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Ultrasound-Guided Transbronchial Biopsies of Solitary Pulmonary Nodules less than 20 mm

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Short title:

EBUS-guided Biopsies of SPN less than 20 mm

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Abstract

Objectives: Transbronchial biopsy of solitary pulmonary nodules (SPNs) is usually performed under fluoroscopic guidance, but success varies widely. Endobronchial ultrasound (EBUS) may increase the likelihood of success. We assessed the ability of EBUS-guided transbronchial biopsies to sample SPNs less than 20 mm in diameter.

Patients and Methods: All patients seen between 06/2004 and 08/2007 in whom computed tomography identified a SPN less than 20 mm underwent bronchoscopy general anesthesia or moderate sedation for a radial EBUS-guided examination. If a typical ultrasonic picture of solid tissue could be identified, specimens were taken through a catheter with forceps. If the node was not detected within 20 minutes, the procedure was terminated.

Results: Of 100 nodules detected in 100 consecutive patients, 67 (mean diameter 15 mm) were visualized with EBUS and biopsied. A diagnosis was established for 46 patients (46%). If the lesion was visualized by EBUS, the diagnostic success was 69% (46/67). The 33 patients whose nodules could not be sampled underwent surgical biopsy. Pneumothorax occurred in 3 patients.

Conclusions: For SPNs less than 20 mm that can be detected with ultrasound, EBUS-guided transbronchial biopsy is safe and effective.

Key words: bronchoscopy; endobronchial ultrasound; lung cancer; solitary pulmonary nodules; transbronchial lung biopsy

Abbreviations

EBUS = endobronchial ultrasound

SPN = solitary pulmonary nodule

RUL = right upper lobe

ML = middle lobe

RLL = right lower lobe

LUL = left upper lobe

LLL = left lower lobe.

Introduction

Flexible bronchoscopy has a variable and often poor success rate in sampling pulmonary lesions during a normal endobronchial examination. The sensitivity of bronchoscopy for detecting malignancy in a solitary pulmonary nodule depends on the size of the nodule, the proximity of the nodule to the bronchial tree, the success in sampling the nodule, and the prevalence of cancer in the study population (1,2). For peripheral lesions between 2.5 cm and 4.0 cm a bronchoscopic diagnostic yield of 62% was reported, but in the same study the diagnostic sensitivity in patients with suspicion for cancer decreased to less than 40%, if the nodules were smaller than 2.5 cm (3). Successful biopsies are mostly achieved with fluoroscopic guidance, but especially nodules less than 20 mm in diameter are difficult or impossible to visualize. Thus, for these nodules Schreiber et al. found in a metaanalysis an overall diagnostic sensitivity of 33% (range 5 – 76 %), and only in 2 of 8 analyzed studies the diagnostic yield was higher(5).

Endobronchial ultrasonography (EBUS) with a radial probe is useful in sampling peripheral pulmonary lesions (4, 6-9). Several articles have reported the success of EBUS-guided transbronchial biopsy in SPNs (4, 6-12), but in the most of these trials, SPNs smaller than 20 mm were not examined.

An alternative to fluoroscopic guidance is electromagnetic navigation, which can guide the biopsy of peripheral lesions. The reported success in sampling lesions less than 30 mm in diameter is around 65% (13-16). However, electromagnetic navigation is not widely available, requires a thin-section computed tomograph (CT) for planning and expensive disposables.

CT-guided transthoracic needle aspiration may result in a diagnosis in 74% up to 96% of patients again depending on the lesion size (17, 18, 19, 24), but it is associated with reported pneumothorax rates that range from 15% to 44% (17-20, 24).

We investigated whether EBUS-guided transbronchial biopsy could be used successfully in patients with small lesions.

Patients and Methods

The research was conducted in accordance with the 1975 Helsinki Declaration. The study was approved by the Institutional Review Board and written informed consent was obtained from all patients before the bronchoscopy.

We collected data on consecutive adult patients, who were older than 40 years and had a positive smoking history and were referred for diagnostic bronchoscopy. We reviewed chest CT scans to identify all patients with SPNs with a diameter of less than 20 mm and characteristics making a malignant lesion likely (e.g.spiculations and no calcifications present). Standard bronchoscopy was performed with the patients receiving general anesthesia or moderate sedation. Several videobronchoscopes (models BF T160; BF T 180 Olympus; Tokyo, Japan) were used. Radial endobronchial ultrasound guidance was provided by a flexible probe and processor unit (UM-3R, UM-4R, US2020R; Olympus; Tokyo, Japan) as described below.

Endobronchial Ultrasound

A 20-MHz mechanical radial-type probe (UM-S20-20R; Olympus, Tokyo, Japan) with an external diameter of 1.7 mm was inserted through a guide sheath (external diameter, 2.7 mm; XB01-836-13; Olympus) in the working channel of the videoscope. The probe was inserted into the bronchi leading to the area in which the lesion was identified on the radiological image. In contrast to the “snowstorm-like” whitish image of air-containing lung tissue, a solid lesion appears darker and more homogeneous on an ultrasound image. Nodules are usually well differentiated against the lung tissue by a bright border because of the difference in impedance (Fig. 1). If a typical ultrasonic image of a nodule could be seen, the probe was removed, but the guide sheath was left in place. Four to six biopsy specimens were obtained through the guide sheath with regular disposable biopsy forceps.

If a nodule was not detected with ultrasound imaging within 20 minutes, the procedure was stopped. Procedures that detected no nodules or that resulted in a non-specific bronchoscopic diagnosis of fibrosis or inflammation were considered to be nondiagnostic. All patients with nondiagnostic results were referred for surgical biopsies.

Statistical Methods

Diagnostic sensitivity, specificity, and accuracy of the EBUS-guided transbronchial biopsy were calculated using the standard definitions. Alpha was set at 0.05, and the SPSS statistical software package was used for all analyses (SPSS version 11.5; SPSS; Chicago, IL).

Results

From July 2004 through June 2007, 122 consecutive patients with SPNs were screened for the trial. After complete inspection of the bronchial tree, including the subsegmental bronchi, fluoroscopy was performed using a monoplanar C-arm (Suprer 50 CP; Philipps Company; Amsterdam, the Netherlands). If the lesion was visible fluoroscopically, the procedure was continued with TBBX in the standard manner, and the patient was excluded from the trial. If the lesion could not be visualized by fluoroscopy, the patient was included in the trial and TBBX was attempted under EBUS guidance. Reasons for non-enrollment in 22 cases have been fluoroscopically visible lesions (13 patients), a diameter of more than 20 mm (5 Patients), contraindication for diagnostic bronchoscopy (2 patients) or the patients refused consent (2 patients).

Of the 122 screened patients, 100 (44 women and 56 men; mean age, 51.7 years; range, 39 to 73 years) presented with SPNs less than 20 mm. The mean (SD) diameter of the lesions was 15 (4.2) mm (range 9 to 20 mm). Mean nodule size did not differ significantly between detected and non-detected nodules or between detected nodules that did or did not return a diagnosis (Table 1). Most nodules were located in the right and left upper lobes (Table 1).

Nodules were localized within 20 minutes in 67 patients (67%), and a diagnosis was established in 46 of the 67 (69%). In the other 21 patients, the lesion was detected and biopsied, but the pathologist was unable to establish a definitive diagnosis (Table 1). Nodules in the right lower and middle lobes were significantly more likely to provide a diagnosis than nodules in other locations (Table 1).

Among the 46 patients (46%) in whom transbronchial biopsy was diagnostic, 41 had malignant disease (3 metastatic renal cancer, 3 metastatic breast cancer, 3 metastatic colon cancer, and 32 non-small cell lung cancer) and 5 had benign disease (4 sarcoidosis; 1 tuberculoma).

Of the 21 nodules for which the transbronchial biopsy was not diagnostic, surgical biopsy established that 16 had malignant disease (3 metastatic colon cancer, 2 metastatic renal cancer, 1 metastatic breast cancer, 10 non-small cell lung cancer) and 5 had benign disease (3 chondroid hamartoma, 1 sarcoidosis, and 1 tuberculoma).

Of 33 patients with SPNs that could not be biopsied transbronchially, surgical biopsies revealed 30 malignant lesions (5 metastatic colon cancer, 2 metastatic renal cancer, and 23 non-small cell lung cancer) and 3 benign lesions (2 sarcoidosis, 1 tuberculoma).

The overall diagnostic yield for EBUS-guided transbronchial biopsy was 46% (46/100). The sensitivity, specifity, negative and positive predicted values for malignancy were 47 %, 100 %, 22 % and 100 %.Diagnostic yield for the 67 nodules that were detected with EBUS was 69% (46/67). The sensitivity, specifity, negative and positive predicted values for malignancy in these cases were 72 %, 100 %, 38 % and 100 %. (Table 1). The mean examination time (including the biopsies) was 21.3 min (range, 6 to 32 min). The mean number of specimens obtained from each nodule was 4.2 (range, 4 to 6). Self-limited bleeding was observed in 3 patients; severe bleeding did not occur. Two patients (2%) suffered from pneumothorax that was treated with tube thoracostomy. One more was observed, but no intervention was necessary. There were no other complications.

Discussion

Bronchoscopy has been used to evaluate solitary pulmonary nodules and masses for more than 30 years. Patients with such nodules frequently undergo transbronchial biopsy under fluoroscopic guidance (21). However, endoscopic transbronchial biopsy often fails to successfully sample lesions smaller than 30 mm or lesions that are fluoroscopically invisible (2, 4, 5). Nodules too small to be visualized by conventional fluoroscopy usually require additional, often surgical biopsy procedures.

Needed, therefore, are new methods for navigation and localization, independent of fluoroscopic visualization, that enhance the technical skills of the bronchoscopist. Promising new technologies are electromagnetic navigation and endobronchial ultrasound (22, 23).

Several studies (4, 6-12) have reported on the efficacy and safety of EBUS-guided transbronchial biopsy. However, no trial has specifically addressed the yield for patients with nodules that are 20 mm in size or less. This is important information, as with the advent of increased CT imaging and screening, the number of detected small abnormalities is increasing.

In the present study of 100 consecutive patients, our overall diagnostic success rate was 46% in nodules with a mean diameter of 15 mm. One of the reasons for this low success rate was the inability to locate the SPNs with the help of EBUS in 33 patients within 20 minutes. For those lesions we were able to detect, the diagnostic success was 69%, which is similar to other studies (4, 6-12). This rate may not be as high as it could be since the EBUS location system must be withdrawn from the guide catheter and replaced

with the biopsy tool. Replacement can displace the tip of the guide catheter, interfering with the biopsy. This problem becomes more important as the target lesion gets smaller.

Some factors of our study need to be acknowledged. It is important to recognize that the prevalence of malignant lesions was high due to the inclusion criteria, therefore the same results may not be applicable in a more general and unscreened population. One of the limitations of this study is that there is no control group diagnosed by the standard approach of fluoroscopy. We did not use fluoroscopy for navigation, because fluoroscopy is known to be unreliable in the identification of small lesions and we wanted to ensure that we would collect data that is specific for one intervention only, namely radial EBUS guidance in this case. PET results were not taken into consideration, as PET imaging was not consistently available at the inception of the study. If performed today, PET results would be taken into consideration, but would not change our findings regarding performance characteristics of the EBUS guided biopsy.

Conclusions

For SPNs less than 20 mm that can be detected with ultrasound, EBUS-guided transbronchial biopsy is safe and effective. Ultrasound guidance may be more successful than fluoroscopic guidance in sampling small SPNs, increasing the likelihood of a diagnosis and decreasing the need for surgical biopsy. Further studies potentially combining guided approaches with EBUS are warranted.

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Table 1. Results of Ultrasound-Guided Transbronchial Biopsies of 100 Single Pulmonary Nodules less than 20 mm in Diameter from 100 Patients. All nodules were detected by computed tomography before biopsy

Node Characteristic	**Overall (n = 100)**	**Detected, diagnosis (n = 46)**	**Detected, no diagnosis (n = 21)**	**Not detected (n = 33)**	**P***
Mean size, mm	15.3	15.7	16	14.5	0.28
Lobe, n (%)					
Right upper	30	13 (43)	7 (23)	10 (33)	0.13
Right Middle	6	5 (83)	1 (17)	0	0.02
Right lower	17	10 (59)	2 (12)	5 (29)	0.047
Left upper	35	12 (34)	7 (20)	16 (46)	0.43
Left lower	12	6 (50)	4 (33)	2 (17)	0.62

Name the test used. Chi Square

Figure Caption

Figure 1. Typical endobronchial ultrasound image of a single pulmonary nodule, in this case, a nodule 14 mm in diameter in the left upper lobe of a 53-year-old man with a suspected diagnosis of lung cancer.