Original article

First 30 endobronchial ultrasound-guided transbronchial needle aspirations: a single institution’s early experience

SUN Jia-yuan, ZHAO Heng, ZHANG Jie, WANG Xiang-dong and HAN Bao-hui

Keywords: endobronchial ultrasound; transbronchial needle aspiration; lung cancer; lymph nodes

Background A new technique developed in 2002, real time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), has been one of the most important tools in lymph nodes (LNs) staging before lung cancer surgery. EBUS-TBNA was introduced into China in 2008.

Methods Between June 2009 and October 2009, 30 patients with mediastinal/hilar lymphadenopathy and thoracic masses previously detected with CT scan underwent EBUS-TBNA without rapid onsite cytological examination.

Results From 30 patients, 33 samples were obtained from LNs and seven samples from intrapulmonary lesions. Twenty out of the 23 lung cancer diagnoses were clarified through the procedure, with sensitivity, specificity, positive predictive value, negative predictive value and accuracy being 87%, 100%, 100%, 70% and 90%, respectively. All three false negative cases were found in the first five procedures. Additionally, among the 33 LNs examined, three specimens that had no lymphocytes were also found within the first five procedures. There were no major complications, and the procedures were uneventful.

Conclusions EBUS-TBNA seems a safe and effective technique in making diagnosis for mediastinal/hilar LNs and intrapulmonary masses. For pulmonologists experienced in bronchoscopy, the sensitivity of the procedure for diagnosing lung cancer should be no less than 90% after the initial five procedures.

METHODS

Characteristics of patients

Among the 30 patients included in the study, 23 were male and 7 were female. The mean age was 56.2 years (22–83 years). Twelve of them were out-patients and 18 were in-patients at the time they received the procedure. EBUS-TBNA was performed according to the guidelines in patients meeting the following criteria: (1) enlarged mediastinal/hilar LN (≥1 cm) and/or intrathoracic peritracheal or peribronchial masses previously revealed by chest CT, (2) informed consent form for EBUS-TBNA examination, and (3) no contraindication to the procedure.

EBUS-TBNA

The experimental protocol was approved by the Ethics Committee of Shanghai Chest Hospital. The patients had no access to solid food and water at least 6 hours before the operation on the day of the procedure. The same bronchoscopist (SUN Jia-yuan) performed all the EBUS-TBNA procedures. After setting up pre-operative vascular access for intravenous transfusion, 3 to 5 spraying of 7% lidocaine solution were administered in the pharynx followed by local anesthesia with 2% lidocaine solution in the mouth. Cough was relieved with...
intramuscular injection of Pethidine (25–50 mg) before the procedure. A common bronchoscopy was performed orally; target LNs and peripheral vessels were examined by EBUS with a linear array ultrasonic bronchoscope (BF-UC260F-OL8, Olympus Ltd, Tokyo, Japan). LNs were classified based on the international staging system. The electronic convex array ultrasound transducer mounted at the distal end of the bronchoscope was covered by a water-inflatable balloon sheath. Scanning was performed at a frequency of 7.5 MHz and images were processed by an Olympus ultrasound processor (EU-C2000; Olympus Ltd.). The diameter of the target LN was measured and recorded under conditions of a frozen ultrasound image. A dedicated 22-gauge needle was used for aspiration (NA-201SX–4022; Olympus Ltd.) from targeted LNs under guidance of real-time ultrasound. Once the tip of the needle was confirmed as having reached the target lesion, the needle was moved back and forth while suction was applied. Before puncturing, integrated color power Doppler ultrasound was used to exclude the presence of interferential vessels within the planned puncture plot.

Three cytological evaluations were performed for each target LN and each mass as recommended. However, two aspirations may be sufficient if a histology specimen was obtained. No on-site cytological evaluation was used. Hematoxylin and eosin staining and light microscopy of cytological smears was carried out by a cytopathologist blinded to details of the cases. Aspirated histology material was formalin-fixed and paraffin-embedded before being examined under a light microscope. All patients underwent a chest radiograph after the procedure.

Evaluation of TBNA smears
Upon examination of TBNA smears, TBNA was considered as a successful intra-LN aspiration (presence of multiple lymphocyte clusters), suspicious intra-mass aspiration (absence of lymphocytes) or failed puncture (substantive red blood cells exclusively or very few nucleated cells). Pathologic specimens were categorized positive with the presence of unambiguous tumor cells, even if the type or differentiation status of the cells remained unclear; or with the presence of tumor cells highly suspicious of malignancy when lung cancer was strongly implied by the patient’s clinical manifestations or when the diagnosis of lung cancer was verified by other cytological or histological examination. The patients were then treated accordingly. Otherwise all smears were considered negative. TBNA result of a certain patient was considered positive when any one of the examined LNs or masses was found to be positive. On the other hand, a patient’s TBNA result was considered negative only when none of the aspirated LN or mass appeared positive.

Statistical analysis
EBUS-TBNA diagnosis was subsequently verified by and compared with results of either other pathological results involving thoracotomy, mediastinoscopy or thoracoscopy, or by clinical follow-up. Patients’ subsequent therapy was performed on the basis of the corresponding final diagnosis. Sensitivity, specificity, positive predictive value, negative predictive value and the diagnostic accuracy rate of EBUS-TBNA in distinguishing benign from malignant LN or thoracic mass were calculated according to standard definitions using the software package SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Final clinical diagnoses
Final diagnoses of the 30 patients included in the study were 23 cases of lung cancer, among which 17 patients had non-small cell lung cancer (NSCLC), including six cases of poorly-differentiated carcinoma, four cases of squamous cell carcinoma, seven cases of adenocarcinoma, and three cases each of small cell lung cancer (SCLC) and unknown type. There were two cases of tuberculosis, two cases of sarcoidosis, and three cases of inflammatory disease (Table 1).

<table>
<thead>
<tr>
<th>LN station/Intrapulmonary mass</th>
<th>Diagnosis obtained through surgery/clinical follow-up and EBUS-TBNA study patients (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Poorly-differentiated carcinoma</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7 (100)</td>
</tr>
<tr>
<td>SCLC</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Unknown type lung cancer</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

Definitive diagnoses were made on the basis of EBUS-TBNA results for 21 cases.

Table 1.

Cytology/histology results
EBUS-TBNA biopsies were performed on 33 LN stations and seven intrapulmonary masses in 30 patients (Table 2), and 2.32 (1–4) puncture attempts were performed at each aspiration site. Histological evidence was obtained from 22 of the 30 patients (73%), and was significant in the clarification of the final diagnoses in 13 cases.

As shown in Table 1, final diagnosis in 20 patients who
Figure 1. Poorly differentiated lung cancer with LN metastasis diagnosed by EBUS-TBNA in a 77-year-old patient with lung cancer of the left lower lobe. Arrow points out needle. CT: computed tomography; SVC: superior vena cava; LN: lymph node. 1A and 1D: Chest CT scan demonstrates enlarged right lower paratracheal LN (4R) (A) and anterior carina LN (4R) (D). 1B and 1E: Measurement of right lower paratracheal LN (B) and anterior carina LN (E) by EBUS. 1C and 1F: EBUS-TBNA of right lower paratracheal LN (C) and anterior carina LN (F) with a needle (arrow) within the aspiration site. 1G and 1H: TBA cytological results of right lower paratracheal LN (G) and anterior carina LN (H) demonstrated poorly-differentiated cancer (original magnification ×20). 1I: TBA histological results of 4R LN demonstrated poorly-differentiated cancer (original magnification ×20). Figure 2. Squamous cell lung carcinoma diagnosed by EBUS-TBNA in a 64-year-old patient with lung cancer of the right upper lobe. 2A: Chest CT scan demonstrates a right upper lung mass coalesced with right lower paratracheal LN. 2B: EBUS-TBNA of right-upper lung mass. 2C: TBA cytological results of right upper lung mass demonstrated squamous cell carcinoma (original magnification×20).

received EBUS-TBNA was lung cancer. Seventeen were diagnosed as NSCLC, including six cases with poorly-differentiated carcinoma, four cases with squamous cell carcinoma and seven cases with adenocarcinoma. The remaining three were SCLC patients (Figures 1–4).

For the two tuberculosis cases, final diagnosis was clarified on the basis of EBUS-TBNA in one case. In the other case, the possibility of tumor was excluded by EBUS-TBNA before the patient’s diagnosis was finalized by detection of Mycobacterium tuberculosis in a sputum culture and improvement from anti-TB therapy.

Learning-curve analysis
Among the 30 subjects who accepted EBUS-TBNA, 20 of the 23 lung cancer diagnoses were clarified by the procedure, with sensitivity, specificity, positive predictive value, negative predictive value and accuracy being 87%, 100%, 100%, 70% and 90%. It is noteworthy that none of the three false negative cases occurred after we had done the first five procedures. Additionally, of the 33 nodes, the three nodes that had no lymphocytes in the specimens also came from the first five procedures. For the two sarcoidosis cases, although potential diagnosis of lung cancer or tuberculosis was excluded by EBUS-TBNA and histological specimen were successfully obtained, only lymphocyte-like cells were observed in the absence of non-caseous epithelioid cell granuloma.

Complications
Although no sedation drugs were applied, all subjects went through the procedure with great comfort and excellent compliance. Except for a little bleeding at the puncture site observed through the endoscope during the procedure, no major complications such as pneumothorax, mediastinal emphysema or bleeding from ruptured major vessels in the mediastinum were reported.
Figure 3. Metastatic lung adenocarcinoma with LN involvement diagnosed by EBUS-TBNA in a 49-year-old patient with lung cancer of the left upper lobe. AO: aorta. A, D and G: Chest CT scan demonstrates enlarged right lower paratracheal LN (4R) (A), anterior carina LN (4R) (D) and left lower paratracheal LN (4L) (G). B, E and H: Measurement of right lower paratracheal LN (B), anterior carina LN (E) and 4L LN (H) by EBUS. C, F and I: EBUS-TBNA of right lower paratracheal LN (C), anterior carina LN (F) and 4L LN (I) with a needle (arrow) within the aspiration site. J and K: TBNA cytological results of 4R LN (J) and 4L LN (K) demonstrated adenocarcinoma (original magnification ×20). L: TBNA histological results of 4R LN and 4L LN demonstrated adenocarcinoma (original magnification ×20).

DISCUSSION

EBUS is a safe and efficient diagnostic tool with a built-in ultrasound probe on the tip of a bronchoscope. Combined with a special aspiration biopsy needle, it can be used for a real-time EBUS-TBNA biopsy, with integrated color-power Doppler ultrasound which facilitates differentiation of the cystic lesion from nearby vascular structures immediately prior to needle puncture. Additionally, the 22-gauge aspiration needle has the potential of getting access to histology cores in some cases. EBUS-TBNA has been used in China since 2008, we present the initial experience of a pulmonologist experienced in bronchoscopy with the procedure.

A 2004 study in which convex probe-EBUS-guided TBNA was performed on mediastinal LNs and hilar LNs of 70 patients reported that sensitivity, specificity and accuracy of the procedure in distinguishing benign from malignant LNs were 95.7%, 100% and 97.1%, respectively. Herth et al reported in another study that, sensitivity, specificity, positive predictive value of EBUS-TBNA performed uneventfully in 572 mediastinal LN stations in 502 NSCLC patients for the purpose of predicting mediastinal metastasis was 93.6%, 100% and 100%, respectively. As demonstrated in multiple prior studies, the pooled sensitivity of real-time EBUS-TBNA in diagnosing lung cancer was 90% but the false negative rate was 20%. With only the aid of pre-operative CT-localization, conventional TBNA is a “blind” procedure without target visualization and therefore the yield for TBNA varies widely. The diagnostic yield of conventional TBNA was related to LN size, but not to LN location. It has been reported in one of previous study that the sensitivity of conventional TBNA in lung cancer diagnosis is 77% at the start of the learning curve to 82% after 32 months of experience. However, the sensitivity of EBUS-TBNA in lung cancer diagnosis went up to 87% in the present study, which may be better than in conventional TBNA studies.

In addition to lung cancer patients, EBUS-TBNA can also be used in subjects with clinically suspected lymphoma, with the reported diagnostic sensitivity being 91%. In the demonstration of non-caseous granulomatous inflammation, EBUS-TBNA has a diagnostic yield for sarcoidosis of 85%–92%. The typical non-caseous epithelioid cell granuloma was not found in either of the patients who had been clinically suspected of suffering from sarcoidosis. The reason for this might be the endoscopists’ lack of experience, as in the subsequent 50 cases that underwent the procedure, non-caseous granuloma originating from epithelioid cells was found in EBUS-TBNA histological specimen from 5/8 patients who had been clinically suspected of stage I/II sarcoidosis (unpublished data). It was also verified in the present study that the diagnosis of tuberculous lymphadenitis can be made on the basis of acid-fast bacillus smears and
Figure 4. Small lung cancer with LN metastasis diagnosed by EBUS-TBNA in a 41-year-old patient with left lung cancer. A and D: Chest CT scan demonstrates enlarged subcarina LN (7) (A) and left lower paratracheal LN (4L) (D). B and E: Measurement of 7 LN (B) and 4L LN (E) by EBUS. C and F: EBUS-TBNA of 7 LN (C) and 4L LN (F) with a needle (arrow) within the aspiration site. G and J: TBNA thin cell test results of 7 LN (G) and 4L LN (J) demonstrated SCLC (original magnification ×20). H and K: TBNA cytological smear results of 7 LN (H) and 4L LN (K) demonstrated SCLC (original magnification ×20). I and L: TBNA histological results of 7 LN (I) and 4L LN (L) demonstrated SCLC (original magnification ×20).

histological testing of EBUS-TBNA LN samples, as shown in a couple of similar case reports.\textsuperscript{13,14} The sensitivity and negative predictive value of EBUS-TBNA in diagnosing lung cancer, as revealed in the present study, were 86.96% and 70%, respectively, consistent with results from prior studies involving learning curve procedures.\textsuperscript{15-17} All of the three false negative cases occurred within the first five procedures. A possible reason for these false negative results was presumed to be that inadequate aspirations were performed, as only three aspirations (one aspiration/LN station) were performed on three LN stations for these three subjects. It was already demonstrated in a study that, for mediastinal staging of NSCLC in the absence of rapid on-site cytopathology examination, at least three cytology aspirations per LN station was recommended except when an adequate core specimen was gained and then two passes sufficed.\textsuperscript{18} According to this principle, the sensitivity and negative predictive value of EBUS-TBNA in predicting mediastinal metastasis were 91%–95% and 96%–97%.\textsuperscript{15} For the patients who had no lymphocytes in their specimens, inaccurate target localization and the targeted metastatic LN being inaccurately punctured by the aspiration needle may also have influenced the false negative results.

Training endoscopists to perform EBUS should cover image interpretation, “knobology” which is the use of the ultrasound processor controls, orientation of endoscopic and ultrasound views, as well as biopsy techniques. Knowledge of thoracic anatomy and competence in basic flexible bronchoscopy/TBNA are pre-requisites. The American College of Chest Physicians recommends at least 50 proctored procedures to gain competence in EBUS and 5–10 procedures per year to maintain the skill.\textsuperscript{19} The European Respiratory Society and American Thoracic Society joint statement suggested 40 supervised procedures for trainees and 25 procedures per year to maintain competency.\textsuperscript{20} These guidelines are for radial EBUS, but no similar recommendations are available for real-time linear EBUS-TBNA. However, according to our experience, sensitivity of the procedure in diagnosing lung cancer should be no less than 90% after the first five procedures if the correct aspiration strategy is applied.

As EBUS-TBNA is a comparatively safe procedure with
few complications, and the patients’ acceptance was identical to common bronchoscopy. As shown in one of our previous reviews, a meta-analysis of 11 EBUS-TBNA studies showed that out of 1299 subjects included in the analysis, only two cases of complications (0.15%) were reported. One of them was pneumothorax found postoperatively in a chronic obstructive pulmonary disease (COPD) patient, which required chest tube drainage, and the other one was intraoperative hypoxemia in a 74-year-old male with COPD who recovered spontaneously soon after the procedure. The main intraoperative complication we experienced was a little bit of bleeding at the puncture site, which ceased spontaneously without any treatment or was stopped by local epinephrine application. More serious potential complications including pneumothorax, mediastinal emphysema and bleeding from ruptured major vessels have rarely been observed. Although mild complications may recover spontaneously, severe ones may require pneumothorax drainage or surgical assistance.

In conclusion, EBUS-TBNA was a safe and effective approach with high diagnostic yield and minimal complications for diagnosing and staging of mediastinal/hilar LN of lung cancer. Satisfactory results can be obtained immediately after a short period training for EBUS-TBNA by pulmonologists experienced in bronchoscopy. In view of the vital role it can play in the management of patients with lung cancer and the short learning curve of EBUS-TBNA, it deserves further promotion.

REFERENCES


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