Endobronchial ultrasound-guided needle aspiration in the non-small cell lung cancer staging

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Abstract

Objective: The aim of the study was to assess the diagnostic yield of the endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-NA) in the mediastinal staging in non-small cell lung cancer (NSCLC) patients.

Methods: Consecutive NSCLC patients with enlarged or normal mediastinal nodes on CT scans underwent EBUS-NA. All patients with negative EBUS-NA subsequently underwent the transcervical extended bilateral mediastinal lymphadenectomy (TEMLA) as a confirmatory test.

Results: Two hundred and twenty-six patients underwent EBUS-NA between 1.02.07 and 30.04.08. There were 320 mediastinal lymph nodes biopsied (stations: 2R — 8, 4R — 83, 2L — 1, 4L — 61, 7 — 167). EBUS-NA revealed metastatic lymph node involvement in 129/226 patients (57.1%) and in 171/320 biopsies (53.4%). In 97 patients with negative EBUS-NA, who underwent subsequent TEMLA, metastatic nodes were diagnosed in 16 patients (7.1%) — in 12 (5.3%) in stations accessible for EBUS-NA (stations: 4R — 3, 4L — 2, 7 — 8) and in 4 (1.8%) in stations not accessible for EBUS-NA (stations: 5 — 4, 6 — 1). All positive N2 nodes diagnosed by the TEMLA contained only small metastatic deposits. A diagnostic sensitivity, specificity, accuracy, PPV and NPV of EBUS-NA were 89.0%, 100%, 92.9%, 100% and 83.5%, respectively. No complications of EBUS-NA were observed.

Conclusions: (1) EBUS-NA is an effective and safe technique for mediastinal staging in NSCLC patients. (2) In patients with negative results of EBUS-NA, surgical exploration of the mediastinum should be performed.

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1. Introduction

The real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-NA) is a recently introduced method of biopsy of the mediastinal, hilar and interlobar lymph nodes. Endobronchial ultrasound enables very accurate localization of the extrabronchial structures, including vessels (using the power Doppler imaging) and lymph nodes. Using 10—40 mm long needles makes a biopsy of nodes located in a relatively remote position from the bronchial wall possible.

The radial bronchoscopic ultrasound probes, introduced in 1992, did not allow for a real-time biopsy [1]. These probes are still in use, particularly in assessment of the peripheral lung lesions and depth of neoplastic infiltration of the mediastinal structures [2,3]. At the beginning of the twenty-first century the linear bronchoscopic ultrasound probes were introduced, which enable the real-time biopsy of lymph nodes and are used mainly for NSCLC staging. Since the introduction of this method the interest in EBUS-NA has continuously been increasing. In many centers its use has significantly reduced the need for surgical exploration of the mediastinum; mainly mediastinoscopies [4—8].

According to the recent European Society of Thoracic Surgeons guidelines, mediastinoscopy is still the gold standard of invasive mediastinal staging [9]. However, mediastinoscopy only enables access to 5 out of 13 mediastinal nodal stations, and in any of the published studies assessing the value of the EBUS-NA in NSCLC staging, its sensitivity and negative predictive value (NPV) was confirmed by the mean of the bilateral mediastinal lymphadenectomy. So, some percentage of the negative results of the EBUS-NA must have been missed, causing a bias in the reported results.

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2. Material and methods

2.1. Clinical question

What is the real sensitivity, accuracy and negative predictive value of the EBUS-NA, assessed using the bilateral mediastinal lymphadenectomy as the confirmatory test?

2.2. Design

Prospective cohort diagnostic study.

2.3. Location

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2.4. Patients

Inclusion criteria: a group of consecutive NSCLC patients (1) clinical stage I—IIIb; (2) with enlarged or normal mediastinal lymph nodes on CT scans; and (3) general condition enabling appropriate pulmonary resection.

Exclusion criteria: (1) histological diagnosis of small cell lung cancer; (2) lack of patient’s consent.

2.5. Intervention

Prior to the procedure the CT scans were carefully analyzed and local anesthesia and i.v. sedation (fentanyl 0.05—0.1 mg, midazolam 1—5 mg) were used. The EBUS-NA was performed using the BF-UC160F-OL8 videobronchoscope (Olympus Medical Systems Corporation, Tokyo, Japan). The videobronchoscope is 6.9 mm wide, has a 2 mm working channel, the 35° optical system and the EU-C60 7.5 MHz ultrasound processor, enabling 20—50 mm depth tissue imaging. As the ultrasound bronchoscope is not designed for detailed assessment of the bronchial tree, the examination was preceded by the standard videobronchoscopy. For the biopsy a cytological 22 G needle with guide wire and marking facilitating its visualization on the ultrasound image was used (NA-201SX-4022, Olympus Medical Systems Corporation, Tokyo, Japan).

The EBUS-NA of all lymph nodes \( \geq 5 \) mm on the short axis was performed (criterion of feasibility of lymph node biopsy according to Herth and Yasufuku [10,11]). All the biopsies were performed through the macroscopically normal bronchial wall. The number of biopsied nodes in one patient was 1—3.

The cytological smear was performed and fixed using 96% ethanol. Then standard hematoxylin-eosin staining was used.

In patients with negative results of the EBUS-NA the bilateral transcervical extended mediastinal lymphadenectomy (TEMLA) was performed. The TEMLA includes bilateral dissection of all the mediastinal lymph nodes, except station 9. The use of a special retractor, elevating the sternum, enables access to the mediastinal structures and safe dissection of lymph nodes. The technique of the TEMLA is described in detail elsewhere [12,13]. The video presenting this technique is available at: www.mp.pl/download/wmv/temla.wmv.

In patients with negative results of the TEMLA, an appropriate pulmonary resection with dissection of the mediastinum was performed. The extent of the mediastinal dissection corresponded to the systematic lymph node dissection. However, due to the completeness of lymphadenectomy with the TEMLA technique, generally no nodes were found at thoracotomy.

The Mountain-Dresler lymph node classification was used [14].

2.6. Statistical analysis

Statistical calculations were carried out using Statistica™ software (Statsoft Inc., USA).

Summary statistics were expressed as mean (M), standard deviation (SD). The chi-square test was used, where appropriate, to compare proportional data. The type I error was set at 0.05 for all analyses. Confidence intervals were calculated to 95% using standard formulae. The sensitivity, specificity, accuracy and NPV were calculated using the standard definitions.

3. Results

There were 181 men and 45 women with a mean age of 62.5 ± 8.9 years (range 39—85). In these 226 patients 320 EBUS-NA were performed, and the diagnosis was established in 129 of them (57.1%).

The mean time of the procedure was 15 min.

There were no complications.

Among these 320 biopsies there were 167 subcarinal node (station 7) biopsies, 83 right lower paratracheal node (4R) biopsies, 61 left lower paratracheal node (4L) biopsies, 8 right upper paratracheal node (2R) biopsies and 1 left upper paratracheal node (2L) biopsy. The mean dimensions of the biopsied nodes were 19.1 ± 11.4 mm in the long axis and 13.8 ± 9 mm in the short axis. In 94 patients (41.6%) biopsy of more than one node was performed.

In 171 out of 320 biopsies the cytological diagnosis of a cancer was established, and the biopsy was technically successful in 306 cases (95.6%).

In 129 patients (57.1%) metastatic involvement of the lymph node was confirmed in 171 nodes (in some patients more than one node was involved). The numbers of metastatic nodes in particular stations were as follows: station 7 — 86, 4R — 49, 4L — 31, 2R — 4 and 2L — 1.

In 81 patients (35.8%) the result of mediastinal lymph node biopsy was true negative. The number of these true negative biopsies was 136: 73 in station 7, 31 in station 4R, 28 in station 4L and 4 in station 2R. In this group the cytological diagnosis of benign, reactive lymph node enlargement was subsequently confirmed by the histological examination of the TEMLA operative specimen and in 54 patients with negative results of the TEMLA, additionally mediastinal dissection during thoracotomy was performed.

In 16 patients (5.3%) the result of EBUS-NA was false negative. In 12 patients TEMLA revealed metastases in nodal stations accessible for EBUS-NA (station 4R — 3 patients, station 4L — 2 and station 7 — 8 patients) and in the next 4 patients (1.8%) in nodal stations not accessible for EBUS-NA
In 19 out of 20 nodal stations with false negative results of the EBUS-NA, the extent of metastatic involvement was low (mean 38.8 ± 25.4% of the nodes, Table 1).

The overall sensitivity of the EBUS-NA calculated per patient was 89% (95% CI — 82—93); specificity, 100% (95% CI — 95—100); accuracy, 92% and NPV , 83.5% (95% CI — 75—90). However , if calculated for the nodal stations accessible for EBUS-NA, these figures were: sensitivity, 91.5% (95% CI — 86—96); specificity, 100% (95% CI — 96—100); accuracy, 94.7% and NPV , 87.6% (95% CI — 79—93).

The diagnostic yield of the EBUS-NA calculated per station is presented in Table 2.

The prevalence of mediastinal lymph node metastases in the present study was 60.9%.

EBUS-NA changed the clinical stage in 64 patients (28.3%): down-staged from N2 to N1 or N0 disease in 56 patients and up-staged from N0 or N1 to N2 disease in 7 patients and from N2 to N3 disease in 1 patient (Table 3).

4. Discussion

The use of the EBUS-NA in NSCLC staging is gaining increasing acceptance due to its efficiency and low invasiveness. Proponents of this method believe that in the near future it may become the gold standard in diagnosis of mediastinal adenopathy, replacing in many cases mediastinoscopy and other invasive techniques such as VATS, Chamberlain procedure and thoracotomy [4,5,11,15,16]. As the risk of complications related to the EBUS-NA is very low, this procedure may be performed in the outpatient settings [8,17].

Gaining skill and experience in the endobronchial ultrasound imaging and performing the biopsy is more time-consuming than in the conventional bronchoscopy. This makes appropriate training necessary. However, because of the real-time imaging, the results are less operator-dependent than these of the blind TBNA. This relation is shown by the wide range of the sensitivity of the blind TBNA (24—89%) [18—21], whereas the reported range of the sensitivity of the EBUS-NA is much narrower (88—95%) [5,7,10,11]. Our results show the 89% sensitivity of the EBUS-NA.

EBUS-NA enables biopsy of stations 2R, 2L, 3P , 4R, 4L and 7 (also N1 stations 10R, 10L, 11R and 11L inaccessible for other invasive techniques which is a unique advantage of EBUS-NA). Although imaging and biopsy of paratracheal nodes (particularly on the left side) are technically more difficult than the subcarinal or hilar nodes, the diagnostic yield of the EBUS-NA was higher in our group in the paratracheal nodes (Table 2). The difficulty in the imaging of the paratracheal nodes is due to the problems with stable positioning of the tip of the endoscope in contact with the wall of the distal trachea and the main bronchi. The second reason is the adherence of the nodes to big vessels.

EBUS-NA can be performed in the outpatient settings [8,17].

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The rate of false negative biopsies was only 4.1%. In most of these cases, noted mainly in the station 7, the extent of metastatic nodal involvement was limited, what was confirmed by the pathological examination of the TELMA specimen (Table 1). Similar correlation between the percentage of the metastatic nodes in a particular station and the sensitivity of biopsy was observed for the blind TBNA [21].

According to the largest series published to date, the NPV of the EBUS-NA is 85%–96%, and for the EUS-NA – 73%–83% [9,11,16,23,24]. In our group the NPV of the EBUS-NA was 83%. The reason is probably the use of the TELMA procedure as the confirmatory test, which is much more accurate in detecting the missed metastatic nodes than the commonly used standard mediastinoscopy.

For NSCLC patients with negative EBUS-NA the surgical staging of the mediastinum may be indicated. It is, however, doubtful, if the standard mediastinoscopy should be used for this purpose [13,25]. Perhaps, in patients with negative results of both EBUS-NA and EUS-NA, additional staging procedures may be omitted, particularly if the PET-CT was also negative. According to the recent guidelines of the American College of Chest Physicians, in patients with moderately enlarged mediastinal lymph nodes and no evidence of distant metastases, invasive mediastinal staging is recommended, using one of the following techniques: mediastinoscopy, EUS-NA, EBUS-NA or the trans thoracic needle aspiration. However, in patients with negative results of the needle biopsy, mediastinoscopy is recommended [16].

5. Conclusions

(1) EBUS-NA is an effective and safe technique for mediastinal staging in NSCLC patients. (2) In patients with negative results of EBUS-NA, surgical exploration of the mediastinum should be performed.

References


Appendix A. Conference discussion

Dr Rami-Porta (Barcelona, Spain): In the paper that you quoted from Paul De Leyn and co-workers regarding the European Society of Thoracic Surgeons (ESTS) guidelines on preoperative staging, we tried to evaluate what good clinical practice would be in mediastinoscopy. There were several opinions that are described in the paper, and finally we arrived at the conclusion that at least three nodal stations should be biopsied, both paratracheal stations and the subcarinal station. Based on your results, when there is no suspicion of any pathological node and you want to confirm clinical N0, what would be the ideal procedure in your hands?

Dr Szlubowski: This is our second favorite technique, which we use during the staging technique. So we join together EBUS and EUS, because the left side, especially group No. 4L, and additionally group 8 and group 9, and also
the posterior part of group 7, can be reached by EUS, and our initial experiences of sensitivity of the joint methods is more than 94% of sensitivity and NPV is about 92.5. Well, of course, there is the possibility to join bioptic methods with PET-CT. It could be too expensive for all the patients with non-small cell lung cancer. But at this moment I would like to point out that mediastinoscopy is not really the best method for referring to bioptic methods. I think lymphadenectomy, well, we show TEMLA, is the best way to verify bioptic methods. So coming back to your question, next biopsy method, EUS or PET joined together, but after then, if there is negative, lymphadenectomy.

Dr S. Mattioli (Bologna, Italy): Yesterday we were told that in nodes smaller than 1.5 cm at the CT scan the performance of EBUS is low, but I see that your performance is very good, because you have 5.6 false negatives in spite of the fact that you have evaluated all the nodes or even those smaller than that. Can you comment on that, please?

Dr Szlubowski: Well, Professor Herth showed the work in 2006 that the sensitivity of EBUS-TBNA in nodes less than 7 mm was 94%, and the prevalence in this group was about 20%. So it showed that this is really a sensitive method, even in smaller nodes. Well, in our opinion, we can puncture nodes where the diameter is less than 5 mm.

Dr T. Lerut (Leuven, Belgium): Just one additional question as to the lymphadenectomy. Your 5.6% false negative, i.e. 16 patients, what would have been the added value of the TEMLA vs a classic mediastinoscopy in those 16 patients? Did you look at that?

Dr Szlubowski: Well, from 16 patients, 7 or 8 of them, they — well, all of them went for chemotherapy and radiotherapy.

Dr Lerut: That is not the question. The question is what was the added value of doing the TEMLA vs doing a classic mediastinoscopy in those specific 16 patients? Did you look at that?

Dr Szlubowski: No, of course not.