A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging — a prospective trial

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Abstract

Objectives: This prospective study aimed to assess the diagnostic yield of the combined approach — endobronchial (EBUS) and endoscopic (EUS) ultrasound-guided needle aspiration (combined ultrasound-needle aspiration (CUS-NA)) in the radiologically normal mediastinum in non-small-cell lung cancer (NSCLC) staging.

Methods: CUS-NA was performed simultaneously under local anaesthesia and sedation in consecutive NSCLC patients with mediastinal nodes that were not enlarged on CT (stage IA—IIB). All patients with negative CUS-NA subsequently underwent the transcervical extended bilateral mediastinal lymphadenectomy (TEMLA) as a confirmatory test.

Results: A total of 120 NSCLC patients underwent CUS-NA between 1 January 2008 and 31 December 2008. There were 318 mediastinal nodes biopsied (158 EBUS-NA — stations: 2R — 2, 2L — 1, 4R — 34, 4L — 33 and 7 — 88 and 160 EUS-NA — stations: 4L — 57, 7 — 101 and 9 — 2). CUS-NA revealed metastatic lymph node involvement in 19 of 120 patients (16%) and in 31 of 318 biopsies (10%). The prevalence was 22%. In 99 patients with negative CUS-NA, who underwent subsequent TEMLA, metastatic nodes were diagnosed in nine patients (8%) in 11 stations: 2R — 2, 4R — 4, 4L — 1, 5 — 3 and 7 — 1. In all but one patient there were 'minimal N2' only. Diagnostic sensitivity, specificity, total accuracy, positive predictive value (PPV) and negative predictive value (NPV) of CUS-NA for normal mediastinum was 68% (95% confidence interval (CI): 48—84), 98% (95% CI: 92—100), 91% (95% CI: 86—96), 91% (95% CI: 70—99) and 91% (95% CI: 83—96), respectively. The sensitivity of CUS-NA was significantly higher than with EBUS-NA alone (p = 0.04) and higher, close to the level of significance than with EUS-NA alone (p = 0.07). The NPV of all techniques was high and that of CUS-NA was significantly higher than EBUS-NA alone and EUS-NA alone (p = 0.01, p = 0.03).

No complications of CUS-NA were observed.

Conclusions: In the radiologically normal mediastinum, CUS-NA is a highly effective and safe technique in NSCLC staging and, if negative, a surgical diagnostic exploration of the mediastinum may be omitted.

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1. Introduction

Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided needle aspiration (EUS-NA) are recently introduced methods of biopsy of mediastinal nodes for non-small-cell lung cancer (NSCLC) staging. Due to high efficiency and low invasiveness, proponents of minimally invasive methods believe that, in the near future, both endoscopic techniques may become the gold standard in diagnosis of mediastinal adenopathy, replacing, in many cases, mediastinoscopy and other invasive techniques [1—6]. A combined ultrasound-needle aspiration (CUS-NA) approach also called the complete 'medical' mediastinoscopy has been presented only in a few publications since 2003 and in any for normal mediastinum [3,7,8]. Most of the publications present both techniques separately. The CUS enables very accurate localisation of the mediastinal structures, including vessels (using colour and power Doppler imaging) and lymph nodes. The CUS-NA enables more accurate assessment of the mediastinum and may increase the diagnostic yield but both methods are being used only in few centres [9,10].
According to the recent European Society of Thoracic Surgeons’ guidelines, mediastinoscopy is still the gold standard of invasive mediastinal staging [11]. However, mediastinoscopy enables access to only 5 out of 13 mediastinal nodal stations, and in any of the published studies assessing the diagnostic value of CUS-NA in NSCLC staging was confirmed by means of the bilateral mediastinal lymphadenectomy.

2. Material and methods

2.1. Clinical question

What is the real sensitivity, specificity, accuracy, positive and negative predictive values of CUS-NA, assessed using the bilateral mediastinal lymphadenectomy as the confirmatory test?

2.2. Design

The study design was a prospective cohort diagnostic study.

2.3. Location

The study was carried out at the Department of Thoracic Surgery, Pulmonary Hospital, Zakopane, Poland.

2.4. Patients

Inclusion and exclusion criteria for the patients are the following:

Inclusion criteria: a group of consecutive NSCLC patients with (1) clinical stage IA–IIB, (2) normal-sized mediastinal lymph nodes seen on computed tomography (CT) scans and (3) general condition enabling appropriate pulmonary resection.

Exclusion criteria include: (1) enlarged mediastinal lymph nodes on CT scans, (2) histological diagnosis of the small-cell lung cancer and (3) lack of patient’s consent.

2.5. Intervention

All procedures were performed under local anaesthesia and intravenous sedation (fentanyl 0.05—0.1 mg, midazolam 1—5 mg).

Initially, the EUS-NA was performed on the patient’s left side, using the GF-UCT160-OL5 videogastroscope (Olympus Medical Systems Corporation, Tokyo, Japan). The videogastroscope’s diameter is 14.6 mm, it has a 3.7-mm working channel, a 55° optical system and an EU-C60 7.5 MHz ultrasound processor, enabling 20- to 50-mm depth tissue imaging. For the biopsy a cytological 80-mm 22G needle with guidewire and marking facilitating its visualisation on the ultrasound image was used (NA-200H-8022, Olympus Medical Systems Corporation, Tokyo, Japan) (Fig. 2).

The EUS-NA of all lymph nodes >3 mm and ≤10 mm on the short axis were performed (criterion of feasibility of lymph node biopsy according to Annema and Rabe [12]). The number of biopsied stations in one patient was 1–2 and the number of biopsied nodes in one station was 1–5.

On completion of EUS-NA, the patient was turned over onto his back and intravenous sedation was added, if necessary.

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, a 35° optical system and an EU-C60 7.5 MHz ultrasound processor. For the biopsy, a cytological 40-mm 22G needle with guidewire and marking facilitating its visualisation on the ultrasound image was used (NA-201SX-4022, Olympus Medical Systems Corporation, Tokyo, Japan).

The EBUS-NA of all lymph nodes >5 mm and ≤10 mm on the short axis were performed (criterion of feasibility of lymph node biopsy according to Herth and Yasufuku [5,13]) (Fig. 1).

All the biopsies were performed through the macroscopically normal bronchial wall. The number of biopsied stations in one patient was 1–3 and the number of biopsied nodes in one station was 1–5. The cytological smear of all biopsies was performed and fixed using 96% ethanol. The standard haematoxillin–eosin staining was used.

In patients with negative results of the CUS-NA, bilateral transcervical extended mediastinal lymphadenectomy (TEMLA) was performed. The TEMlA includes bilateral dissection of all the mediastinal lymph nodes, except station A.
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 [14,15] and the video presenting this technique is available at: www.mp.pl/download/wmv/temla.wmv.

In patients with negative results of 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 [16].

2.6. Statistical analysis

Statistical calculations were carried out using StatisticaTM software (Statsoft Inc., Tulsa, OK, USA).

Summary statistics were expressed as mean (M) and standard deviation (SD). The McNemar test was used, where appropriate, for paired comparisons. Confidence intervals were calculated to 95% using standard formulae, based on the asymptotic normality of maximum likelihood estimators and the delta method for logit function. The comparison of NPV values was based on the multinominal distribution, the asymptotic normality of frequency vector and the delta method. The type I error was set at 0.05 for all analyses.

The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated using the standard definitions.

3. Results

There were 94 men and 26 women in the mean age of 61.8 ± 8.4 years (range 41—82 years). In these 120 patients, 318 biopsies were performed. CUS-NA established a diagnosis in 19/120 patients (16% true-positive results): by EBUS-NA alone in five patients (4%), by EUS-NA alone in six patients (5%) and by both methods in eight patients (7%).

Among these 318 biopsies, there were 158 EBUS-NAs performed — stations: 7 (subcarinal) — 88 biopsies, 4R (right lower paratracheal) — 34 biopsies, 4L (left lower paratracheal) — 33 biopsies, 2R (right upper paratracheal) — two biopsies and 2L (left upper paratracheal) — one biopsy and 160 EUS-NAs performed — stations: 7 — 101 biopsies, 4L — 57 biopsies and 9 (pulmonary ligament) — two biopsies.

The mean diameters of the biopsied nodes were 8.6 ± 2.2 mm in the long axis and 7.4 ± 2.8 mm in the short axis.

CUS-NA revealed metastatic lymph node involvement in 31 of 318 biopsies (10%) and the biopsy was technically successful in 292 cases (92%).

In 19 patients with metastatic involvement of the lymph node, in 3 of 120 patients (3%) more than one station was involved. The numbers of 31 metastatic nodes, in particular, stations were as follows: EBUS-NA: station 7 — eight, 4L — five and 4L — three and EUS-NA: station 4L — nine and 7 — six.

In 90 patients (75%) the result of mediastinal lymph node biopsy was true negative in 265 biopsies — 127 EBUS-NAs: 73 in station 7, 26 in station 4R, 26 in station 4L, one in station 2R and one in station 2L and 138 EUS-NAs: 89 in station 7, 47 in station 4L and two in station 9. In this group, the cytological diagnosis of benign, reactive lymph node was subsequently confirmed by the histological examination of the TEMLA operative specimen and in 81 patients (68%) with negative results of TEMLA, in addition, mediastinal dissection during thoracotomy was performed and no positive N2–3 nodes were found. The next nine patients after the TEMLA did not undergo lung resection: six of them had a significant impairment of pulmonary function tests that made lung resection impossible, one patient had a myocardial infarction and two out of them refused the second surgery.

In some patients, after the TEMLA, asymptomatic widening of the mediastinum on chest X-ray was seen and in two patients transitory left recurrent nerve palsy was observed.

In nine patients (8%), the result of 11 CUS-NA (4%) was false negative (EBUS-NA — 15 patients and EUS-NA — 14 patients) in stations: 2R — two, 4R — four, 4L — one, 5 — three and 7 — one. In six patients (5%), the TEMLA revealed metastases in nodal stations accessible for CUS-NA (station 2R and 4R — four patients, station 4L — one patient and station 7 — one patient — Table 1) and in the next three patients (3%) in nodal stations not accessible for CUS-NA (station 5 — three patients).

In two patients (2%), the result of CUS-NA was false positive (EBUS-NA — one patient and EUS-NA — one patient) in station 7 — two.

The prevalence of mediastinal lymph node metastases in the present study was 22%.

The overall sensitivity of the CUS-NA for normal mediastinum calculated per patient was 68% (95% confidence interval (CI): 48–84), specificity — 98% (95% CI: 92—100), total accuracy — 91% (95% CI: 86–96), PPV — 91% (95% CI: 70–99) and NPV — 91% (95% CI: 83–96). The diagnostic yield of EBUS-NA, EUS-NA and CUS-NA calculated per patient basis is presented in Table 2.

The sensitivity of CUS-NA was significantly higher than EBUS-NA alone (p = 0.04) and higher, close to the level of significance than EUS-NA alone (p = 0.07). The NPV calculated per patient basis of all techniques was high and the NPV of CUS-NA was significantly higher compared with EBUS-NA.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lymph node station</th>
<th>Diameter of the nodes long axis (mm)</th>
<th>Percentage of metastatic lymph nodes in the station mean: 38 ± 32%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4L</td>
<td>10/10</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>2</td>
<td>2R</td>
<td>7/10</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td></td>
<td>4R</td>
<td>10/10</td>
<td>1/8 (13%)</td>
</tr>
<tr>
<td>3</td>
<td>4R</td>
<td>3/7</td>
<td>7/10 (70%)</td>
</tr>
<tr>
<td>4</td>
<td>2R</td>
<td>7/10</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td></td>
<td>4R</td>
<td>7/10</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>5</td>
<td>4R</td>
<td>7/10</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>5/7</td>
<td>1/5 (20%)</td>
</tr>
</tbody>
</table>
and EUS-NA alone ($p = 0.01$, $p = 0.03$). The sensitivity of CUS-NA calculated per station 7 basis was significantly higher compared with EBUS-NA alone ($p < 0.01$) and EUS-NA alone ($p < 0.01$). The sensitivity of CUS-NA calculated per station 4L basis was significantly higher compared with the sensitivity of EBUS-NA alone ($p = 0.04$) but not the sensitivity of EUS-NA alone ($p = 0.1$). The sensitivity of EUS-NA alone calculated per station 4L basis was significantly higher compared with the sensitivity of EBUS-NA alone ($p = 0.03$).

The diagnostic yield of EBUNA, EUS-NA and CUS-NA calculated per station basis is presented in Table 3.

The mean time of CUS-NA was 28.6 min (range 19–37 min).

No complications were observed after CUS-NA.

4. Discussion

The use of CUS-NA performed simultaneously, under local anaesthesia and sedation, in the radiologically normal mediastinum has never been presented as a standard method in minimally invasive endoscopic NSCLC staging.

Among patients with enlarged lymph nodes seen on CT scans, the reported range of the sensitivity of the EBUS-NA is 79–95%, NPV − 85–96% [2,3,5,17] and the sensitivity of EUS-NA is 71–100%, NPV − 73–79% [2,9,12,18]. A study by Herth et al. demonstrated 100 patients with radiologically normal mediastinum; the sensitivity of EBUS-NA was 92%, NPV was 96% and the prevalence of N2 or N3 disease was 17% [13]. Among patients without enlarged mediastinal lymph nodes, the sensitivity of EUS-NA was 35–61% and NPV was 73–79% [19,20]. In these studies, the prevalence of N2–3 involvement was 36%, which is higher than the expected rate of 20–25% based on the CT scan data for normal-sized mediastinal nodes [21]. The decreased diagnostic yield in small nodes may be due to sampling error — especially technical difficulty in sampling small nodes or detecting error; nodes with a normal sonographic appearance are just not biopsied [10,22]. Although not enlarged, nodes are more difficult to identify with any imaging modalities (including EBUS and EUS); in the present study, biopsies were technically successful in 92%. The overall sensitivity of the CUS-NA for the normal mediastinum calculated per patient was 68%, NPV was 91% and the prevalence of N2–3 disease was 22%. Moreover, small nodes probably contain less metastatic deposits, making a cytological diagnosis difficult; but our results are comparable to the largest series published to date for enlarged nodes [5–7,11,18].

In the current study, the sensitivity of CUS-NA is significantly higher compared with the sensitivity of EBUS-NA and EUS-NA alone ($p = 0.04$, $p = 0.07$). Further, the NPV of CUS-NA is significantly higher compared with the NPV of EBUS-NA and EUS-NA alone ($p = 0.01$, $p = 0.03$). The reason is probably a better access to the anterior and posterior parts of station 4L and 7 using both methods. In such circumstances, EUS-NA and EBUS-NA may be a valuable supplement to each other.

The sensitivity of CUS-NA calculated per station 7 basis was significantly higher compared with EBUS-NA alone ($p < 0.01$) and EUS-NA alone ($p < 0.01$). The sensitivity of CUS-NA and EUS-NA calculated per station 4L basis was significantly higher compared with the sensitivity of EBUS-NA alone ($p = 0.04$; $p = 0.03$). It confirms our observation in routine practice that EUS-NA has much better access to station 4L than EBUS-NA. The access to station 4R may be reached only by EBUS; the sensitivity of EBUS-NA calculated per station 4R basis was 38% but NPV was 84%. Imaging and biopsy of the paratracheal nodes may be more difficult technically than of the subcarinal ones. A difficulty in the imaging of 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 small nodes to big vessels and, in rare cases, the paratracheal nodes are located too far from the tracheal wall to be caught by 40-mm needles [17]. As the risk of complications related to the EBUS-NA and EUS-NA is very low, both procedures may be performed in the outpatient settings and also, in the present study, no complications were observed [4,8,9].

The rate of false-negative biopsies was only 4%. In most of these cases, noted mainly in station 4R, the extent of metastatic nodal involvement was limited, which was confirmed by the pathological examination of the TEMLA specimen (Table 1).

The reason is probably the use as the confirmatory test the TEMLA procedure, which is much more accurate in detecting the missed metastatic nodes than the commonly used standard mediastinoscopy [15,23], although in patients with negative results of the needle biopsy, mediastinoscopy is recommended according to the recent guidelines of the American College of Chest Physicians [6].

5. Conclusions

1. In the radiologically normal mediastinum, CUS-NA is a highly effective and safe technique for NSCLC staging.
2. CUS-NA of nodes that are not enlarged has a higher diagnostic yield than EBUS-NA and EUS-NA alone.
3. The current findings suggest that in patients with negative results of CUS-NA in the radiologically normal mediastinum a surgical diagnostic exploration of the mediastinum may be omitted.

References