Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Staging of Patients with Non-Small Cell Lung Cancer without Mediastinal Involvement at Positron Emission Tomography-Computed Tomography

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Keywords

EBUS-TBNA · Endobronchial ultrasound · Mediastinum · PET-CT · Mediastinal staging · Lung cancer · Lung cancer staging

Abstract

Background: Staging of lung cancer is essential to the treatment, which is curative only in cases of localized disease. Previous studies have suggested that endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is unnecessary when positron emission tomography-computed tomography (PET-CT) shows no mediastinal involvement. **Objective:** The aim of the study was to investigate how often EBUS-TBNA resulted in a clinically relevant upstaging in patients with lung cancer without mediastinal involvement at PET-CT. **Methods:** A total of 981 consecutive patients from 2009 to 2014 were referred for preoperative EBUS-TBNA. We included 167 patients with lung cancer without involvement of the mediastinum at PET-CT (115 N0 and 52 N1). **Results:** Of the 167 patients included, 10 (6.0%) were upstaged to N2 or N3 by EBUS-TBNA; 9 of these were originally classified as N1

at PET-CT. Therefore, 17.3% of the included N1 patients were upstaged to N2/N3 after EBUS-TBNA. This compares to only 0.9% of the N0 patients. After both EBUS-TBNA and PET-CT, 115 patients were operated, and 12 (10.4%) of these proved to be N2/N3. We calculated the sensitivity as 42.9%, the specificity as 99.0%, and the negative predictive value as 89.6%. **Conclusions:** The overall probability of a clinically relevant upstaging by EBUS-TBNA in patients judged as N0/N1 at PET-CT was 6.0%, compared to 0.9% in patients classified as N0 and 17.3% in patients classified as N1. The risk of overlooking N2/N3 disease after both PET-CT and EBUS-TBNA was 10.4%.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for about 85–90% of all lung cancer cases [1]. Accurate staging is essential for the planning of the treatment, which is curative only in cases of localized disease [2]. In general, surgery is not advisable in patients

with NSCLC and N2 or N3 disease. Computed tomography (CT) and positron emission tomography (PET) is recommended for initial staging [3], followed by endosonography as the next step [4], especially in cases with an abnormal mediastinum (recommendation grade A), whereas the recommendation grade is lower (C) in the case of patients with a normal mediastinum [4]. Previous studies have indicated that endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is advisable when PET-CT shows no mediastinal involvement [5], but this matter remains under discussion since data are scarce [4]. Given this background, we decided to investigate the results of EBUS-TBNA in patients with suspected or proven lung cancer without involvement of the mediastinum at PET-CT.

The aims of the study were the following: (1) to investigate how often EBUS-TBNA in general anesthesia, with the intention of taking biopsies from at least station 4R, 4L, and 7, resulted in a clinically relevant change in the classification of the disease in patients with NSCLC without mediastinal involvement at PET-CT; (2) to calculate the sensitivity, specificity, and negative predictive value (NPV) of EBUS-TBNA in the patients mentioned, and (3) to calculate how often representative tissue from all 3 mediastinal stations (4R, 4L, and 7) was achieved when performing the procedure as described (general anesthesia, lymph nodes <1 cm on CT).

Patients and Methods

A total of 981 consecutive patients were identified in the hospital's database as having been referred for preoperative EBUS-TBNA with suspected or proven lung cancer between June 2009 and October 2014. We found 219 patients suspected of lung cancer without involvement of the mediastinum at PET-CT (all mediastinal lymph nodes <1 cm in size and without metabolic activity). Of these patients, 52 were diagnosed with nonmalignant disease, metastasis from other cancers, carcinoid tumors, or small-cell lung cancer. The rest, 167 patients, suffered from NSCLC (Table 1). A total of 115 patients were staged as N0 and 52 as N1. EBUS-TBNA was performed on all 167 patients in general anesthesia to achieve tissue from all lymph node stations 4R, 4L, and 7. A flexible ultrasound bronchoscope (Olympus XBF-UC40P or Pentax EB-1970UK) and 22-gauge needles were used.

The study was a retrospective observational study that aimed to examine the quality of previously acquired biopsies. There was no randomization or intervention in the treatment of the patients. These types of studies are exempt from approval by the local Research Ethics Committee according to Danish legislation. The study was approved by the Danish Data Protection Agency (GEH-2015-082).

Table 1. Patient and tumor characteristics (N = 167)

Sex	
Male	89 (53.3)
Female	78 (46.7)
Age, years	68.0±0.7
Tumor size, mm	39.4±1.6
Affected lobe	
Right upper lobe	56 (33.5)
Right middle lobe	9 (5.4)
Right lower lobe	29 (17.4)
Left upper lobe	50 (29.9)
Left lower lobe	23 (13.8)
Tumor type	
Adenocarcinoma	110 (65.9)
Squamous cell carcinoma	46 (27.5)
Non-small cell lung cancer, unspecified	8 (4.8)
Adenosquamous carcinoma	1 (0.6)
Sarcomatoid carcinoma	1 (0.6)
Large-cell neuroendocrine carcinoma	1 (0.6)

Values are expressed as *n* (%) or mean ± standard deviation.

Results

No Clinically Relevant Change

In 157 (94.0%) of the 167 patients, EBUS-TBNA did not upstage the mediastinal PET-CT classification of the patients to N2 or N3. This was the case for 114 of the N0-patients (99.1%) and for 43 of the N1-patients (82.7%). Approximately two-thirds of these 157 patients (115, 73.2%) were admitted for surgery with curative intention, whereas 42 patients (26.8%) were considered inoperable because of comorbidity, poor lung function, dissemination of the disease, or other reasons. Radio- and/or chemotherapy were considered for these patients. In 3 of the patients (1.9%), PET-CT N0 was upstaged to EBUS-TBNA N1, but this did not change the indication for surgical treatment and was therefore not considered clinically relevant.

Clinically Relevant Change

EBUS-TBNA resulted in upstaging of the disease to N2/N3 in 10 of the 167 patients (6.0%). Of these patients, 1 was originally classified as N0 at PET-CT, and the remaining 9 were classified as N1. This means that 17.3% of the 52 N1 patients were upstaged to N2 or higher. This was the case for only 0.9% of the N0 patients. One of the upstaged patients was operated because the results from EBUS-TBNA were ambiguous, resulting in a final classification of N0 after operation. The rest were submitted for

Table 2. Characteristics of the 10 patients upstaged by endobronchial ultrasound-guided transbronchial needle aspiration

Patient No.	Nodal stage (PET-CT)	Nodal stage (EBUS)	Malignant lymph node station	Primary tumor localization	Tumor histology	Primary tumor size, mm
1	N1	N2	4R	RUL	Squamous-cell carcinoma	35
2	N1	N3	4R, 4L, 7	RLL	Adenocarcinoma	93
3	N1	N2	4R, 10R, 11R	RUL	Adenocarcinoma	23
4	N1	N2	4R	RUL	Squamous-cell carcinoma	70
5	N0	N2	4R	RUL	Adenocarcinoma	55
6	N1	N2	7, 11L	LLL	Squamous-cell carcinoma	55
7	N1	N2	7	RLL	Adenocarcinoma	100
8	N1	N2	4R, 10R, 11R	RUL	Adenocarcinoma	25
9	N1	N2	4L	LLL	Adenosquamous carcinoma	25
10	N1	N2	7	LUL	Squamous-cell carcinoma	30

PET-CT, positron emission tomography-computed tomography; EBUS, endobronchial ultrasound; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 3. Characteristics of the 12 patients upstaged by operation

Patient No.	Nodal stage (PET-CT)	Nodal stage (EBUS)	Nodal stage (post-OP)	Malignant lymph node station	Primary tumor localization	Tumor histology	Primary tumor size, mm
1	N1	N0	N2	5, 6, 10L	LUL	Adenocarcinoma	45
2	N0	N0	N2	5	LUL	Squamous-cell carcinoma	51
3	N1	N1	N2	7, 11R	RLL	Adenocarcinoma	24
4	N0	N0	N2	5	RLL	Adenocarcinoma	49
5	N1	N1	N2	5	LUL	Squamous-cell carcinoma	52
6	N0	N0	N2	2R, 4R, 7, 8, 10R, 11R	RLL	Squamous-cell carcinoma	52
7	N1	N1	N2	2R, 4R	RUL	Adenocarcinoma	35
8	N1	N1	N2	5, 6, 11L	LUL	Adenocarcinoma	16
9	N1	N1	N2	7	LLL	Adenocarcinoma	8
10	N0	N0	N2	9R, 11R	RLL	NSCLC	68
11	N1	N0	N2	7, 10R	RML	Adenocarcinoma	20
12	N0	N0	N2	2R, 7, 8	RLL	Adenocarcinoma	25

PET-CT, positron emission tomography-computed tomography; EBUS, endobronchial ultrasound; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; NSCLC, non-small cell lung cancer.

consideration of radio- and/or chemotherapy. Table 2 shows the characteristics of the 10 patients who were upstaged by the EBUS-TBNA procedure.

Operations (video-assisted thoracic surgery or thoracotomy) were performed in 115 of the patients without mediastinal spread judged on both PET-CT and EBUS-TBNA. No change in mediastinal staging after operation was seen in 103 (89.6%) of the operated patients. Change in mediastinal staging after operation was seen in 12 (10.4%) of the patients. Table 3 shows the characteristics of these patients.

Figure 1 shows a flowchart of the patients in the study.

Preoperative mediastinoscopy was performed in 4 of the 167 patients (2.4%). Malignancy in the mediastinum was not demonstrated in any of these cases, which indicates that there was no change in mediastinal nodal staging and no change in the treatment plan.

The primary tumor was located centrally in 4.2% of the patients and peripherally in the remaining 95.8%. In 22.8% (38 patients), the tumor was <3 cm in diameter and classified as N0 at PET-CT, and none of these patients were upstaged by EBUS-TBNA to N2/N3. However, 1 patient was upstaged to N2 by operation (Tables 2, 3).

Fig. 1. These 5 patients were operated with a finding of either inoperable lung cancer (T-classification higher than expected), metastases from a primary tumor other than lung cancer, or benign disease (in 1 case, the tumor was shown to be a hamartoma).

Table 4. Number of mediastinal lymph nodes (4R, 4L, and 7) with lymphatic tissue

Number of lymph nodes	Number of patients (%)
3	109 (65.3)
2	31 (18.6)
1	20 (12.0)
0	7 (4.2)

Table 5. Size range of lymph nodes measured by EBUS

Lymph node station	Mean $\pm$ SEM, mm	Number of measured lymph nodes
4R	7.9 $\pm$ 0.4	140
4L	5.8 $\pm$ 0.3	131
7	10.5 $\pm$ 0.5	141
10R	4.5 $\pm$ 0.5	2
10L	14.4 $\pm$ 2.7	5
11R	11.8 $\pm$ 1.0	19
11L	25.0 $\pm$ 5.0	2

Based on the above data, the sensitivity for EBUS-TBNA to detect N2/N3 disease was calculated as 42.9% (confidence interval [CI] 21.8–66.0), the specificity as 99.0% (CI 94.8–100.0), and the NPV as 89.6% (CI 85.6–92.6).

Table 4 shows how often lymph node biopsies from stations 4R, 4L, and 7 contained lymphatic tissue, meaning that they were representative. In 109 patients (65.2%), this was the case for all 3 lymph node stations mentioned.

Table 5 shows the mean sizes of biopsied lymph nodes when measured with EBUS-TBNA.

Discussion

PET-CT is recommended in order to evaluate the TNM classification in patients with suspected or proven lung cancer. Mediastinal lymph nodes with a short axis larger than 10 mm and/or lymph nodes with increased metabolic activity are indicators of malignant disease [6]. However, PET-CT is suboptimal for accurate staging [7]. Therefore, more thorough evaluation of mediastinal lymph node involvement is required [8] in patients with NSCLC, both with and without mediastinal involvement judged by PET-CT [9, 10]. With regard to the latter group, an increased risk of mediastinal involvement is seen, firstly, in cases with hilar lymph nodes that are enlarged or show increased metabolic activity; secondly, if the lung tumor is ≥ 3 cm in size, and thirdly, in cases without increased metabolic activity in the lung tumor [9–11].

Mediastinoscopy has been challenged as the gold standard for mediastinal staging by endosonography, which

improves mediastinal staging, reduces futile thoracotomies, and is cost-effective [12]. The current European guidelines recommend the use of endosonography with tissue sampling in the mediastinum (recommendation grade C) in the above-mentioned cases [4]. If endosonography with tissue sampling does not show malignant mediastinal involvement, it is suggested that mediastinoscopy should be considered (recommendation grade C).

We investigated whether EBUS-TBNA was necessary in patients with proven or suspected lung cancer presenting with a normal mediastinum at PET-CT. In the vast majority of cases (94.0%), we found that the procedure did not change treatment strategy, since no clinically relevant upstaging was seen. In these cases, therefore, it could be argued that the procedure was unnecessary. Thus, the overall risk of mediastinal nodal involvement in these patients was 6.0%.

Our finding that the risk of mediastinal involvement is 17.3% in patients classified as N1 at PET-CT is in accordance with the study by Dooms et al. [13], which found a comparable risk of 24% in similar patients. That study included 100 patients and did not look at patients classified as N0.

In our study, when PET-CT classified the patient as N0, this risk of a clinically relevant upstage by EBUS-TBNA was only 0.9%, which supports the recommendations in the guidelines [4]. Herth et al. published 2 studies, in 2006 and 2008 [5, 14], which included 100 patients and 97 patients, respectively; the overall risks of detecting malignant lymph nodes with EBUS-TBNA were found to be 16% in the former study and 8% in the latter. However, in the 2006 study, only CT was performed prior to EBUS-TBNA, not PET-CT. In the 2008 study, which had significantly fewer findings of malignant lymph nodes by EBUS-TBNA, PET-CT preceded the procedure.

Our data showed adenocarcinoma as a final lung cancer diagnosis in 5 out of the 10 upstaged patients; however, these numbers are too small for us to draw any conclusion with respect to the importance of the type of cancer. In addition, we do not consider our material large enough to correlate the size or location (peripherally/centrally) of the lung tumor to the risk of mediastinal involvement. We found 38 patients who underwent EBUS-TBNA with a tumor size <3 cm and a classification of N0 at PET-CT. The fact that none of these were upstaged to N2 or N3 supports the recommendation in the guidelines to omit EBUS-TBNA in patients with this type of tumor. This recommendation is of course restricted to peripherally located lung tumors.

We found a relatively low sensitivity of EBUS-TBNA, which is in accordance with what has previously been reported [13, 15, 16]. It has been shown that the combination of EBUS-TBNA and endoscopic ultrasound-guided fine-needle aspiration (or endoscopic ultrasound-guided fine-needle aspiration using the EBUS scope) has a higher sensitivity and NPV and gives access to more lymph nodes than EBUS-TBNA alone [17–21]. Therefore, it could be speculated that this combination of procedures would have resulted in fewer overlooked N2 diseases in our patients.

The NPV of EBUS-TBNA was calculated based on all patients with an N-classification of N2 or higher at operation. However, it must be remembered that in half of these cases (6 out of 12), upstaging by operation was based on lymph node stations that EBUS-TBNA does not give access to. Therefore, one could argue that a more correct NPV would be 94.8% (CI 90.7–97.1) and a sensitivity of 60.0% (CI 32.3 to 83.7). Three other studies found the sensitivity to be 38, 46, and 76%, and the NPV to be 81, 86, and 99%, respectively [13, 22, 23]. The same logic applies to the risk of overlooking N2/N3 disease, which we calculated as 10.4%. If we calculate this risk based only on the patients upstaged by lymph nodes reachable by EBUS-TBNA, it decreases to 5.2%.

Secondly, for obvious reasons, patients who were not operated could not be included in the calculation of the sensitivity.

The current guidelines suggest that at least 3 lymph node stations (4R, 4L, and 7) should be biopsied in case of an abnormal mediastinum at PET-CT (recommendation grade D) [4]. We decided to follow this recommendation, even in the case of a normal mediastinum. In our study, it was possible to achieve representable tissue from all 3 lymph node stations that were “invisible” at PET-CT (i.e., no metabolic activity and <1 cm in size) in 109 patients (65.3%).

One of the strengths of this study is that we have presented more patients with PET-CT N0/N1 with suspected or proven lung cancer than any other published study [5, 13, 14]. Moreover, the procedure was performed by 5 different experienced respiratory physicians under conditions that were considered optimal for the procedure [23], although it has not been proven in a randomized study that general anesthesia increases the diagnostic yield compared to conscious sedation. In our patients, tissue sampling was done systematically from all 3 lymph node stations 4R, 4L, and 7, with lymphatic tissue found in all 3 stations in 109 patients (65.3%). Even very small lymph nodes (<5 mm) were biopsied, unlike other studies, where only lymph nodes >5 mm were biopsied [5, 13]. Furthermore, we systematically conducted rapid onsite

evaluation in our study [4], which also contrasts with other studies. It seems unlikely that the performance of EBUS-TBNA under other circumstances would have upstaged more patients.

Among the limitations of the present study are the fact that no randomization was done and that the study was conducted retrospectively as a single-center study; this contrasts with the study performed by Dooms et al. [13], which was conducted prospectively and involved multiple centers.

Based on our findings, one could speculate that EBUS-TBNA should be omitted in patients with NSCLC classified as N0 by PET-CT, since the probability of a clinically relevant upstage by the procedure is very low. However, EBUS-TBNA still seems highly relevant in patients classified as N1 by PET-CT.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest to disclose.

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