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# Endoscopic ultrasound-guided needle aspiration in lung cancer

## Abstract

**Introduction:** The aim of the study was to assess the diagnostic yield of transoesophageal endoscopic ultrasound-guided needle aspiration (EUS-NA) in lung cancer (LC).

**Material and methods:** Real time EUS-NA was performed under local anaesthesia and sedation in consecutive LC patients. All negative EUS-NA results in NSCLC patients were verified by transcervical extended bilateral mediastinal lymphadenectomy (TEMLA).

**Results:** In 146 patients there were 206 biopsies performed in lymph node stations: subcarinal (7):124, left lower paratracheal (4L):70, paraoesophageal (8):9 and pulmonary ligament (9):3. A mean short axis of punctured node was 10 $\pm$ 6.3 (95% CI) mm. Lymph node biopsy was technically successful in 95.6% and was diagnostic in 40.1% of LC patients. In NSCLC staging, the sensitivity of EUS-NA calculated on the per-patient basis was 85.5%, specificity 100%, accuracy 93.6% and negative predictive value (NPV) 89.7% in stations accessible for EUS-NA, but in all mediastinal stations it was 70.7%, 100%, 84.3% and 74.7, respectively ($p = 0.009$). The sensitivity of EUS-NA in NSCLC staging patients, calculated on the per-biopsy basis was 88.6%, specificity 100%, accuracy 95.4% and NPV 91.4%. A diagnostic yield of EUS-NA on the per-biopsy basis was higher for station 4L than 7, but the difference was not significant ($\chi^2$ $p = 0.4$).

**Conclusions:** The diagnostic value of EUS-NA in LC is high. In NSCLC staging EUS-NA is insufficient and should be complemented by other invasive techniques, especially those that give access to the right paratracheal region.

**Key words:** endoscopic ultrasound-guided needle aspiration, transcervical extended bilateral mediastinal lymphadenectomy, non-small cell lung cancer

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## Introduction

Real-time endoscopic transoesophageal ultrasound-guided needle aspiration (EUS-NA) together with real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), are the latest techniques used for visualization and biopsy of mediastinal lymph nodes helpful especially in lung cancer staging (N stage) [1–3]. The left paratracheal (station 2L and 4L), aorto-pulmonary window (station 5), paraaortic (station 6), subcarinal (station 7), paraoesophageal (station 8) and pulmonary ligament (station 9) lymph nodes can be visualized by EUS. The sensitivity of EUS alone in the assessment of metastatic nodes is 78%, specificity71% and negative predictive value (NPV)79%. So it should always be complemented by a biopsy, if possible [4, 5].

Moreover, EUS allows very accurate localization of the mediastinal structures, including heart vessels (using the power Doppler imaging), main bronchi, vertebral column and diaphragm. It enables an assessment of potential infiltration of such structures as aorta, pulmonary trunk and left atrium (T stage). Sensitivity in the assessment of infiltration of mediastinal structures ranges widely (39–88%) and depends mainly on the experience of the endoscopist [5, 6]. Using 10–80 mm long needles, it is possible to locate lesions relatively remote from the oesophageal wall, both lymph

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nodes and lung tumors located bilaterally in upper lobes. During the examination, the abdominal organs can also be assessed (liver — particularly its left lobe, spleen, left kidney and left suprarenal gland), paying special attention to distant metastases (M stage). Transgastric biopsy of these organs can be performed. In enlarged left suprarenal glands metastases were confirmed by EUS-NA in 42% of patients, and accuracy was 81% [7].

Because EUS-NA is performed under local anaesthesia and sedation, it can be done in outpatient settings. The risk of dangerous complications (such as bleeding or mediastinitis) related to EUS-NA is very low (< 0.8%).

In some thoracic surgery centers, the use of EUS-NA reduced the number of invasive mediastinal staging techniques (mainly mediastinoscopies) [8, 9]. The latest data show that the diagnostic yield from bioptic methods, especially EBUS-TBNA, can be higher than from mediastinoscopy [10, 11].

According to the recent American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines and the European Society of Thoracic Surgeons (ESTS) guidelines, several alternative invasive techniques to confirm N2,3 node status are suggested as reasonable (including EUS-NA), in case of availability of personnel with appropriate experience. But in case of negative results from needle biopsy, mediastinoscopy as the 'gold standard' of invasive lung cancer staging should be further performed before the pulmonary resection, regardless of the findings of positron-emission tomography integrated with computed tomography (PET-CT) [12–14].

The aim of the present study is to assess the diagnostic yield of EUS-NA in lung cancer.

## Material and methods

The EUS-NA was performed in consecutive patients suspected of having lung cancer and in patients with confirmed non-small cell lung cancer (NSCLC), with enlarged or normal size of mediastinal lymph nodes on CT scans to assess N stage of disease.

In all cases, CT was performed prior to the EUS procedure. A comparison of the CT scans with the real-time imaging of EUS helped to find the optimal site for a biopsy.

The endoscope was inserted into the oesophagus under local anaesthesia and with intravenous sedation (fentanyl 0.05–0.1 mg, midazolam 1–5 mg). The GF-UCT160-OL5 videogastroscope (Olympus Medical Systems Corporation, Tokyo, Japan) with external diameter 14.6 mm, working channel 3.7 mm and 55° oblique anterior optical system with the linear ultrasound head was used. The EU-C60 7.5 MHz ultrasound processor (Olympus Medical Systems Corporation, Tokyo, Japan) enables precise 20–50 mm depth mediastinal tissue penetration. Real-time EUS guided biopsies were performed simultaneously. For the biopsy, we used a cytological 80 mm 22G needle with guide wire and marking, helping its visualization on the ultrasound image (NA-200H-8022, Olympus Medical Systems Corporation, Tokyo, Japan).

In most cases one station was biopsied but in some patients two or three stations were biopsied. After aspirating the material with vacuum syringes, a cytological smear was performed and fixed using 96% ethanol. The standard hematoxillin-eosin staining was used and the cytologic examination was performed.

In NSCLC patients with negative results of the EUS-NA, transcervical extended bilateral mediastinal lymphadenectomy (TEMLA) was performed. 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 also from the left side — stations 5, 6, 3A and 8. The bilateral total mediastinal lymphadenectomy can verify precisely the effectiveness of previously performed mediastinal needle biopsies [15, 16]. TEMLA is in fact the most accurate pre-operative method of assessing mediastinal lung cancer (with sensitivity of 94.1% and NPV 97.2% [16]). In case of negative results of TEMLA, an appropriate pulmonary resection with dissection of the mediastinum was performed, searching for the possible missed nodes.

In case of positive results of cytological examination, invasive staging was not continued. The Mountain-Dresler lymph node classification was used [17].

Statistical calculations were carried out using Statistica™ software (Statsoft Inc., USA). The sensitivity, specificity, accuracy and NPV were calculated using standard definitions. To compare proportional data, the $\chi^2$ test was used. The type I error was set at 0.05 for all analyses.

## Results

Between November 2007 and July 2008 206 EUS-NA were performed in 146 consecutive patients in lung cancer diagnostics and staging.

The examined group consisted of 28 women and 118 men, mean age 61.2 ± 8.7 years (range

**Table 1. Characteristics of 140 NSCLC patients**

| | Number of patients | Percentage of patients |
|---|---|---|
| Sex: M/F | 114/26 | 81.4/18.6 |
| Definite diagnosis of NSCLC | 75 | 53.6 |
| CT stage (I–IV) | | |
| IA | 21 | 15 |
| IB | 11 | 7.9 |
| IIA | 2 | 1.4 |
| IIB | 4 | 2.9 |
| IIIA | 85 | 60.7 |
| IIIB | 10 | 7.1 |
| IV | 7 | 5 |
| Side of primary tumor | | |
| Right side | 64 | 45.7 |
| Left side | 76 | 54.3 |
| Right upper lobe | 27 | 19.3 |
| Right medium lobe | 6 | 4.3 |
| Right lower lobe | 28 | 20 |
| Central right | 3 | 2.1 |
| Left upper lobe | 46 | 32.8 |
| Left lower lobe | 25 | 17.9 |
| Central left | 5 | 3.6 |

39–84). The EUS-NA helped to establish a proper staging in 59 of them (40.1%).

The biopsies were performed in particular stations as follows: station 7 — 124, 4L — 70, 8 — 9, 9 — 3. The mean diameter of the biopsied nodes was 15.4 ± 9.4 (95% CI) mm in the long axis and 10 ± 6.3 (95% CI) mm in the short axis.

In 39 patients (26.7%) biopsies were performed in two or even three stations.

No complications of EUS were observed.

In 80 biopsies (38.8%), metastatic involvement of the lymph node was confirmed and the biopsy was technically successful in 197 cases (95.6%), meaning a high technical yield of EUS-NA. In the examined group, the percentage with small cell lung cancer (SCLC) was 4.1%.

In six SCLC patients 10 EUS-NA were performed and all biopsies were positive, the SCLC group was omitted from further calculations.

### NSCLC staging

In 140 NSCLC patients, staging of disease with EUS-NA was performed (196 biopsies, mean 1.4 biopsy per patient) (Table 1). In 53 NSCLC patients (37.9%) metastatic involvement of the lymph node was confirmed, in some of them in two or three stations. There were 70 positive biopsies: station 7 — 42, 4L — 20, 8 — 8.

In all 87 NSCLC patients (62.1%) with a negative result of EUS-NA, TEMLA was performed.

In 65 patients (46.4%) the result of mediastinal lymph node biopsy was true negative (117 biopsies: station 7 — 72, 4L — 42, 9 — 3). In this group cytologic diagnosis of benign, reactive lymph node enlargement was subsequently confirmed by the histological examination of the operative specimen.

Among patients with a negative result with TEMLA, in 57 (40.7%) mediastinal dissection during thoracotomy was performed. Eight patients did not undergo lung resection following TEMLA because a significant impairment of pulmonary function.

In 22 patients (15.7%) the result of EUS-NA was a false negative, because the TEMLA revealed metastatic nodes. In nine of them (6.4%) there were nine false negative EUS-NA (4.6% of all biopsies) as follows: station 7 — 6, and 4L — 3. In the remaining 13 patients from this group (9.3%),TEMLA revealed metastases in nodal stations not accessible for EUS-NA (station 4R — 9, stations 5 and 6 — 4).

Metastatic nodes were found in none of the 57 patients who after TEMLA underwent dissection at thoracotomy. The prevalence of mediastinal lymph node metastases in the present study was 53.8%. In 27 patients (19.3%), a NSCLC diagnosis and staging (N stage) was made, based only on EUS-NA. These patients were qualified for biopsy with pathologically undiagnosed peripheral tumors, radiologically suspicious of cancer.

The overall sensitivity of the EUS-NA in NSCLC staging (N stage) calculated per patient basis was 70.7%, specificity: 100%, accuracy: 84.3% and NPV: 74.7%. However, if calculated per patient basis for the nodal stations accessible for EUS-NA, these figures were: sensitivity: 85.5%, specificity: 100%, accuracy: 93.6% and NPV: 89.7%. The difference was statistically significant ($\chi^2$ test, $p = 0.009$). The overall sensitivity of EUS-NA in NSCLC staging calculated per station basis was 88.6%, specificity: 100%, accuracy: 95.4% and NPV: 91.4%. The diagnostic yield of EUS-NA calculated for station 8 was 100%. The diagnostic yield of EUS-NA calculated for station 4L was higher than for station 7, but not significantly ($\chi^2$, $p = 0.4$). The results are presented in Table 2.

## Discussion

Our results confirm an effectiveness and safety of EUS-NA (no complications in our series).

**Table 2. Results of EUS-NA in NSCLC staging in different groups of mediastinal lymph nodes based on number of biopsies**

| Lymph node stadion | Specificity (%) | Sensitivity (%) | Accuracy (%) | Negative predictive value (%) |
|---|---|---|---|---|
| 7 — subcarinal | 100 | 87.5 | 95.0 | 92.3 |
| 4L — lower left paratracheal | 100 | 90.9 | 96.9 | 95.5 |
| All biopsied groups | 100 | 88.6 | 95.4 | 91.4 |

According to the 16 largest series published to date,the sensitivity ranged from 35 to 100%, specificity was 88–100% and accuracy was 76–98%. But these results were calculated per mediastinal stations accessible for EUS-NA only [2, 5, 9, 18]. The EUS-NA allows the visualization and precise biopsy of the whole station 4L, 8, 9 and 7 — particularly its posterior part. All these listed stations can not be reached by mediastinoscopy, and station 9 can not even be reached by TEMLA. In the presented study, a high diagnostic yield of EUS-NA was obtained for station 8: sensitivity: 100%, accuracy: 100% and NPV: 100%; and for station 4L: 90.9%, 96.9% and 95.5%, respectively.

Because EUS-NA provides no access to stations 2R and 4R and only limited access to the anterior part of station 7, this method should not be used as the only one in NSCLC staging. Our results showed a significantly higher diagnostic yield for EUS-NA if calculated for the nodal stations accessible for EUS-NA than for all mediastinal stations (sensitivity: 85.5% *v.* 70.7%; accuracy: 93.6% *v.* 84.3%; NPV: 89.7% *v.* 74.7%, $p = 0.009$).

Our study confirmed the observations of other authors that EUS-NA may be a valuable supplement to other methods of accurately assessing the mediastinum, including mediastinoscopy and EBUS-TBNA [19, 20].

EUS allows to visualize lymph node stations 5 and 6, and the ultrasound imaging may confirm their metastatic character. In our series, enlarged and suspected for metastases lymph nodes in stations 5 and 6 were confirmed in three quarters of cases as metastatic by surgery. Surgical access to these stations may be performed by left video-assisted thoracoscopic surgery, extended mediastinoscopy, mediastinotomy and TEMLA [21, 22]. According to a few papers, EUS-NA of nodal station 5 is possible [5, 21]. But in our experience this seems to be only theoretical, because the biopsy must have been performed across the aorta. A misunderstanding may have arisen from the distal and lateral part of station 4L being wrongly considered to be station 5.

In NSCLC staging there were 6.4% false negative results and only 4.6% false negative biopsies.

The NPV in NSCLC staging based on the largest series to date varies from 73–83% (in our study: 74.7%) [23]. However, NPV calculated on a per biopsy basis is 91.4%. So it seems reasonable to continue invasive staging by EBUS-TBNA (and later by surgical methods) in the case of a negative result of EUS-NA. This is in accordance with actual ACCP and ESTS guidelines which indicate the necessity of performing mediastinoscopy in cases of negative results of bioptic techniques (TBNA, EBUS-TBNA, EUS-NA), regardless of PET-CT results [13, 14]. Some data confirms that the use of mediastinoscopy with EUS-NA increases a diagnostic yield of lung cancer staging [8, 20]. The latest data regarding the combination of EBUS-TBNA and EUS-NA is very interesting and confirms they are both very useful in assessing the mediastinum [18, 24–26].

The question arises whether NSCLC patients with a negative result of EBUS-TBNA and EUS-NA should be considered for primary lung resection without surgical staging. This could make a breakthrough in diagnosing lung cancer [24].

In our study, lymph node biopsy was successful in 95.6% of cases. Among all needle aspiration techniques, EUS-NA provides the best material for cytologic examination due to the fact that in a biopsy performed through the oesophageal wall the samples consist only of squamous epithelium and lymph node tissue.

In the opinion of some authors, the diagnostic yield of EUS does not depend so heavily on the endoscopist experience compared to other bioptic techniques, especially TBNA [23, 26]. One limitation in implementing EUS-NA is still small number of teaching centers, particularly in Europe [5].

## Conclusions

The results of our study confirm the high degree of effectiveness of EUS-NA in lung cancer staging.

In NSCLC mediastinal staging EUS-NA may be not sufficient, and should be complemented by other invasive techniques, especially those enabling access to the right paratracheal region.

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