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Endobronchial ultrasound-guided lymph node biopsy with transbronchial needle forceps: a pilot study

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ABSTRACT: One limitation of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the size of the available needles, frequently yielding only cells for cytological examination. The aim of this pilot study was to evaluate the efficacy and safety of newly developed needle forceps to obtain tissue for the histological diagnosis of enlarged mediastinal lymph nodes.

Patients with enlarged, positron emission tomography (PET)-positive lymph nodes were included. The transbronchial needle forceps (TBNF), a sampling instrument combining the characteristics of a needle (bevelled tip for penetrating through the bronchial wall) with forceps (two serrated jaws for grasping tissue) was used through the working channel of the EBUS-TBNA scope. Efficacy and safety was assessed.

50 patients (36 males and 14 females; mean age 51 yrs) with enlarged or PET-positive lymph nodes were included in this pilot study. In 48 (96%) patients penetration of the bronchial wall was possible and in 45 patients tissue for histological diagnosis was obtained. In three patients TBNF provided inadequate material. For patients in whom the material was adequate for a histological examination, a specific diagnosis was established in 43 (86%) out of 50 patients (nonsmall cell lung cancer: n=24; small cell lung cancer: n=7; sarcoidosis: n=4; Hodgkin's lymphoma: n=4; tuberculosis: n=2; and non-Hodgkin's lymphoma: n=2).No clinically significant procedure-related complications were encountered.

This study demonstrated that EBUS-TBNF is a safe procedure and provides diagnostic histological specimens of mediastinal lymph nodes.

KEYWORDS: Endobronchial ultrasound, lung cancer, mediastinal lymph node, staging, transbronchial needle aspiration

Since the introduction of a flexible needle for use through the bronchoscope more than 20 years ago, transbronchial needle aspiration (TBNA) has become an accepted technique for obtaining diagnostic samples from enlarged mediastinal lymph nodes [1]. Although a number of studies have recently reported that endobronchial ultrasound (EBUS) guided-TBNA has a significantly better diagnostic yield than conventional TBNA, the amount of tissue that can be recovered with 21- or 22-gauge needles is limited and may be considered insufficient to establish a diagnosis by the pathologist [2–4].

Mini-forceps biopsy, performed under real-time EBUS guidance, can be used to obtain tissue specimens from subcarinal masses adjacent to the airway, but the procedure requires multiple passes of different instruments and therefore appears promising, but impractical [5, 6]. In order to improve the ease of obtaining tissue for histological examination from mediastinal lesions, a new bronchoscopic sampling instrument called transbronchial needle forceps (TBNF) has been developed for the EBUS-TBNA scope. In this pilot study the efficacy and safety of EBUS-transbronchial needle biopsy (TBNB) with this new tool is reported.

MATERIAL AND METHODS

From August 2009 to April 2010, consecutive patients referred for bronchoscopy and with mediastinal lesions >15 mm in the short axis on chest computed tomography (RECIST (response evaluation criteria in solid tumours) 1.1 measurement of lymph nodes) and patients with positron emission tomography-positive lymph nodes were enrolled prospectively in the study.

The study was approved by the Hospital Ethics Committee in Heidelberg, Germany, where the

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study was performed by four of the authors (F.J.F. Herth, R. Eberhardt, S. Gasparini and A. Ernst) and written informed consent was obtained before bronchoscopy from all patients.

The TBNF biopsy of the mediastinal lesions, subsequently described in detail, always preceded other bronchoscopic procedures such as washings, brushing and endobronchial biopsy. All procedures were performed under general anaesthesia through a rigid bronchoscope. The primary end-points were the diagnostic yield of the technique and technical success of the nodal puncture and biopsy.

A pathologist blinded to the patients' details performed the cytopathological examinations. Rapid on-site cytopathological examination was not performed. A specific diagnosis made on a TBNF specimen was considered a true positive diagnosis. A diagnosis of sarcoidosis was considered if the specimen identified noncaseating granulomas with a compatible clinical phenotype and adequate exclusion of other causes for granulomatous inflammation, including clinical history, follow-up, and a combination of negative tissue staining for acid-fast bacilli and fungal organisms and negative fungal and mycobacterial cultures. If the pathology from the EBUS-TBNB samples resulted in a formal diagnosis, this was judged to be a true positive finding. No further tissue confirmation was undertaken in these cases.

Complications were recorded as either minor, which included bleeding controlled with routine bronchoscopic manoeuvres, and major, including bleeding requiring transfusion, pneumothorax or pneumomediastinum, respiratory failure or unscheduled admission.

Endobronchial ultrasound-guided transbronchial needle biopsy

A real-time EBUS-TBNA scope (BF-UC180F; Olympus Medical Systems Corp., Tokyo, Japan) was used in all cases. After detection of the lesion, the TBNB samples were obtained by passing dedicated sharp biopsy forceps (conical type; Olympus Medical Systems Corp.) through the airway wall and into the lesion under real-time ultrasound control. This company-developed instrument is not yet food and drug administration approved.

The TBNF is a dedicated sampling instrument that combines the characteristics of a needle (bevelled tip for penetrating through the bronchial wall) with that of forceps (two serrated jaws that can be manipulated in the open and closed position) (fig. 1).

The distal end of the TBNF is stiff along a length of 15 mm. This is to avoid bending of the sampling instrument when pressure is applied in order to penetrate the bronchial wall. Like the traditional needles, the TBNF is housed in a plastic sheath (external diameter, 1.5 mm; length, 1,020 mm) that protects the tip and prevents working channel damage during insertion through the bronchoscope.

The TBNF is inserted with the sheath into the EBUS-TBNA scope. Once the TBNF is inserted into the bronchoscope and the distal end of the sheath is visible outside the instrument, the needle forceps can be pushed forward into the lesion. After the TBNF has penetrated the bronchial wall, the proximal slider is pushed to open the jaws, just as in traditional forceps (fig. 2).

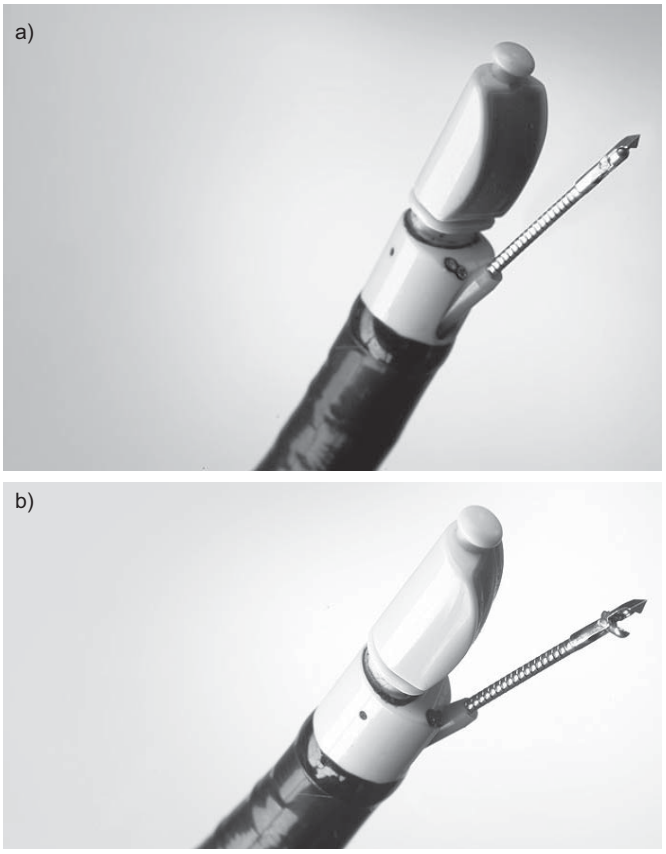

FIGURE 1. Image of the bevelled tip of the transbronchial needle forceps extended through the working channel of the endobronchial ultrasound bronchoscope: a) open and b) closed. One jaw has a sharpened end while the other jaw has a shorter and rounded edge. The length of the cups is 5 mm for the longer sharpened jaw and 3 mm for the other.

Integrated colour power Doppler was used to exclude intervening vessels immediately before needle puncture, when appropriate. Three to four biopsies were taken from each site.

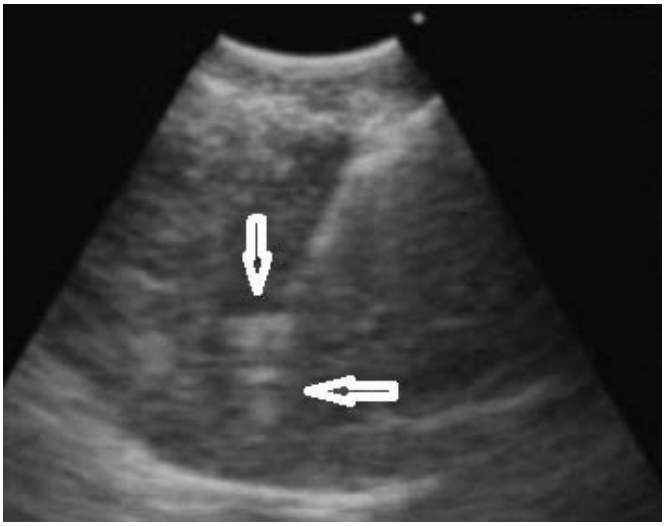

FIGURE 2. Ultrasound image of a lymph node in the 4 L location. The arrows mark the open jaws of the endobronchial ultrasound-transbronchial needle forceps.

Specimen handling

Tissue specimens obtained by needle forceps were placed immediately in formalin. Samples in saline solution were also sent for culture. Papanicolaou staining, light microscopy and histological analysis were performed by a single pathologist.

Statistical analysis

The sensitivity, specificity and predictive values were calculated using the standard definitions. Groups were compared with Chi-squared analysis. All analyses were performed with SPSS 11.5 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

50 patients (36 males and 14 females) with a median (range) age of 51 (27–71) yrs were enrolled and underwent the procedure. The mean (range) size of the mediastinal lesions sampled was 2.27 (1.5–2.6) cm, and no significant correlation was observed between the size of the lesions and the likelihood of obtaining a diagnostic specimen with TBNF. Three to five passes were necessary to obtain three specimens. Most of the nodes were located in the mediastinum: station 7 (n=18), station 4R (n=8), station 4L (n=4), station 2R (n=3), station 2L (n= 3). Hilar lymph node stations were also accessible: station 10R (n= 5), station 11R (n= 4), station 10L (n= 3) and station 11L (n= 2).

TBNF provided a diagnosis in 43 (86%) patients. In two (4%) patients, despite several attempts, the TBNF could not be passed through the bronchial wall. In both patients the target nodes were station 7. In three patients no material was obtained even though the instrument was inserted into the lymph node. In two patients the retrieved sample was suitable for histological examination but not diagnostic (evidence of fibrotic tissue without atypical structures).

Histological diagnosis was possible with the examination of TBNF samples in 43 patients (24 were diagnosed with nonsmall cell lung cancer (NSCLC), seven with small cell lung cancer, four with sarcoidosis, four with Hodgkin's lymphoma, two with non-Hodgkin's lymphoma and two with tuberculosis).

After bronchoscopy, seven (14%) patients remained undiagnosed (three with inadequate material, two with adequate material and two without material (unable to penetrate the wall)). Five of these underwent a cervical mediastinoscopy and two underwent endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-FNA) (all produced diagnostic tissue). Two patients were diagnosed with NSCLC and one with sarcoidosis. In four patients tissue obtained was nondiagnostic, but follow-up imaging showed regression of the nodal sizes and further work up was not pursued. Figure 3 describes the flow of patients throughout the study.

In all 24 patients with NSCLC a specific subtyping with the help of immunohistochemistry was possible (13 adenocarcinomas: thyroid transcription factor-1, Napsin; eight squamous cell cancer: cytokeratin 5/69; and three large cell cancers). Following the national guidelines, all of the nonsmoker or minimal smoker (<15 pack-yrs) patients (seven females and one male) with an adenocarcinoma underwent an epidermal growth factor receptor mutation analysis. In all cases the specimens were suitable for a PCR test.

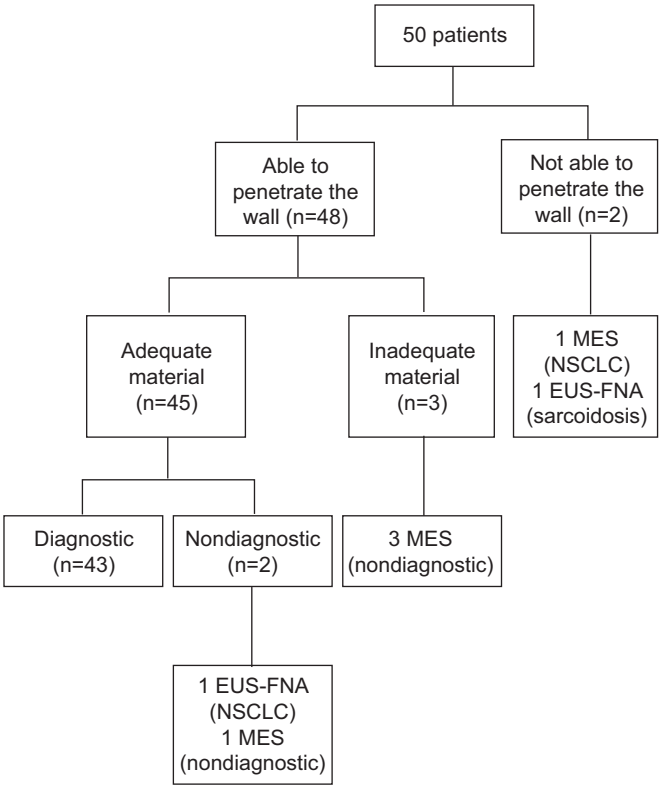

FIGURE 3. Patient flow through the trial. MES: mediastinoscopy; NSCLC: nonsmall cell lung cancer; EUS-FNA: endoscopic ultrasound with bronchoscope-guided fine-needle aspiration.

The two patients in whom we were unable to penetrate the wall were discussed in a multidisciplinary tumour board. One patient underwent EUS-FNA as a staging procedure (sarcoidosis) and one patient underwent a mediastinoscopy (adenocarcinoma).

For patients in whom the material obtained with TBNF was adequate for a histological examination a specific diagnosis was established in 86% (43 out of 50 patients).The sensitivity, specificity, positive-predictive and negative-predictive value, and accuracy value for the sampling techniques was 88%, 100%, 100%, 17% and 88%, respectively.

The mean (range) procedure time was 18 (6–25) min including all other diagnostic techniques, which were used during the bronchoscopy (such as transbronchial lung biopsy, bronchoalveolar lavage and bronchial lavage).

No clinically significant complications were encountered during the procedure or after follow-up in all patients up to 3 weeks after bronchoscopy. No damage of the working channel of the bronchoscopes was recorded after the procedures.

DISCUSSION

The advent of endoscopes incorporating ultrasound has increased interest in noninvasive sampling of mediastinal lymph nodes [7, 8]. In particular, in the setting of staging of NSCLC, where nodal involvement is key to patient management, ultrasound-guided needle aspiration has been found to perform very well, with sensitivities for EUS-FNA of 88–100% [9] and from 92% to 96% for

EBUS-TBNA [10, 11]. The excellent results were also obtained for normal sized and hilar lymph nodes [12–14].

One of the perceived limitations of the EBUS technique is the small sample size obtained by the 22-gauge needle. The small amount of material obtained may make it difficult for the pathologist to diagnose benign disorders. An additional future application, the use of biomarkers and tumour genetics on cytology specimens [15], makes it important to assess ways of obtaining more high-quality material and real histology.

In a previously published trial, our group showed that transbronchial mediastinal lymph node biopsy performed under real-time ultrasound guidance is feasible and safe due to the excellent visualisation of mediastinal structures by the EBUS technology. In addition, it performed significantly better than classical TBNA alone in the diagnostic evaluation of Hodgkin's disease, non-Hodgkin's lymphoma and sarcoidosis [6]. Unfortunately, standard biopsy forceps cannot penetrate the bronchial wall itself, so a classical TBNA has to be performed first to create an entry for the biopsy forceps. This approach leads to an increase in the length of the bronchoscopic procedure and requires a change of scopes, starting with a conventional bronchoscope for the puncture, followed by the EBUS-guided biopsy.

In order to improve the likelihood of obtaining histological tissue from mediastinal lymph nodes and to avoid the sequential use of separate needles and forceps, the EBUS-TBNB technique that combines the penetration capability of a needle and the grasping potential of serrated biopsy forceps was developed. We present the first description of this procedure in a clinical trial. The use of this instrument allowed for a more focused and shortened procedure by using one accessory and one scope only. It was technically successful, as the nodes could be accessed in almost all patients and a diagnosis was obtained in most.

There are limitations. In a few cases it was not possible to penetrate the bronchial wall, preventing tissue sampling. This problem is probably related to the larger and stiffer tip of the instrument (1.5 mm), which is approximately equivalent to a 17-gague needle. It has been demonstrated that the insertion of a 19-guage needle (equivalent to 1.067 mm) is easier when compared to an 18-guage needle (1.270 mm) and that even a small difference in size could be enough to make the insertion process through the bronchial wall more difficult [16]. Also, the trial design does not allow for comparison with current or conventional EBUS-TBNA needles. The trial was designed as a pilot trial and feasibility was the focus.

Although EBUS-TBNA alone has excellent sensitivity for diagnosis of metastatic nodal disease of lung cancer, the ability to obtain larger samples through the EBUS-TBNB may allow for more detailed analysis of lymph node metastases, which in turn may help provide additional prognostic information to guide disease-specific therapy. Other diseases, such as granulomatous diseases and lymphoma, may require histological assessment for better diagnostic definition [17]. Even though it has been suggested in the literature that expert centres may be able to obtain all the necessary information based on material from EBUS-TBNA 21-gauge needles [18–20], the clinical reality suggests that pathologists prefer more material.

It should be noted that all procedures were performed by experienced bronchoscopists in a high-throughput, specialist centre. All examinations were performed under general anaesthesia with the rigid bronchoscope. Further trials confirming the technical success in other centres and comparing the sample size and quality when compared with TBNA are justified and necessary in order to define the possible added value of incorporating TBNB into clinical practice.

CLINICAL TRIAL

This study is registered at ClinicalTrials.gov with clinical trial identifier number NCT01145924.

STATEMENT OF INTEREST

None declared.

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