The value of mediastinal staging with endobronchial ultrasound-guided transbronchial needle aspiration in patients with lung cancer

Henrik Ømark Petersen a,*, Jens Eckardt a, Ardesir Hakami a, Karen Ege Olsen b, Ole Dan Jørgensen a

a Department of Cardio-thoracic Surgery, Odense University Hospital, Odense, Denmark
b Department of Pathology, Odense University Hospital, Odense, Denmark

Received 11 September 2008; received in revised form 27 March 2009; accepted 31 March 2009; Available online 6 June 2009

Abstract

Objective: To evaluate the diagnostic yield, the learning curve and the safety of endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNA) in mediastinal staging of patients with lung cancer. Methods: Mediastinal staging was performed with EBUS-TBNA according to the Danish national guidelines in patients fulfilling one or more of the following criteria: (1) central tumour; (2) enlarged (>10 mm) mediastinal lymph nodes on computed tomography; or (3) positron emission tomography (PET)-positive mediastinal lymph nodes. The study period began in January 2006 when EBUS-TBNA was introduced in the department and ended in December 2007. All records were reviewed retrospectively. None of the four examiners had any previous experience with EBUS-TBNA or ultrasound when the study began. All examinations were performed under general anaesthesia. Patients without useful cytological material from the EBUS-TBNA were subjected to a supplementary standard cervical mediastinoscopy if the mediastinal lymph nodes were found to be enlarged (>10 mm), PET positive or if the examiner was insecure of the result of the EBUS-TBNA. Patients with mediastinal lymph node involvement, detected by EBUS-TBNA or standard cervical mediastinoscopy, were referred to oncological treatment, while those without mediastinal lymph node involvement underwent — if they were otherwise eligible for surgery — resection and systematic lymph node sampling either by thoracotomy or by video-assisted thoracoscopic. Final mediastinal staging was defined as positive if mediastinal lymph node involvement was detected by EBUS-TBNA, standard cervical mediastinoscopy or surgery, or defined as negative otherwise. Results: A total of 157 patients were included in the study. N2/N3 disease was found in 67 patients (42.6%). EBUS-TBNA missed the mediastinal spread in 10 patients. Five of the ten patients had lymph node metastases in station 5, 6 or 8 — out of reach of EBUS-TBNA or standard cervical mediastinoscopy. EBUS-TBNA had a sensitivity of 0.85 (0.74—0.93) and a negative predictive value of 0.90 (0.82—0.95). No complications occurred from EBUS-TBNA. The number of supplementary standard cervical mediastinoscopies decreased significantly in the study period. Conclusion: The results of this study suggest that staging of the mediastinum with EBUS-TBNA is safe and easy to learn — even without previous experience with ultrasound. The diagnostic yield of EBUS-TBNA is in accordance with the yield of standard cervical mediastinoscopy reported in the literature. We do not find any indications in the present study of the recommended necessity for mediastinoscopy in all EBUS-TBNA-negative patients. © 2009 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Endobronchial ultrasound-guided transbronchial needle aspiration; Lung cancer; Lymph node metastases; Staging

1. Introduction

The first linear scope for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was made commercially available by Olympus in 2005. The scope is a flexible video bronchoscope integrated with a convex 7.5-MHz ultrasound transducer that makes it possible to visualise mediastinal and hilar structures. The ultrasound picture is obtained by direct contact of the probe or through a saline-inflated balloon to facilitate air-free contact with the bronchial wall. An integrated biopsy channel makes it possible to introduce a needle into most peribronchial targets and aspirate material for cytological examination under real-time visual control. The size of lesions can be measured in two dimensions and vascular structures can be identified with Doppler mode.

In this study, we evaluate the diagnostic yield, the learning curve and the safety during our first 2 years of experience with EBUS-TBNA for staging of the mediastinum in patients with lung cancer.

2. Methods

Lung cancer patients eligible for mediastinal staging were included in the study from January 2006 to December 2007.
Mediastinal staging was performed with EBUS-TBNA according to the national guidelines in patients fulfilling one or more of the following criteria: (1) central tumour; (2) enlarged (>10 mm) mediastinal lymph nodes on computed tomography (CT); or (3) positron emission tomography (PET)-positive mediastinal lymph nodes. All records were reviewed retrospectively. EBUS-TBNA examinations were done with the linear scanner (BF-UC160F, Olympus, America Inc., Center Valley, PA, USA) and aspiration was done with a 22-G needle (NA-201SX-4022, Olympus, America Inc., Center Valley, PA, USA). Two or more aspirations were taken from all lesions visualised measuring more than 5 mm. Aspirated material was expelled onto glass slides and smeared for cytological examination. The remaining material was expelled into saline for histological examination. No rapid on-site cytological evaluation was used. None of the four examiners had any previous experience with EBUS-TBNA or ultrasound when the study began. All examinations were performed under general anaesthesia.

All patients had a CT scanning before the EBUS-TBNA. PET/CT was not done routinely — but at the discretion of the referring centre. Supplementary standard cervical mediastinoscopy was performed in patients without useful cytological material in the following situations: (1) enlarged lymph nodes (>10 mm); (2) PET-positive lymph nodes; or (3) if the examiner was insecure of the result of the EBUS-TBNA. Patients with mediastinal lymph node involvement, detected by EBUS-TBNA or standard cervical mediastinoscopy, were referred to oncological treatment, while those without signs of mediastinal lymph node involvement underwent — if they were otherwise eligible for surgery — resection and systematic lymph node sampling by either thoracotomy or video-assisted thoracoscopy. Final mediastinal staging was defined as positive if mediastinal lymph node involvement was detected by EBUS-TBNA, standard cervical mediastinoscopy or surgery, or defined as negative otherwise. Lymph nodes were systematically mapped according to the Mountain—Dresler classification [1].

All calculations were done with the Microsoft Excel spreadsheet [2]. Proportions are presented with 95% confidence limits. 2 x 2 tables were analysed by the chi-square test [3].

3. Results

A total of 157 patients (75 in 2006 and 82 in 2007) with lung cancer were staged with EBUS-TBNA in the study period. All 157 patients were included in the study. The results of EBUS-TBNA staging compared to the final stage are shown in Table 1. Fifty-seven patients were found to have mediastinal lymph node involvement by EBUS-TBNA and a further 10 (false negative) were later detected at either mediastinoscopy or surgery. Lymph node involvement in five of the 10 false-negative patients was solely in station 5, 6, or 8. Ninety patients were classified as not having mediastinal lymph node involvement. The sensitivity of EBUS-TBNA was therefore 0.85 (0.74—0.93) and the predictive value of a negative (PVneg) test was 0.90 (0.82—0.95). The prevalence of mediastinal lymph node involvement among all patients was 0.43 (0.35—0.51).

Supplementary standard cervical mediastinoscopy was performed in 61 patients (53 in 2006 and eight in 2007 (p < 0.01)) and surgery was performed in 88 (47 in 2006 and 41 in 2007 (not significant)). Mediastinal lymph node involvement was detected in eight patients at surgery (six in 2006 and two in 2007 (not significant)) Final evaluation (mediastinoscopy or surgery) in six of the 90 patients, classified as not having mediastinal lymph node involvement by EBUS-TBNA, was not done because of detection of distant metastases or deterioration of the physical condition. Representative lymph node material with no sign of malignancy was found by EBUS-TBNA in all six. One patient examined with EBUS-TBNA had a specimen with suspected malignancy in station 7, which prompted a supplementary mediastinoscopy that confirmed the suspicion. The staging result of this patient was not considered a failure of EBUS-TBNA.

We found an increase in sensitivity from 0.82 (0.66—0.92) to 0.89 (0.72—0.98) (not significant) and an increase in PVneg from 0.84 (0.69—0.93) to 0.95 (0.85—0.99) (not significant) when the first half of the study period (2006) was compared to the second (2007). The prevalence of mediastinal lymph node involvement changed from 0.52 (0.40—0.64) in 2006 to 0.34 (0.24—0.45) in 2007 (not significant).

No complications occurred from EBUS-TBNA.

4. Discussion

A growing number of studies about minimally invasive staging of the mediastinum have emerged in the literature [4—6], but no randomised studies exist. This retrospective study evaluates our first 2 years of experience with EBUS-TBNA for mediastinal staging of patients with lung cancer. Mediastinoscopy has so far been the gold standard [7] and Toloza et al. found — in a review of 14 studies involving a total of 5687 lung cancer patients — that standard cervical mediastinoscopy had a sensitivity of 0.81 (range 0.67—0.92) and a PVneg of 0.91 (range 0.82—0.97) [8]. These figures are in accordance with our results with EBUS-TBNA.

Although the six EBUS-TBNA-negative patients not being subjected to supplemental mediastinoscopy or surgery is a concern for the validity of our estimate of the sensitivity and PVneg, we find no reason to change our conclusions. The sensitivity would be lowered to 0.78 in the unlikely case that all six were false negative; however, this is still in accordance with the results of Toloza.

In our study, 10 out of 67 patients with mediastinal lymph node involvement were EBUS-TBNA false negative. Fifty percent of these patients had lymph node metastases in station 5, 6 or 8, which is not out of reach for both EBUS-TBNA and

---

Table 1 Results of mediastinal lymph node staging with EBUS-TBNA in patients with lung cancer versus final mediastinal staging. Final staging is defined as positive if mediastinal lymph node involvement was detected at either EBUS-TBNA, standard cervical mediastinoscopy or surgery and negative otherwise.

<table>
<thead>
<tr>
<th>N2/N3</th>
<th>EBUS-TBNA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>57</td>
<td>100</td>
</tr>
<tr>
<td>(−)</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>100</td>
</tr>
</tbody>
</table>

**Note:** N2/N3 represents the stages of lymph node involvement, with N2 being more proximal and N3 more distal.
standard cervical mediastinoscopy. This finding suggests that a complete staging of the mediastinum must include more than one examination modality. The lesions in stations 5, 6 or 8 were not detectable on CT; however, it is possible that PET/CT might have been positive. [9,10] Stations 5 and 6 are reachable through left-sided thoracoscopie and that would be our strategy in case of enlarged or PET-positive lymph nodes. Stations 8 and 9 are reachable through oesophageal ultrasound fine-needle aspiration (EUS-FNA) [11] and that would be our choice in case of enlarged or PET-positive lymph nodes in these stations.

Among the other five patients with false-negative examinations — but with positive lymph nodes within the reach of EBUS-TBNA (station 2, 3, 4 and 7) — we performed a supplementary standard cervical mediastinoscopy in two patients that also proved false negative. This advocates against the recommendation that all patients with a negative EBUS-TBNA examination should have a supplementary mediastinoscopy [7].

Examination by EUS-FNA alone has shown a sensitivity and PVneg of 0.88 and 0.77, respectively [8], while the combination of EBUS-TBNA and EUS-FNA has shown sensitivity for detection of mediastinal lymph node involvement of up to 100% [12,13]. These two examination modalities are complementary and are a possible minimal invasive strategy for evaluating the mediastinum. Furthermore, the left adrenal gland can be reached by EUS-FNA, giving the opportunity to distinguish between hyperplasia and M1 disease [14]. However, it can be questioned whether the cost of examining all patients with EUS-FNA, in addition to EBUS-TBNA, can justify the avoidance of a relatively small number of futile operations.

All four EBUS-TBNA examiners in the present study are thoracic surgeons with routine in flexible bronchoscopy, but without any previous experience with ultrasound or EBUS-TBNA. A learning curve is therefore to be expected. We found a small but not significant increase in sensitivity and PVneg, but a large decrease in the need for supplementary mediastinoscopy in the study period. This reflects the increasing confidence in the new method and indicates that supplemental cervical mediastinoscopy is necessary in only a few selected patients after a negative EBUS-TBNA.

The choice of performing all EBUS-TBNA examinations under general anaesthesia can be questioned. Our concern was diagnostic yield, patient comfort and compliance under sedation. We find that further studies are needed to address this question.

We conclude that EBUS-TBNA is a safe procedure with a learning curve that is easily overcome — even without previous experience with ultrasound. The diagnostic yield of EBUS-TBNA in the present study is in accordance with the results of standard cervical mediastinoscopy reported in the literature and, furthermore, EBUS-TBNA is less invasive. We do not find any indications in the present study of the recommended necessity for mediastinoscopy in all EBUS-TBNA-negative patients.

References


Appendix A. Conference discussion

Dr. R. Milton (Leeds, United Kingdom): In our units and in most of the units in the UK, we are always trying to shorten the time period from referral to definitive treatment, and one of the arguments put forward by our respiratory colleagues is that EBUS will get the results of the N2 disease earlier. Do you have any figures on the time saved by using EBUS as opposed to being sent for mediastinoscopy?

Dr Omarm Petersen: Well, in our institution we do both procedures and the time schedule does not differ until definitive treatment.

Dr M. Saute (Petach-Tikva, Israel): In your last conclusion you say that you do not recommend mediastinoscopy in EBUS-negative patients. What about the patients who have a positive PET-CT scan of the mediastinum who are EBUS-negative?

Dr Omarm Petersen: We don’t use a PET-CT scan as a standard prior to the EBUS-TBNA, so I can’t answer that question, if I understood you correctly.

Dr W. Klepetko (Vienna, Austria): How many investigators performed the EBUS?

Dr Omarm Petersen: Four.

Dr Klepetko: And in your unit it is possible to have an endoerosophageal ultrasound and biopsy as well in addition to EBUS to approach the more lower region of the paraesophageal nodes?

Dr Omarm Petersen: Yes, that is a very important question. If we find enlarged lymph nodes or PET-positive lymph nodes in case a PET-CT scan has been performed, in stations 5 and 6 we do a VATS biopsy and in stations 8 and 9 we do an EUS.

Dr E. Ruﬀini (Torino, Italy): I have a couple of questions.

First, how do you insert the PET scan in your algorithm? I mean with a negative PET scan, do you suggest EBUS-TBNA and so on? Second, I’m concerned that you don’t have an on-site cytologist in your room. How can you be sure that your biopsies are correct? We have a similar experience with bronchoscopy, so we know the importance of having an on-site cytologist to
assess that your biopsies are appropriate. Third, probably one of the messages with the utility of mediastinoscopy is also to assess the invasion, maybe the extracapsular extension that you cannot assess from EBUS-TBNA. This is just a comment.

Dr Ømark Petersen: I would like to answer your first question, which is?

Dr Ruffini: How can you use a PET scan in your algorithm? Do you suggest EBUS-TBNA for all PET-negative patients?

Dr Ømark Petersen: Yes, we do, because right now we do not have a standard for using PET-CT scan, so we do it systematically for everyone.

Dr Ruffini: Second, is the on-site cytologist important for you?

Dr Ømark Petersen: Well, it would optimal if that was possible, but unfortunately at our institution we could not get an on-site pathologist. I think time has shown that we have a pretty good feeling when we have hit the lymph node with just us looking at the smear, but I think that would be optimal.