Minimally invasive diagnostics and immunotherapy of lung cancer

Talebian Yazdi, M.

Chapter 2

EUS-FNA in the preoperative staging of non-small cell lung cancer

M. Talebian Yazdi[1]
M.B. von Bartheld[1]
J. Braun[2]
M.I.M. Versteegh[2]
O.M. Dekkers[3]
K.F. Rabe[1]
J.T. Annema[1]

1. Department of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands
2. Department of Cardio-Thoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands
3. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Background

According to current guidelines, transesophageal ultrasound-guided fine needle aspiration (EUS-FNA) can be performed as an alternative for surgical staging to confirm mediastinal metastases in patients with non-small cell lung cancer (NSCLC). To date however, data regarding the routine use of EUS-FNA in the preoperative staging of unselected patients with NSCLC are limited.

Aims and Objectives

1. To evaluate the diagnostic value of EUS-FNA in consecutive patients with NSCLC regardless of nodal size at CT.
2. To determine the impact of EUS-FNA on the prevention of surgical staging procedures.
3. To assess the accuracy of mediastinal staging by combining EUS-FNA and mediastinoscopy.
4. To investigate whether a subgroup of patients exists that can be accurately staged by EUS-FNA alone.

Methods

152 consecutive operable patients with proven or suspected NSCLC who underwent EUS-FNA were retrospectively analyzed. In the absence of mediastinal metastases, mediastinoscopy and/or thoracotomy with lymph node dissection was performed.

Results

The prevalence of mediastinal metastases was 49%. Sensitivity, negative predictive value (NPV) and accuracy of EUS-FNA for N2/N3 disease were 74%, 73% and 85%, respectively, whereas these values for the combined staging of EUS-FNA and mediastinoscopy were 92%, 85% and 95%. Additional surgical staging in patients staged N0 at EUS-FNA reduces the false negative EUS-findings by 55%. The NPV of EUS-FNA for left-sided tumors was 68%. EUS-FNA prevented surgical staging procedures in 60 of 152 patients (39%). No major complications occurred during EUS-FNA.

Conclusion

Routine use of EUS-FNA in unselected patients with NSCLC reduces the need for surgical staging procedures in nearly half of patients. Additional surgical staging in patients without nodal metastases at EUS-FNA reduces the false negative EUS-FNA findings considerably regardless of the location of the primary lung tumor.

INTRODUCTION

Preoperative staging of non-small cell lung cancer (NSCLC) defines the anatomic extent of the disease at the time of the diagnosis and will determine treatment recommendations and prognosis. The basis for NSCLC staging is the TNM system [1]. In the absence of distant metastases, regional lymph node status is critical for determining treatment options. Contrast enhanced computed tomography (CT) scanning of the chest is useful in providing anatomic detail, but the accuracy of chest CT scanning in differentiating benign from malignant lymph nodes in the mediastinum is limited[2]. Therefore, tissue verification of mediastinal lymph nodes is indicated to ensure accurate nodal staging.

Mediastinoscopy is considered the reference standard for invasive staging of patients with potentially operable NSCLC. Though invasive, mediastinoscopy is an accurate staging method, but it has limited access to posterior subcarinal lymph nodes and the lower mediastinum[3]. Transesophageal ultrasound-guided fine needle aspiration (EUS-FNA) is a safe and minimally invasive staging procedure with a diagnostic reach complementary to mediastinoscopy. EUS-FNA added to mediastinoscopy in the preoperative staging of lung cancer has been shown to result in improved nodal staging and to prevent futile thoracotomies [4,5]. EUS-FNA is useful for confirming mediastinal metastases, but has its limitations regarding its negative predictive value (73–83%) [6,7]. EUS-FNA has been shown to prevent surgical staging procedures in 50–70% of patients by demonstrating the presence of lymph node metastases [8,9]. Therefore, EUS-FNA has been advocated in recent guidelines as the first mediastinal staging test to provide tissue confirmation (but not exclusion) of nodal metastases [3,6]. The impact and accuracy of EUS-FNA have mostly been investigated in cohorts of selected patients with nodal enlargement on CT or with positron emission tomography (PET) positive lymph nodes[7]. To date, however, its merits in the routine preoperative staging of unselected patients with NSCLC are as yet unclear.

Therefore, we evaluated a lung cancer staging strategy involving consecutive patients with potentially operable lung cancer who were initially staged by EUS-FNA. Sensitivity, NPV and accuracy of EUS-FNA in the preoperative nodal staging of NSCLC were assessed. We also investigated whether a subgroup of lung cancer patients exists that can be accurately staged by EUS-FNA alone without subsequent surgical staging. Finally, we determined the impact of EUS-FNA on the prevention of surgical staging procedures.

MATERIALS AND METHODS

Design and patients

We retrospectively evaluated a lung cancer staging strategy over a 3.5-year period (between August 2003 and February 2007) in which patients with operable lung cancer

were initially staged by EUS-FNA. Consecutive patients with (suspected) NSCLC who were medically fit to undergo surgical resection of the lung tumor were discussed at the weekly Lung Oncology Board meeting of the Leiden University Medical Center. All patients had previously undergone a contrast enhanced chest computed tomography (CT) scan and fiberbronchoscopy. CT reports were examined to establish the location of the lung tumor and presence of enlarged (>10mm on the short axis) mediastinal lymph nodes. PET scans were not part of the standard staging protocol and did not influence the inclusion of patients.

EUS-FNA was used as the first mediastinal tissue staging procedure and was performed regardless of mediastinal nodal size at chest CT. Patients without locoregional nodal metastases (N2/N3) after EUS-FNA either underwent subsequent surgical staging by mediastinoscopy or direct thoracotomy with lymph node dissection. The choice of which subsequent procedure was to be performed was based on a consensus decision of the Lung Oncology Board. Negative EUS-FNA findings were compared to surgical-pathological staging. All complications which occurred during EUS-FNA and subsequent surgical procedures were recorded.

Procedures: EUS-FNA

The EUS-FNA examinations were performed in an ambulatory setting at the Department of Pulmonary Medicine, Leiden University Medical Center. A Pentax FG 34 UX echoendoscope (Pentax GmbH, Hamburg, Germany) was used with a longitudinal convex ultrasound transducer and an adjustable ultrasonic frequency of 5, 7.5 or 10MHz in combination with a Hitachi EUB 6500 ultrasound scanner (Hitachi Medical Systems Ltd., Reeuwijk, the Netherlands). Patients were under conscious sedation of midazolam intravenously. All mediastinal lymph node stations within diagnostic reach of EUS-FNA (stations 2L, 4L, (5), and 7–9) were evaluated in a standardized fashion. All visible lymph node stations were checked for certain features such as size, shape, sharp demarcated borders and echotexture. The decision on which mediastinal lymph nodes were to be aspirated, was made by the endoscopist based on this information. Enlarged, hypoechoic nodes with a round shape and well-demarcated borders were always aspirated while very small elongated flat nodes with an isoechoic texture and vague borders were mostly not. A mean number of 2.2 (range 0–6) different mediastinal lymph node stations were sampled. Aspiration of mediastinal lymph nodes was performed under ultrasound guidance from the esophagus with a 22-gauge needle and vacuum (Hancke/Vilmann type, GIP/Medi-Globe Inc., Tempe, Ariz). On-site staining and examination was done to determine whether representative material was obtained. Afterwards, all lymph node aspirates were judged by an experienced cytopathologist. Patients were observed for 2 h after the procedure and were instructed to contact the hospital if chest or other discomfort occurred.

Procedures: Surgery

Mediastinoscopy was performed according to current guidelines stating that at least both the lower paratracheal (4L and 4R) and the subcarinal (7) lymph node stations are to be biopsied. All mediastinoscopies (n = 40) were successful in targeting these lymph node stations and were therefore considered to be adequate. A mean number of 4.2 (range 3–6) different mediastinal lymph node stations were sampled at mediastinoscopy. Resected mediastinal lymph node tissue was examined according to standard procedures (in lymph nodes <1 cm, sliced once in the midline; in lymph nodes >1 cm, lamination of the lymph node and staining with hematoxylin-eosin).

When thoracotomy was performed, the primary tumor was resected by lobectomy or pneumectomy. A complete and systematic dissection of regional lymph node stations was performed according to the current guidelines[3]. A mean number of 5.9 (range 2–10) lymph node stations were sampled at thoracotomy.

Outcome measures

The main outcome measures were EUS-FNA test results such as sensitivity (the ability to detect mediastinal metastases), negative predictive value (the proportion of patients that do not have mediastinal metastases among all negative tested patients) and diagnostic accuracy (the total of correctly classified cases by EUS-FNA as a proportion of the whole cohort). They were also determined for specified subgroups such as (a) patients with metastases in lymph nodes within reach of EUS-FNA, (b) patients who underwent EUS-FNA and mediastinoscopy combined, and (c) patients who underwent EUS-FNA as the only mediastinal staging procedure. Furthermore, all patients were categorized according to tumor location and their lobe-specific diagnostic values were calculated accordingly. Finally, the number of surgical procedures prevented by EUS-FNA was determined. Surgery was defined as prevented in all cases in which EUS-FNA demonstrated the locoregional metastasis of lung cancer or in which EUS-FNA yielded a diagnosis other than lung cancer. All statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 152 patients were included in this study. There were 101 males and 51 females with a median age of 66 years (range 38–82). Contrast enhanced CT scans of the chest showed the primary lung tumor to be located in the LUL (n = 44), LLL (n = 30), lingula (n = 1), central left lung (n = 6), RUL (n = 31), ML (n = 8), RLL (n = 28) and central right lung (n = 3). There was 1 patient with a double tumor on CT. 103 of 152 patients were shown to have nodal enlargement (short axis >10mm) on CT. Based on CT, 32% of patients were

staged as I/II and 68% as stage III. Final diagnoses and stage of all patients are presented in **Table 1**. 140 patients were diagnosed with NSCLC; 50 patients had a squamous cell carcinoma, 51 patients had an adenocarcinoma, 31 patients had an undifferentiated NSCLC, 4 patients had a neuroendocrine carcinoma and 4 patients had adenosquamous, metaplastic, sarcomatoid and mixed carcinoma, respectively.

Table 1. Overview of final diagnoses and tumor stage of the 152 patients with (suspected) NSCLC who underwent EUS-FNA as the initial mediastinal tissue staging procedure.

Final diagnoses (n=152)	
NSCLC	140
Stage I/II	40
Stage IIIA	50
Stage IIIB	41
Stage IV	9
SCLC	5
Carcinoid tumor	1
Metastasized extrathoracal cancer	2
Lymphoreticular malignancy	1
Sarcoidosis	1
Chondroid hamartoma	1
Infectious	1

EUS-FNA outcomes

It was feasible to perform a standardized examination in all 152 patients who were scheduled for EUS-FNA. In 56 patients (37%) EUS-FNA provided tissue proof of locally advanced stage III or stage IV NSCLC. Mediastinal lymph node metastases (N2/N3) were found in 51 patients (34%). Distant metastases (M1), localized either in the left adrenal gland (n = 2), the contralateral lung (n = 2) or celiac lymph nodes (n = 1), were proven by EUS-FNA in 5 patients (3%). In 7 patients (5%) with suspected NSCLC, EUS-FNA revealed a diagnosis other than NSCLC. In 4 patients the lymph node aspirate indicated the presence of small cell lung cancer. In 1 patient a metastasis of a carcinoid tumor was found in the mediastinal lymph nodes. Two patients were diagnosed with metastasized renal cell carcinoma and sarcoidosis, respectively.

Surgical-pathological staging

No mediastinal metastases (N0) nor distant metastases (M0) were found at EUS-FNA in 89 patients (59%). In 40 patients mediastinoscopy was subsequently performed as a second mediastinal staging method (**Fig. 1**). In 27 of these 40 patients the tumor location was right-sided: RUL (n = 12), ML (n = 3), RLL (n = 11) and central right lung (n = 1).

13 patients had a left-sided tumor: LUL (n = 7), LLL (n = 4), lingula (n = 1) and central left lung (n = 1). CT showed nodal enlargement in 26 of 40 patients (65%).

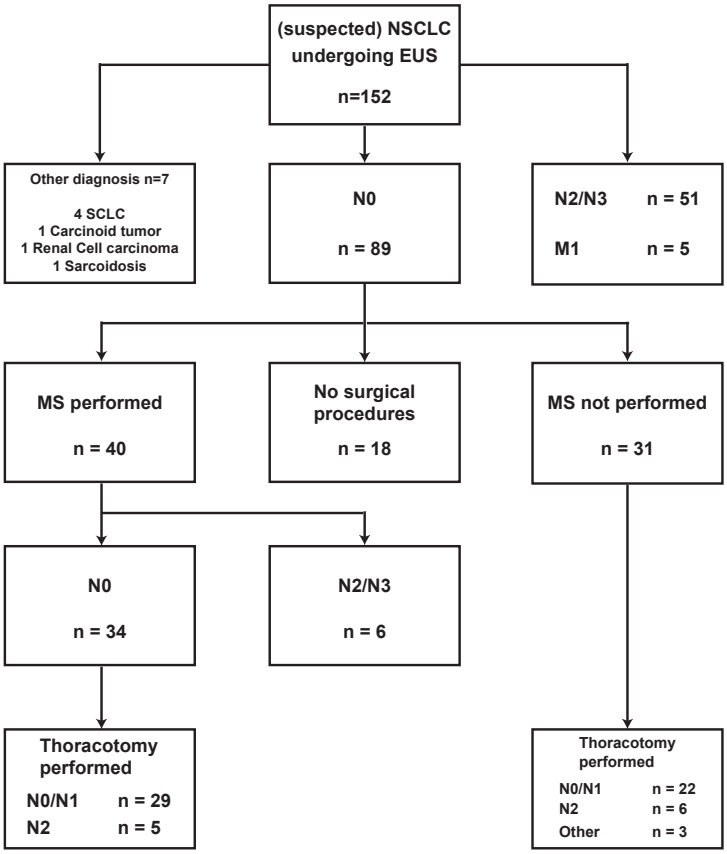

Figure 1. Flow chart of 152 consecutive patients with (suspected) NSCLC who underwent EUS-FNA in the preoperative mediastinal staging
Abbreviations: MS Mediastinoscopy

In 6 out of 40 patients (15%) with prior negative EUS-FNA, mediastinoscopy detected mediastinal metastases (N2/N3). These were located in lymph node stations 4L (n = 1), 4R (n = 2) and 7 (n = 3). The remaining 34 patients, in whom both EUS-FNA and mediastinoscopy did not detect nodal metastases, underwent thoracotomy with lymph node dissection. In 29 patients the absence of mediastinal metastases was confirmed. However, in 5 patients mediastinal metastases were found that were neither detected by EUS-FNA nor by mediastinoscopy. These metastases were located in lymph node stations 8 (n=1), 7 (n = 3) and 5/6 (n = 1).

31 patients who were staged N0 by EUS-FNA underwent thoracotomy with lymph node dissection without additional surgical staging (**Fig. 1**). 5 of these 31 patients had a right-sided tumor: RUL (n = 4) and RLL (n = 1). 26 patients had a left-sided tumor: LUL (n = 18), LLL (n = 7) and central left lung (n = 1). CT showed nodal enlargement in 12 of 31 patients (39%).

In 22 of the above 31 patients, the absence of mediastinal metastases was confirmed. However, in 6 patients mediastinal metastases were detected by thoracotomy. These were located in lymph node station 9 (n=3), 5 (n=1) and 7(n = 1). In 1 patient tumor cells were found in multiple lymph node stations (2L, 5, 6, and 8). In 3 patients histological examination of resected lung tissue revealed a diagnosis other than NSCLC. They had a pulmonary chondroid hamartoma, a cryptococcal infection and a metastasis of a resected sigmoid carcinoma, respectively.

No surgical verification of EUS-FNA findings

18 patients staged N0 by EUS-FNA did not undergo surgical procedures (**Fig. 1**). In 2 patients, surgery was not performed because endobronchial ultrasound revealed mediastinal metastases. One patient was staged N2 after detection of tumor cells in lymph node stations 5 and 7; the other was diagnosed with small cell lung cancer. In 8 patients, EUS-FNA ultrasound images were highly suspicious for invasion of the primary lung tumor in either the mediastinum or centrally located vessels (T4). These patients were staged IIIb and were not considered to be candidates for surgical treatment. Five patients were not considered for further surgical procedures due to the strong suspicion of T4 or M1 disease after additional non-invasive staging methods (MRI, PET). In 1 patient with suspected lung cancer a lymphoreticular malignancy was diagnosed after several diagnostic procedures. Two patients died shortly after the EUS-FNA procedure due to a deterioration of their clinical condition. There was no relation between the deterioration and the EUS-FNA procedure.

False negative EUS-FNA results

In this cohort, there were 89 patients in whom EUS-FNA found no mediastinal metastases. For 71 patients there was a surgical-pathological reference standard available. In 19 patients, EUS-FNA findings turned out to be false negative. Mediastinal metastases were detected by endobronchial ultrasound (n = 2), mediastinoscopy (n = 6) or thoracotomy (n = 11). Of these 19 patients, 13 patients had a left-sided tumor and 6 had a right-sided tumor. An overview of EUS-FNA false negative findings can be found in **Table 2**.

In 5 of 19 EUS-FNA false negative findings, nodal metastases were found in lymph node stations that are not within reach of EUS-FNA. Lymph node station 4R can often not be visualized due to intervening air in the trachea. Furthermore, lymph node stations

Table 2. Overview of false negative EUS-FNA findings.

Tumor localization	MS performed	Nodal metastasis detected by	Malignant lymph node	EUS-FNA type of error
LUL	Yes	Thor	7	Detection error
LUL	No	Thor	2L, 5,6, 8	Sampling error
LUL	Yes	Thor	5,6	Not within reach
LUL	Yes	Thor	7	Sampling error
LUL	No	Thor	5	Not within reach
LUL	Yes	MS	4L	Detection error
LUL	Yes	MS	7	Detection error
LUL	Yes	MS	4R	Not within reach
LLL	No	Thor	9	Detection error
LLL	No	Thor	7	Sampling error
LLL	No	Thor	9	Detection error
LLL	No	Thor	9	Interpretation error
LLL	Yes	EBUS	5,7	Sampling error
RUL	Yes	MS	7	Detection error
RUL	Yes	Thor	7,8	Detection error
RUL	Yes	MS	4R	Not within reach
RUL	No	EBUS	4R	Not within reach
RLL	Yes	Thor	7,8	Sampling error
RLL	Yes	MS	7	Sampling error

Types of error:

- Not within reach: the false negative finding is located in a lymph node station (4R,5 and 6) not within the diagnostic reach of EUS-FNA
- Detection error: the false negative finding is located in a lymph node station within reach of EUS-FNA, but has nevertheless not been detected by EUS-FNA.
- Sampling error: the false negative lymph node station has been detected by EUS-FNA. However, it was either not targeted because it was considered to be not suspect, or it was targeted but the aspirated lymph node failed to demonstrate tumor metastasis.
- Interpretation error: the false negative lymph node station was echographically suspect and located adjacent to the primary tumor. The aspirate demonstrated tumor cells but failed to show any lymphocytes, which made it unclear whether a mediastinal lymph node or the primary tumor was targeted.

Abbreviations: LUL left upper lobe, LLL left lower lobe, RUL right upper lobe, RLL right lower lobe

5 (aorto-pulmonary window) and 6 (para-aortal) are, even when visualized, difficult to target due to the intervening pulmonary artery (station 5) and aorta (station 6).

In 7 patients, EUS-FNA false negative findings were located in mediastinal lymph nodes that were principally within reach but had not been detected by EUS-FNA. Therefore, these false negative test results are considered to be detection errors.

In 6 patients the malignant lymph node was detected by EUS-FNA, but malignancy could not be confirmed. In 2 patients the malignant lymph node was not biopsied because it was echographically considered not to be suspected. In 4 patients the

malignant lymph node was targeted, but the aspirate demonstrated only lymphocytes without tumor metastasis. These 6 EUS-FNA false negative findings are considered to be sampling errors.

In 1 patient the malignant mediastinal lymph node was located adjacent to the primary tumor. Despite echographic visualization and cytological tumor diagnosis, it was unclear if the biopsied structure was a lymph node or the primary tumor. To avoid the possibility of a EUS-FNA false positive finding, this patient underwent subsequent thoracotomy despite doubts about possible presence of malignant mediastinal lymph nodes. This EUS-FNA false negative finding is considered an interpretation error.

Diagnostic values

The prevalence of mediastinal metastases in this cohort of 152 patients was 49%. EUS-FNA test results for the assessment of mediastinal lymph nodes were determined in a subgroup (n = 125) which is formed by NSCLC patients staged N2/N3 by EUS-FNA (n = 51), by suspected NSCLC patients who were diagnosed with SCLC (n = 4), by NSCLC patients staged N0 by EUS who underwent endobronchial ultrasound (n = 2) and by NSCLC patients staged N0 by EUS who underwent surgical procedures (n = 68). These test results are presented in **Table 3**. EUS-FNA had a sensitivity, NPV and diagnostic accuracy of 74%, 73% and 85%, respectively in the detection of all mediastinal lymph node metastases. These values do not take into account the fact that certain lymph node stations cannot be detected (station 4R) or safely biopsied (stations 5 and 6) by EUS-FNA. Therefore we also determined these EUS-FNA test results for the subgroup of patients (n = 120) with mediastinal metastases in lymph node stations located within reach of EUS-FNA. These were 80%, 78% and 88%, respectively. These test results were also determined for the subgroup of patients (n = 87) with nodal enlargement on CT. They were 83%, 74% and 89%, respectively.

Table 3. EUS-FNA diagnostic values for the detection of malignant mediastinal lymph nodes in patients with lung cancer. Sensitivity, NPV and accuracy of EUS-FNA are determined for the following subgroups:

	Sensitivity (%)	NPV (%)	Accuracy (%)
EUS-FNA overall (n=125)	74	73	85
EUS-FNA with nodal enlargement on CT (n=87)	83	74	89
EUS-FNA without nodal enlargement on CT (n=38)	40	71	76
EUS-FNA within reach (n=120)	80	78	88

- EUS-FNA overall: all mediastinal lymph nodes
- EUS-FNA with nodal enlargement on CT (short axis of > 10 mm)
- EUS-FNA without nodal enlargement on CT (short axis of < 10 mm)
- EUS-FNA within reach: for those mediastinal lymph nodes that are within the diagnostic reach of EUS (lymph node stations 2L, 4L, 7,8,9)

In the subgroup of patients (n = 40) who underwent EUS-FNA and mediastinoscopy combined, sensitivity, NPV and diagnostic accuracy were 92%, 85% and 95%, respectively. In the subgroup of patients (n = 31) in which EUS-FNA was the only staging method performed prior to thoracotomy, EUS-FNA had a sensitivity, NPV and diagnostic accuracy of 89%, 79% and 92%, respectively.

Several subgroups were identified in this cohort based on tumor location and nodal enlargement on CT. Sensitivity, NPV and diagnostic accuracy were calculated for all subgroups. These diagnostics values are shown, together with the prevalence of metastases and number of false negatives in the respective subgroups, in **Supplementary Table 1**.

Complications

152 patients were staged by EUS-FNA. Only two minor complications occurred. In 1 patient, the procedure was prematurely stopped due to a tachycardia of 150 beats per minute and restlessness. In the other patient, a small blood extravasate appeared surrounding the aspirated lymph node after EUS-FNA. However, the patient did not report any complaints and hospital admission was not required.

A total of 40 mediastinoscopies were performed. One procedure was complicated by right pulmonary artery hemorrhage requiring conversion to thoracotomy. The patient died later due to septic shock caused by double sided pneumonia. Another patient required sternotomy to treat an azygos vein hemorrhage.

A total of 65 thoracotomies were performed. Two patients died within 30 days of surgery. One patient died due to cardiac failure following completion pneumonectomy for extensive mediastinal and thoracic wall invasion. Autopsy showed dilating cardiomyopathy. Another patient died 6 weeks after bilobectomy due to bronchopleural fistula and empyema.

There were 3 cases of bronchopleural fistula (including the patient mentioned above), 2 following bronchial sleeve resection. One patient had paraplegia after lobectomy with extensive chest wall resection.

DISCUSSION

In this cohort of 152 consecutive operable patients with (suspected) NSCLC who were unselected by PET or CT, EUS-FNA had a sensitivity, NPV and accuracy of 74%, 73% and 85% for detecting malignant mediastinal lymph nodes. For the subgroup of 40 patients who were staged by both EUS-FNA and mediastinoscopy, these test results were 92%, 85% and 95%. Based on EUS-FNA findings, surgical staging procedures were prevented in 60 of 152 patients (39%) with lung cancer due to tissue proof of locally advanced disease (N2/N3 (n = 51), M1 (n = 5) or small cell lung cancer (n = 4)). Finally, the present

study demonstrated that it was feasible and safe to perform a standardized EUS-FNA examination routinely as the initial mediastinal tissue staging procedure in patients with NSCLC.

In a recent meta-analysis, a pooled EUS-FNA sensitivity and NPV of 83% and 78% was found[7]. In the present study, several factors accounted for the slightly lower test results. Firstly, the prevalence of mediastinal metastases in our study (49%) was relatively low compared to studies included in the meta-analysis (33%–85%)[7]. NPV is known to improve when the prevalence of mediastinal metastases in a given cohort is high. Secondly, sensitivity and NPV increase when NSCLC patients with nodal enlargement on CT are enrolled. In our unselected cohort of (suspected) lung cancer patients the proportion of patients with nodal enlargement on CT (68%) is also relatively low. EUS-FNA has been shown to have a low sensitivity (29–61%) for NSCLC patients without nodal enlargement on CT [10,11]. When sensitivity, NPV and accuracy are calculated for the subset of patients with nodal enlargement on CT (n = 82), these values improve to 83%, 74% and 89%, respectively. Thirdly, the overall EUS-FNA test results do not take into account the limited diagnostic reach of EUS-FNA. Lymph node stations 4R (due to intervening air) as well as 5 and 6 (due to intervening vascular structures) are notoriously difficult to visualize and target. When sensitivity, NPV and accuracy are determined for lymph node stations within reach of EUS-FNA, these test results improve to 80%, 78% and 88%, respectively.

For the subgroup of patients in which EUS-FNA and mediastinoscopy were combined, sensitivity, NPV and accuracy were 92%, 85% and 95%, respectively. Additional surgical staging in patients staged N0 at EUS-FNA reduces the false negative rate by half. The data from this retrospective study confirm our previous report in which we found that EUS-FNA added to mediastinoscopy improves the preoperative mediastinal staging of patients with NSCLC [4].

In a recent study, a high EUS-FNA sensitivity was found for left-sided tumors [12]. Left-sided tumors predominantly metastasize to lymph node stations 4L and 7 that can accurately be assessed by EUS-FNA. It could be argued that patients with left-sided tumors without nodal enlargement on CT could be staged accurately by EUS-FNA without the need for subsequent surgical staging. However, EUS-FNA sensitivity, NPV and accuracy for left-sided tumors in this cohort were only 65%, 68% and 80%, respectively (**Supplementary Table 1**). We could not identify a subgroup of patients, defined by tumor localization or nodal enlargement, for which EUS-FNA as the only mediastinal staging method could suffice.

EUS-FNA prevented additional surgical staging in 60 of 152 unselected patients (39%). This high proportion is in concordance with other studies in which patients were included who were selected by CT or PET [4,9,12]. Our retrospective study thus confirms that

EUS-FNA, as a minimally invasive alternative to surgical staging, reduces the need for surgical procedures.

In our study, only two minor complications occurred during EUS-FNA which did not require hospital admission or treatment. EUS-FNA has already established itself as a safe and minimally invasive modality for the staging of lung cancer [4,6,9,12]. One patient died after mediastinoscopy, suggesting a high mortality rate for mediastinoscopy. Including this patient however, the mortality rate after a mediastinoscopy in our hospital is 0.5% (3 deaths out of 590 mediastinoscopies) over the last 15 years, which is a lower mortality rate than reported in literature [6]. Morbidity rate for mediastinoscopy in our study (2.5%) as well as morbidity and mortality rate for thoracotomy correspond to rates reported in other studies [6,13].

This study has several limitations. Firstly, this is a retrospective analysis with all its inherent drawbacks. A lung cancer staging strategy was investigated which reflects actual clinical practice. The staging protocol that was in effect in the 3.5-year study period did not contain fixed rules indicating when patients staged N0 by EUS-FNA had to undergo additional surgical staging or when to proceed directly to thoracotomy with lymph node dissection. In a multidisciplinary meeting by the Lung Oncology Board the clinical condition and all preoperative staging methods for each patient were discussed and a consensus decision was made. Secondly, PET scans were not part of the standard staging protocol and did not influence the inclusion of patients. Finally, 18 patients who were staged N0 at EUS-FNA, did not undergo surgical procedures. These EUS-FNA results, indicating absence of mediastinal metastases, could not be verified by a surgical reference standard.

In conclusion, routine performance of EUS-FNA detects advanced disease in nearly half of patients with (suspected) NSCLC and therefore qualifies as a minimally invasive alternative for surgical staging. In patients without nodal metastases at EUS, additional surgical staging is indicated regardless of the location of the primary tumor or mediastinal nodal size.

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Supplementary Table 1. Subgroup analysis of EUS-FNA based on tumor location and nodal enlargement on CT. Sensitivity, NPV and diagnostic accuracy are shown, together with the prevalence of metastases and number of false negative.

Tumor localization	EUS-FNA Sensitivity (%)	EUS-FNA NPV (%)	EUS-FNA Accuracy (%)	Prevalence of metastases (%)	False negatives
Left sided (n=67)	68	68	81	40/67 (60%)	n=13
Left sided with nodal enlargement (n=41)	79	67	85	29/41 (71%)	n=6
Left sided without nodal enlargement (n=26)	37	68	73	11/26 (42%)	n=7
Right sided (n=58)	81	82	90	31/58 (53%)	n=6
Right sided with nodal enlargement (n=44)	85	81	91	27/44 (61%)	n=4
Right sided without nodal enlargement (n=14)	50	83	86	4/14 (29%)	n=2
LUL (n=40)	65	68	80	23/40 (58%)	n=8
LUL with nodal enlargement (n=25)	74	55	80	19/25 (76%)	n=5
LUL without nodal enlargement (n=15)	25	79	80	4/15 (27%)	n=3
LLL (n=23)	69	58	78	16/23 (70%)	n=5
LLL with nodal enlargement (n=12)	89	75	92	9/12 (75%)	n=1
LLL without nodal enlargement (n=11)	43	50	64	7/11 (64%)	n=4
RUL (n=26)	69	76	85	13/26 (50%)	n=4
RUL with nodal enlargement (n=17)	78	80	88	9/17 (53%)	n=2
RUL without nodal enlargement (n=9)	50	71	78	4/9 (44%)	n=2
RLL (n=24)	86	83	92	14/24 (58%)	n=2
RLL with nodal enlargement (n=19)	86	71	89	14/19 (74%)	n=2
RLL without nodal enlargement (n=5)	-	100	100	0/5 (0%)	n=0

Abbreviations: LUL left upper lobe, LLL left lower lobe, RUL right upper lobe, RLL right lower lobe