedure was carried out under local anaesthesia and nitrous oxide/oxygen inhalation with the unique help of the ENB to confirm the right position of the extended working channel before sampling. The primary end point was the accuracy of ENB and the secondary end point was the feasibility in outpatients. ***Results:*** Among 54 screened patients, 53 completed the study protocol. The overall diagnostic success rate to diagnose malignancy was 71.4% in tumours of 28 mm in median size. ENB classified correctly peripheral lesions according to malignity in 41 cases (30 cases of cancer, 11 benign diagnosis) and failed in 12 cases (1 probable lung metastasis, 11 lung cancers). All patients but 1 were dismissed 1 h after the procedure and the tolerance of the procedure was excellent in all cases except 2 (agitation and anxiety). In two cases (4%) a pneumothorax was recorded, 1 requiring drainage with a chest tube during a short hospitalisation. ***Conclusions:*** ENB under nitrous oxide/oxygen sedation seems to be an accurate and safe procedure. In our series, it allowed us to obtain the diagnosis in 71.4% of the tumours, with a good tolerance and an outpatient strategy.

Introduction

The diagnosis of peripheral lung nodules, which is always difficult, is a frequent clinical problem, being observed in about 25% of all cases of lung cancers [1]. In the future, this clinical situation will increase with the growing incidence of adenocarcinomas, and could also be promoted through the use of low-dose spiral CT scans able to detect early small nodules. With conventional bronchoscopy, positive diagnosis is obtained in about 60% of

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0025–7931/09/0783–0293$26.00/0

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Jean-Michel Vergnon
Department of Chest Diseases and Thoracic Oncology
University Hospital of St Etienne and Université Jean Monnet
FR–42000 Saint-Etienne (France), Tel. +33 4 7782 8314, Fax +33 4 7782 8090
E-Mail jean.michel.vergnon@univ-st-etienne.fr

cases of tumours larger than 2 cm and in 30% of cases in smaller lesions. In the outer third of the lungs, the diagnosis yield falls to 14% [1–5]. Navigation to the peripheral bronchi is now possible with electromagnetic navigated bronchoscopy (ENB) from the SuperDimension® company. Several recent papers underline the interest in this technology [6–12]. In the first reports of its use, the correct position of the sensor before sampling was controlled by fluoroscopy or echoendoscopy, but in the most recent papers, the sampling was performed without another guidance technique. In each case, the procedure was conducted under general anaesthesia or i.v. sedation.

The goal of this clinical study, which was carried out in a French academic department of chest diseases and thoracic oncology, was to analyze the accuracy and feasibility of ENB during a simple outpatient flexible bronchoscopy, performed under local anaesthesia and nitrous oxide/oxygen inhalation, without any other location control before sampling and without rapid on-site cytology examination, in non-selected patients.

The primary end point was to assess the accuracy of ENB in the diagnosis of pulmonary opacities in 'real life', in a French academic department of chest diseases and thoracic oncology. The accuracy was studied by recording dimensions and localization (particularly distance to the pleura) of the opacity, the average fiducial target registration error (AFTRE) score and the diagnostic yields.

The secondary end point was the feasibility in outpatients with the efficacy of an original inhalation of nitrous oxide/oxygen mixture, which was evaluated by length, tolerance and safety of the procedure.

Protocol and Methods

Protocol

The ENB was installed in our bronchoscopy suite in June 2005. This device is approved for clinical use in the European community.

In our institution, in case of a solitary PET-positive nodule or peripheral opacity, without endoluminal lesions detected on standard bronchoscopy, in a low-risk operable patient, surgery (with peroperative diagnosis) was considered as the best approach.

In other cases (e.g. high-risk surgery or inoperable patient), ENB was proposed as the first-choice method in absence of endobronchial pathology.

Diagnostic yield was defined as follows: when ENB provided a malignant tissue, the diagnosis was presumed true (true-positive cases). When ENB gave a non-malignant diagnosis, which was consistent with additional procedures (clinical and radiological long-term follow-up or surgery), the diagnosis was assumed to be true (true negative for cancer).

When ENB-guided biopsies showed non-malignant tissue and additional procedures [surgery, trans-thoracic needle aspiration (TTNA) or new bronchoscopy] lead to a diagnosis of cancer, we concluded the ENB method had failed (false negative).

According to French ethics regulations, all cases were discussed in a multidisciplinary team conference and the protocol was approved by the local ethics committee. The patients were treated after informed consent. All consecutive patients were included prospectively from June 2005 to December 2006, and in each case a follow-up of more than 18 months was obtained.

Mapping

The method has been extensively described in previous papers [6–12]. In short, the digitized information from the CT scan (Sensation 16; Philips) was downloaded to the ENB SuperDimension software (SuperDimension Europe GmbH, Düsseldorf, Germany) in DICOM format. Between 200 and 350 images were used (slice thickness 2.0 mm, slice increment 1.0 mm). All the CT scans were performed less than 2 weeks before the bronchoscopy. The ENB SuperDimension software reconstructs graphical axial, coronal and sagittal views of the chest and generates virtual bronchoscopy images. On these bronchoscopy images, 6 or 7 virtual fiducial landmarks (main carena and 3 s or third order carenas on each side) as well as the centre of the tumour were tagged. The size of the tumour in each dimension and the minimal distance from the tumour to the pleura were recorded.

Bronchoscopic Procedure

First, the patient is installed in a lying position on a horizontal table. Under his back, close to the thorax, the electromagnetic location board is installed, which induces an electromagnetic field surrounding the thorax of the patient. Three reference sensors are fixed on the thorax to compensate for respiratory and body movements during the procedure. The flexible bronchoscopy was performed through a nasal route (bronchoscopist behind the patient's head) with a large flexible fibre bronchoscope with a 5.9-mm bronchoscope and a 2.8-mm operative channel (Olympus T10). The local anaesthetic (lidocaine 2% spray solution) was first applied with a nebulizer in the nasal lumen and subsequently by spraying through the fibre-bronchoscope on to the vocal cords. According to the experience of Atassi et al. [13], the patient breathed a 50%/50% nitrous oxide/oxygen mixture (Kalinox®; Air liquide, France) through a facial mask. Kalinox inhalation started 3 min before the bronchoscope insertion and continued throughout the procedure. The bronchoscope was passed in a small hole made in the silicone cap of the mask.

All the procedures were performed by the same bronchoscopist (J.-M.V.). A standard bronchoscopy was first performed in order to check the bronchi and to register the landmarks previously selected on the virtual images of the planning software. To reduce respiratory movement errors, each of the real landmarks was touched with the sensor probe at the end of the inspiration phase. The software of the system then aligns virtual registration marks and real-time anatomy. The accuracy of the navigation, assessed with the AFTRE score was registered for each patient.

The bronchoscope can be navigated under direct vision in the correct segmental bronchus (as assessed by virtual bronchoscopy). Then, the bronchoscope was fixed, and the sensor probe mounted in a 1.9 flexible catheter was pushed forward and navigated to the best position with a steerable knob. At the minimal

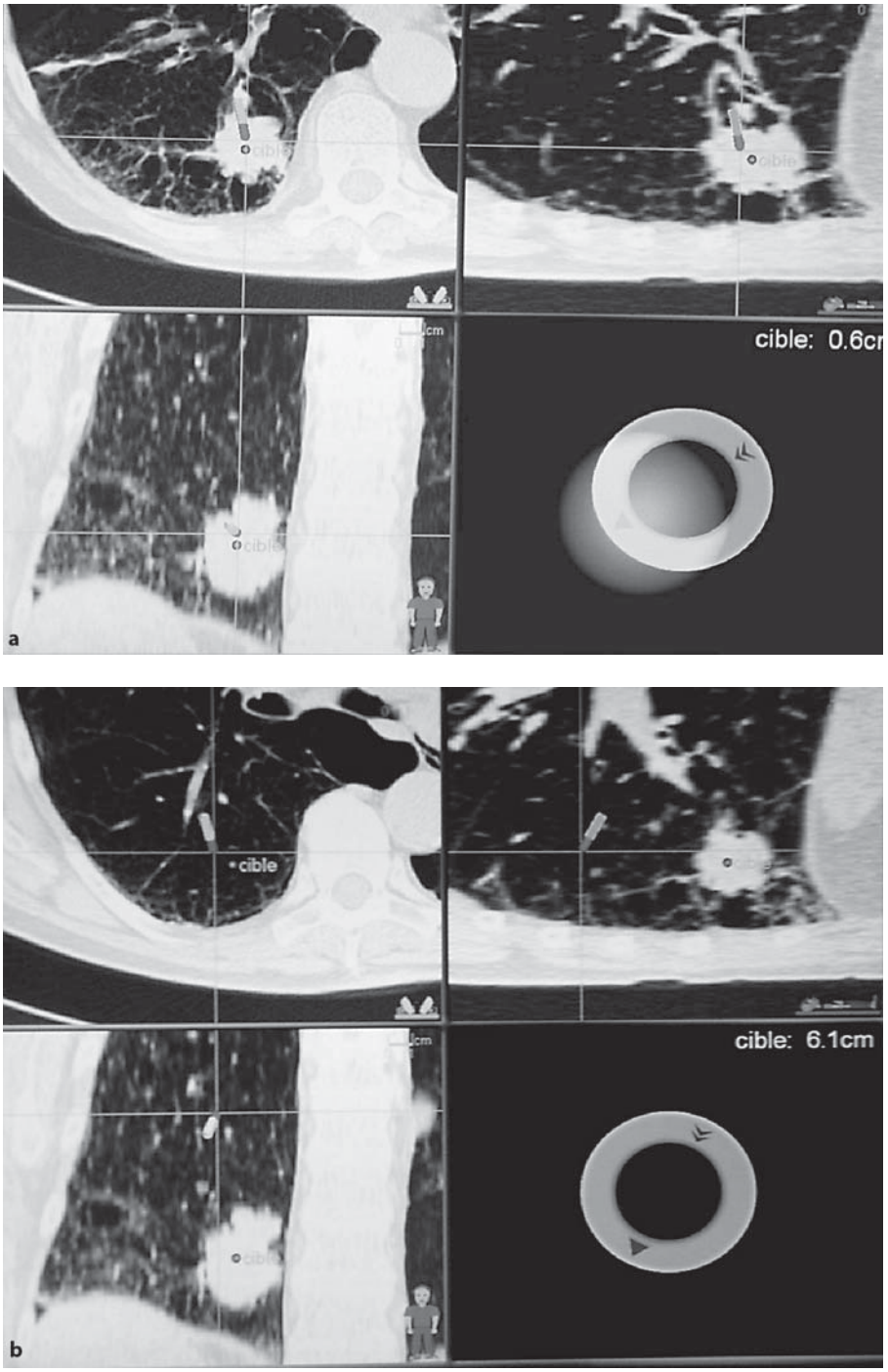

Fig. 1. a Position of the sensor and the target at the end of the inspiratory phase. **b** Variation of the position of the sensor and of the target during the expiratory phase. Note the 6-cm difference between 1 and 2, without extended working channel movement, in the lesion near to the diaphragm.

distance between the sensor and the centre of the target (registered data), the extended working channel was fixed and the locatable guide was removed.

Sampling

A disposable biopsy forceps was passed through the extended working channel left in place and 5 successive biopsies were performed. To reduce respiratory movement errors, the biopsies were taken at the end of the inspiration phase (fig. 1a, b is the same patient and the same position but during the expiratory time). Then, the locatable guide with sensor was introduced again to check the correct position on the computed images. If a significant deviation was found, the sensor was positioned at a better position and 3–5 new biopsies were taken. After the biopsies, the sensor was

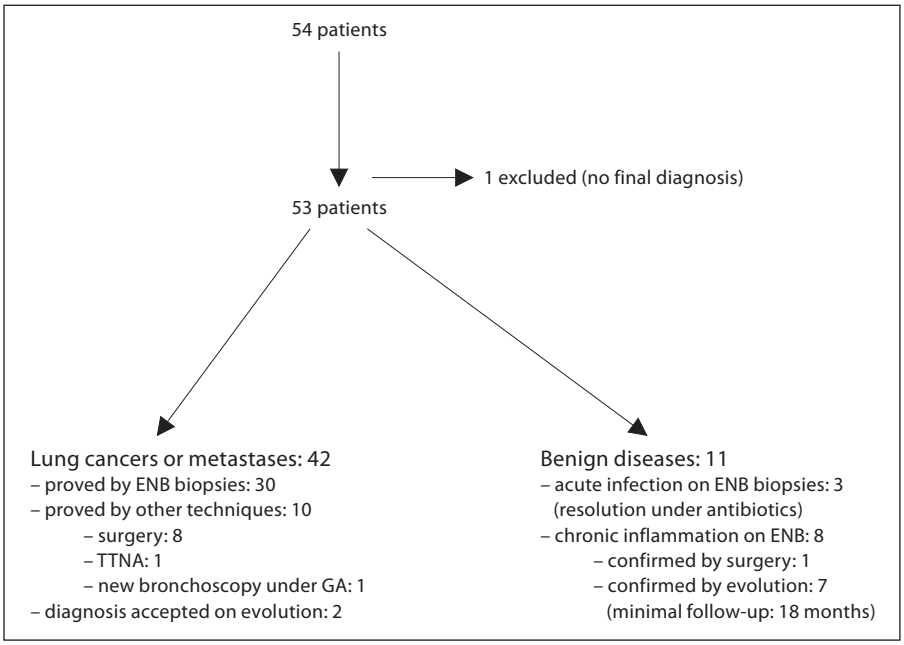

Fig. 2. Global results in our population. ENB = Electromagnetic navigated bronchoscopy; GA = general anaesthetic; TTNA = trans-thoracic needle aspiration.

removed again to perform a brushing in the same area. The bronchoscope was then removed. Total duration of the procedure and tolerance were recorded for analysis.

No fluoroscopic or echo-endoscopic control of the location of the locatable guide were carried out before biopsies were performed and no cytologist on site checked the accuracy of sampling.

Follow-Up

A chest X-ray was performed 1 h after the biopsies in each case to check for any pneumothorax occurrence before the patient was discharged.

Results

Accuracy of ENB in Diagnosis of Pulmonary Opacities

54 patients (47 males, mean age 67 years) were selected for ENB and submitted to virtual navigation during the study period, but only 53 were analysed. The patient who was excluded was a 69-year-old man who presented with a peripheral opacity with benign samples (chronic inflammation). He died 6 months later from a unrelated disease with stable pulmonary lesion. We could not confirm the pulmonary diagnosis. Figure 2 summarizes our results.

In each case, the standard exploration of the bronchi was normal and all samples performed on global aspirates were negative.

The mean procedure duration (from the introduction of the bronchoscope in the nose to withdrawal) was 29.5 min (from 15 to 55 min).

Table 1 shows the mean (and range) of the nodule size, the mean (and range) distance of the tumour from the pleura, the AFTRE score and the minimal distance between the sensor probe and the tumour centre at the sampling time.

Table 2 presents our results for the diagnostic yield and the impact of the tumour size. ENB allowed a correct diagnosis for malignancy in 41 cases. For 30 cases ENB gave an accurate diagnosis of cancer, in particular in the 5 metastasis cases (thymus carcinoma, 2 breast cancers, melanoma, urothelial carcinoma). In malignant nodules, ENB obtained the diagnosis both by cytology and biopsies in 24 of the 30 cases in which ENB gave a diagnosis of cancer. For the diagnosis of cancer, the overall predictive negative value was 48%. But the size influences greatly the results: the failure rate was 4/5 (80%), 7/28 (25%) and 2/10 (20%) for cancer under 20 mm, between 20 and 40 mm and more than 40 mm, respectively.

In 11 patients, ENB revealed benign acute or chronic inflammation. In 3 of these cases, it was an acute pneumonia, proved by regression under antibiotics in the 3 cases and microbiological agent in one. It was a surprise in the absence of clinical or biological signs of infectious diseases. In the 8 other cases, histological findings did not reveal tumoural components but only chronic in-

Table 1. Opacities, characteristics and ENB results

Nodule size, mm	Distance to pleura, mm	AFTRE, mm	Distance between sensor probe and tumour centre at sampling time, mm
31.2 ± 14.4	9.1 ± 11	4.7 ± 1.3	10 ± 5.9
Median: 28	Median: 5.5	Median: 4.6	Median: 9
<20 (n = 7)	12 ± 9.2	4.3 ± 0.8	8.1 ± 3.3
[20; 40] (n = 36)	10.2 ± 11.7	4.9 ± 1.4	8.8 ± 4.1
>40 (n = 10)	3.4 ± 8.1	4.35 ± 1.3	14.3 ± 9.7

Data are means ± standard deviations.

Table 2. Usefulness of ENB for malignancies and impact of size

	n	Positive diagnostic yield, n	ENB failure, n	PPV (cancers)	NPV
Malignant diseases	42	30 (71.4%)	12 (28.5%)		
In primary lung cancer	36	25	11		
In metastatic cancer	6	5	1		
Non malignant diseases	11	11	0		
Proved infection	3	3	0		
Chronic fibrous lesions	8	8	0		
Total number	53	41	12	71.4%	52%
Opacity size <20 mm	7	3	4		
In malignant diseases	5	1	4		
In non-malignant diseases	2	2	0		
Opacity size 20–40 mm	36	29	7		
In malignant diseases	28	21	7		
In non-malignant diseases	8	8	0		
Opacity size >40 mm	10	8	2		
In malignant diseases	10	8	2		
In non malignant diseases	0	0	0		

PPV = Positive predictive value; NPV = negative predictive value.

flammation or fibrosis. A precise diagnosis could not be given on these biopsies in the absence of typical features. A surgical biopsy was obtained for the first patient, showing the same hyaline fibrosis. The others were followed. Clinical and radiological data were stable for more than 18 months and we retained a benign process, without a precise aetiology.

Failure Analysis

The ENB technique failed to give the correct diagnosis in 12 cases. In 10 cases, further investigation (surgery, TTNA or new bronchoscopy) proved lung cancer.

For 2 patients, no proven diagnosis existed. In the first case, this patient had hepatic metastasis melanoma and presented with an isolated pulmonary nodule. This presumed tumour was very small (15 mm) and very peripheral (6 mm to the pleura). The AFTRE score was high when compared to the tumour size (10 mm). No tumoural tissue was obtained with ENB and the opacity had grown by 20% in 1 year. We concluded a probable lung metastasis of melanoma. In the second case, an 87-year-old lady, a myocardial infarction occurred 1 month after the bronchoscopy and surgery was cancelled. The diagnosis of lung cancer was assumed on tumour growth during the follow-up and on the high fixation on PET scan. For this very tired patient, the procedure had to be shortened, and failed. The tumour size was 37 × 32 × 30 mm.

In the 6 other patients, the tumours were very small: 12.5, 14, 14.5, 14.7, 20.5 and 21.5 mm. All were in the upper lobes. Access to the largest one (21.5 mm) was worsened by bronchial distortions and we could not approach nearer than 15 mm from the centre of the tumour. Diagnosis of cancer was obtained by surgical biopsies.

One case was marked by a technical failure. The patient was suffering from severe emphysema and had undergone a lobectomy in the past. This induced enough bronchial distortions to provoke a large difference between virtual and real navigation (AFTRE = 10.1mm). Biopsies were not done on this tumour (22 × 26 × 26 mm). Surgery confirmed lung cancer.

One other patient was very anxious, despite the nitrous oxide inhalation (Kalinox) and presented an uncontrollable cough during the examination. No biopsy of the target was made during ENB. The diagnosis of left upper lobe lung cancer was made later by distal lung biopsies during bronchoscopy under general anaesthesia.

In the last 2 malignant cases, the tumours were the largest of our series (54 and 71 mm). We could not approach nearer than 25 and 35 mm from the centre of the tumours, respectively. In one case, the diagnosis was obtained by TTNA (showing an important tumoural necrosis). In the last case, ENB showed only metaplasia, and diagnosis was difficult to obtain even by TTNA (which only showed necrosis) and by surgical biopsies (cancerous cells were revealed only after a second assessment and preparation of the histological fragments).

The overall success rate to diagnose malignancy was 71.4%.

Feasibility in Outpatients with Efficacy of Original Inhalation of NO/O_2 Mixture

All patients but 1 were discharged 1 h after the procedure. The tolerance of the procedure was excellent in all cases except 2 (agitation and anxiety) in which the procedure had to be shortened, inducing 2 ENB failures. No significant bleeding was recorded after sampling. No oxygen desaturation occurred. In 2 cases (4%) a pneumothorax was recorded. One was minimal, requiring no treatment or hospitalisation. The second pneumothorax required drainage with a chest tube during a short hospitalisation. Both occurred in patients with upper-lobe lesions with a distance between the tumour and the pleura shorter than 6 mm.

Discussion

Accuracy

Different techniques have been proposed to improve the accuracy of bronchoscopic biopsies in peripheral opacities, including fluoroscopic guidance, echo-guidance with radial miniprobes [3, 14], CT guidance with virtual bronchoscopies and ultrathin bronchoscopes [15, 16], and electromagnetic navigation. Among the publications with electromagnetic guidance, our overall results (71.4% success in diagnosis of malignancy) are quite similar to the previous reported data which included an additional guidance technique (Becker et al. [6] 69%, Gildea et al. [9] 74%, Schwartz et al. [12] 69%, Wilson and Bartlett [17] 70%). Similar to our study, 3 very recent papers [7, 8, 10] reported the accuracy of this technique using ENB alone. The diagnostic yield seems to be a little bit lower, with 59% in the ENB arm reported by Eberhardt et al. [7], 62.5% in a paper by Makris et al. [10] and 67% in a second paper by Eberhardt et al. [8] using the same criteria as our study. In all these studies, rapid on-site examination was never performed. Two recent studies used this procedure [17, 18], but with the help of fluoroscopy in the first [17] and the other focused only on 13 patients. Pneumothorax was the main side effect of this technique reported in these papers but at a very low level.

These results seem quite similar to published results with echo-guidance (always with the help of fluoroscopic guidance) [3, 14]. A combination of the 2 technologies may improve the diagnostic yield as suggested in a recent study [7] (with 88% diagnostic yield), by compensating for the insufficiencies of each method alone.

According to our study, the tumour size is one of the most predictive factors of accuracy or failure.

With lesions smaller than 20 mm, we have observed a failure rate of more than 50%, contrasting with less than 20% in larger lesions. This point is confirmed in Makris et al. [10] where the diagnostic yield is only of 62.5% in lesions of mean 23.5 mm. This point is less clear in Eberhardt et al. [8] , but the diagnostic yield reaches only 62% in tumours less than 20 mm.

The explanation can be found in the non-real time guidance, and in the respiratory movements, which have a greater impact on the diagnosis of small tumours. In the upper parts of the lung, the respiratory movements are limited, and the 3 patient location sensors attached to the anterior thorax wall are sufficient to correct for the position. In contrast, in lower lobes, close to the diaphragm, these movements are too large and not attenuated enough by the ventilation sensors (fig. 1). To reduce this pitfall,

we advise performing the mapping and the sampling at the end-inspiratory phases (like CT-scan acquisitions). Following this simple physiological concept, we did not encounter significant differences in diagnostic yield between upper-lobe tumours and those close to the diaphragm for lesions of more than 20 mm. Echo-guidance is more efficient without the negative impact of the tumour size on the diagnostic rate. These results are probably due to a near real-time procedure. In contrast to echo, ENB can reach with equal accuracy upper lobes and lower lobes, whereas the accuracy of echo is lower in upper lobes (failure risk increases up to 60% in upper-lobe zones [14]).

In the two largest tumours, we met another cause of failure: bronchial distortions and very necrotic tumours.

As underlined by Makris et al. [10], the relation between size, AFTRE score and distance between the sensor probe and the tumour centre at the sampling time are important criteria of success.

Feasibility

An original inhaled nitrous oxide sedation was used in this study. For 4 years, this technique has been widely used in our department. The efficacy of this method has been proved by Atassi et al. [13] in a double-blind trial during flexible bronchoscopies. We can confirm here the efficacy and safety of this technique as applied to ENB. No side effects were recorded and in all cases but 1 (and, in part, a second) the procedure was conducted with an excellent tolerance. During sedation, the patient is perfectly awake and can follow instructions, so he can maintain a full inspiration during the landmark registration and during the target biopsies. Thus, errors associated with ventilation movements can be reduced. That could explain our positive results, comparable with other series, adding another location control.

Nitrous oxide inhalation offers a safety profile better than i.v. sedation. Due to its safety, this method can be applied without the presence of an anaesthetist and the patient can be immediately discharged. This technique simplifies the procedure and so decreases the cost. In contrast, i.v. sedation requires the use of hospital and anaesthetic resources. In many countries (including France) regulations require the presence of an anaesthetist, in practice in an operating theatre.

A pre-operative sedation with diazepine or midazolam has been proposed but the effectiveness remains controversial [19].

Conclusions

We confirm that ENB under nitrous oxide sedation is an accurate and safe method in outpatients. Using a simple and cheap method (without anaesthetist, operating theatre, on-site cytologist or fluoroscopy) we have obtained a diagnostic accuracy of 71.4% for malignancy in peripheral tumours of 28 mm median size.

For us, the tumour size remains a limitation. This electromagnetic navigation technology could be improved in the following 2 ways: better ventilation correction obtained through better mathematic algorithms to compensate for these movements, and/or the addition of a real-time control of the final position of the extended working channel before sampling (endoluminal images).

References

1 Gould MK, Lillington GA: Strategy and cost in investigating solitary pulmonary nodules. Thorax 1998;53:32S–337S.

2 Baaklini W, Reinoso M, Gorin A, et al: Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest 2000;117:1049–1054.

3 Paone G, Nicastri E, Lucantoni G, et al: Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest 2005;128:3551–3557.

4 Schreiber G, McCrory DC: Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest 2003;123:115S–128S.

5 Swensen SJ, Jett JR, Sloan JA, et al: Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002;165:508–513.

6 Becker HD, Herth F, Ernst A, et al: Bronchoscopic biopsy of peripheral lung lesions under electromagnetic guidance: a pilot study. J Bronchology 2005;12:9–13.

7 Eberhardt R, Anantham D, Herth F, et al: Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions. Chest 2007;131:1800–1805.

8 Eberhardt R, Anantham D, Armin E, et al: Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med 2007;176:36–41.

9 Gildea TR, Mazzone PJ, Karnak D, et al: Electromagnetic navigation diagnostic bronchoscopy: a prospective study. Am J Respir Crit Care Med 2006;174:982–989.

10 Makris D, Scherpereel A, Leroy S, et al: Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions. Eur Respir J 2007;29:1187–1192.
11 Schwarz Y, Mehta AC, Ernst A, et al: Electromagnetic navigation during flexible bronchoscopy. Respiration 2003;70:516–522.
12 Schwarz Y, Greif J, Becker HD, et al: Real-time electromagnetic navigation bronchoscopy to peripheral lung lesions using overlaid CT images: the first human study. Chest 2006;129:988–994.
13 Atassi K, Mangiapan C, Lasry S, et al: Prefixed equimolar nitrous oxide and oxygen mixture reduces discomfort during flexible bronchoscopy in adult patients: a randomized, controlled, double-blind trial. Chest 2005;128:863–868.
14 Kurimoto N, Miyazawa T, Okimasa S, et al: Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 2004;126:959–965.
15 Shinagawa N, Yamazaki K, Onodera Y, et al: CT-guided transbronchial biopsy using an ultrathin bronchoscope with virtual bronchoscopic navigation. Chest 2004;125:1138–1143.
16 Shinagawa N, Yamazaki K, Onodera Y, et al: Factors related to diagnostic sensitivity using an ultrathin bronchoscope under CT guidance. Chest 2007;131:549–553.
17 Wilson DS, Bartlett RJ: Improved diagnostic yield of bronchoscopy in a community practice: combination of electromagnetic navigation system and rapid on-site evaluation. J Bronchol 2007;14:227–232.
18 Lamprecht B, Porsch P, Pirich C, et al: Electromagnetic navigation bronchoscopy in combination with PET-CT and rapid on-site cytopathologic examination for diagnosis of peripheral lung lesions. Lung 2009;187:55–59.
19 Hatton MQF, Allen MB, Vathenen AS, et al: Does sedation help in fibreoptic bronchoscopy? BMJ 1994;309:1206–1207.