Towards a minimally invasive staging strategy in NSCLC: analysis of PET positive mediastinal lesions by EUS-FNA

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KEYWORDS
Endoscopic ultrasound guided fine needle aspiration; Non-small cell lung cancer; Mediastinal lymph nodes; Positron emission tomography; Staging

Summary
Study objective: To assess the value of endoscopic ultrasound guided fine needle aspiration (EUS-FNA) in the nodal staging of patients with (suspected) non-small cell lung cancer (NSCLC) and a 18FDG positron emission tomography (PET) scan suspect for N2/N3 mediastinal lymph node (MLN) metastases.

Background: Due to the imperfect specificity of positron emission tomography, PET positive MLN should be biopsied in order to confirm or rule out metastasis. Currently, invasive surgical diagnostic techniques such as mediastinoscopy/tomography are standard procedures to obtain MLN tissue. The minimally invasive technique of EUS-FNA has a high diagnostic accuracy (90–94%) for the analysis of MLN in patients with enlarged MLN on computed tomography of the chest (CT).

Design and patients: Thirty-six patients with proven (n = 26) or suspected (n = 10) non-small cell lung cancer and a PET scan suspect for N2/N3 lymph node metastases underwent EUS-FNA. When EUS-FNA did not confirm metastasis and the PET lesion was within reach of mediastinoscopy, a mediastinoscopy was performed. EUS-FNA negative patients with PET lesions beyond the reach of mediastinoscopy or those with a negative mediastinoscopy were referred for surgical resection of the tumour and MLN sampling or dissection.

Results: EUS-FNA confirmed N2/N3 disease in 25 of the 36 patients (69%) and was highly suspicious in one. In the remaining 10 patients, one PET positive and one PET negative N2 metastasis was detected at thoracotomy. The PPV, NPV, sensitivity, specificity and accuracy of EUS-FNA in analysing PET positive MLN were 100%, 80%, 93%, 100% and 94%, respectively. No complications

Abbreviations: EUS-FNA, endoscopic ultrasound guided fine needle aspiration; 18FDG PET, 18F-fluorodeoxyglucose positron emission tomography; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; MLN, mediastinal lymph nodes; CT, computed tomography of the chest; N0, no regional lymph node metastasis; N2, metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes; N3, metastasis to contralateral mediastinal lymph nodes

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Conclusions and significance: EUS-FNA yields minimally invasive confirmation of MLN metastases in 69% of the patients with potential mediastinal involvement at FDG PET. The combination of PET and EUS-FNA might qualify as a minimally invasive staging strategy for NSCLC.

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1. Introduction

Accurate mediastinal staging is of major importance for the prognosis and assignment of patients to optimal treatment for non-small cell lung cancer (NSCLC). A recent retrospective study showed that up to 36% of thoracotomies performed for treatment of (presumed) non-small cell lung carcinoma are futile, due to locally advanced, irresectable or benign lesions, despite preceding staging procedures [1]. This observation stresses the need to improve preoperative staging in NSCLC in order to identify those patients who will benefit from surgical resection. Recent developments in positron emission tomography (PET) and endoscopic ultrasound guided biopsies (EUS-FNA) may provide new staging opportunities for NSCLC.

Mediastinal staging by 18F-fluorodeoxyglucose (18FDG) PET is superior in both sensitivity (79—91%) and specificity (86—91%) compared to computed tomography (CT) scan of the chest (60—75%) and (61—75%), respectively [2—4]. Moreover, the addition of a PET scan to conventional staging may prevent unnecessary surgery in one out of five patients, resulting in a 51% relative reduction of futile thoracotomies as compared to conventional work up alone according to prevailing guidelines [5]. With respect to mediastinal staging, the main value of PET is its high negative predictive value [4]. However, the false positive rate ranges from 9 to 39% [2,3,6,7] so that PET positive lesions should be biopsied to preclude that patients are denied a potentially curative resection. To this end, invasive surgical procedures such as mediastinoscopy, mediastinotomy, VATS or even exploratory thoracotomies are performed.

Transesophageal endoscopic ultrasound guided fine needle aspiration has demonstrated high sensitivity (83—92%) and specificity (100%) in analysing mediastinal lymph nodes (MLN) in NSCLC [8—12]. It should be noted that these results are largely obtained in selected patients with enlarged MLN on CT. EUS-FNA is a safe and minimally invasive technique which can be performed in an outpatient setting. EUS-FNA is complementary to mediastinoscopy in its diagnostic range. EUS-FNA provides easy access to the following MLN stations: the retrotracheal station (3), the lower paraatracheal station on the left (4L), the aortopulmonary window (5), the subcarinal (7), the lower paraesophageal (8), as well as those stations in the ligamentum pulmonale (9), whereas mediastinoscopy provides good access to both the upper (2R, 2L), lower paratracheal areas (4R, 4L) and the anterior subcarinal area (7). The diagnostic reach of EUS-FNA and mediastinoscopy are largely complementary (Fig. 1). In a comparison study the combination of CT and PET was as accurate as EUS-FNA in the mediastinal staging of suspected lung cancer [12].

In this study, we assessed the feasibility and yield of EUS-FNA to demonstrate MLN metastases in patients with (suspected) NSCLC and possible N2/N3 involvement at FDG PET. If so, the combination of PET and EUS-FNA might qualify as a minimal invasive staging strategy, thereby reducing the need for invasive diagnostic surgical procedures. A staging strategy was used starting with PET, while PET is a non-invasive staging tool, has a high negative predictive value and can be helpful to detect distant metastasis [3].

2. Patients and methods

2.1. Study design

Patients with (suspected) NSCLC and a 18FDG PET scan suspect for N2 or N3 involvement were referred for further mediastinal staging by EUS-FNA. This involved patients with focally enhanced FDG uptake in N2/N3 stations as well as patients with a centrally located tumour in which adjacent MLN metastases could not be ruled out at FDG PET. In the text these patients are referred to as being PET positive. All patients were judged to be medically operable and had a potentially resectable lung tumour. All patients sent to our hospital for this indication were studied regardless of the location of the PET positive lesion(s) or CT scan results. If EUS-FNA confirmed the presence of a lymph node metastasis, patients were clinically staged as N2 or N3 (stages IIIA or IIIB) and no immediate surgical treatment was performed. When EUS-FNA did not confirm a MLN metastasis and the PET positive mediastinal lesion was within the reach of mediastinoscopy, a mediastinoscopy was performed. Biopsies were taken in a standardised way of at least the upper and lower paraatracheal (4L, 4R) and subcarinal LN (7).
Patients with a negative EUS-FNA with PET lesions beyond the reach of mediastinoscopy and those with a negative mediastinoscopy were referred for surgical resection of the tumour and MLN sampling or dissection. Only patients in which intraoperative mediastinal staging of at least the PET positive MLN station(s) is performed, are included in this study.

2.2. Patient characteristics

Thirty-six patients between October 2000 and July 2003 with either established \( n = 26 \) or suspected \( n = 10 \) NSCLC in whom mediastinal staging was suggested by the PET reader underwent EUS-FNA. Twenty-six patients had separate hot spots suspect for N2/N3 disease, eight had centrally located tumours in which adjacent N2 metastases were likely \( n = 4 \) or could not be excluded \( n = 4 \), and two patients had uptake in an N1 lymph node station but N2 lymph node metastases could not be excluded. The primary tumours were located in the left upper lobe \( n = 6 \), left lower lobe \( n = 13 \), lingula \( n = 2 \), right upper lobe \( n = 9 \), right lower lobe \( n = 5 \), middle lobe \( n = 1 \), respectively. Twenty-six of the 36 (72%) patients had enlarged MLN (>1 cm) based on CT. The majority of the study population was male \( m:f = 28:8 \), with a mean age of 63 years (42–78). The study population consisted of patients from the VU Medical Center and four community hospitals.

2.3. Procedures

2.3.1. \(^{18}\)FDG PET

PET scans were performed with a Siemens ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) at the clinical PET center of the Vrije Universiteit Medical Center, Amsterdam \( n = 34 \), and two community hospitals \( n = 2 \). Patients fasted for 6 h before the scan. Glucose levels were within normal limits. One hour after injection of 370 MBq \(^{18}\)FDG, a whole body acquisition was performed. The mid-femur-skull trajectory was imaged with emission scans for 5 min. Images were reconstructed using ordered subset expectation maximization (OSEM) with two iterations and 16 subsets following post-smoothing of the reconstructed image using a 5 mm full width half maximum Gaussian filter.

2.3.2. EUS-FNA

EUS-FNA examinations were performed at the department of Pulmonology of the Leiden University Medical Center using a Pentax FG 34 UX echo-endoscope with a longitudinal convex ultrasound transducer with an adjustable ultrasonic frequency of 5, 7.5 or 10 MHz in combination with a Hitachi EUB 6500 ultrasound scanner. EUS-FNA
was performed, after informed consent, on an outpatient basis under conscious sedation using midazolam (1–5mg i.v.). Prior to EUS-FNA, a CT scan of the chest and a written report of the PET scan were available to the investigators. As PET false negative mediastinal LN have been described, a standardised examination [13], regardless of the PET and CT results, of all MLN stations which are accessible from the esophagus (Fig. 1), was performed in each patient. After introduction, the echo-endoscope is advanced into the distal oesophagus and then slowly withdrawn while making circular movements. Anatomical landmarks such as inferior vena cava, right and left atrium, vena azygos, truncus pulmonalis and aorta are identified. Lymph nodes are described, videotaped and numbered according to the regional lymph node classification for lung cancer staging [14]. Lymph nodes (diameter >5mm) are biopsied under ultrasound guidance from the esophagus with a 22-gauge needle using suction (GIP/MEDI-Globe, type Hancke/Vilmann). If the investigators visualised MLNs at N3 as well as N2 positions in the same patient, the N3 station was biopsied first and the needle changed. From each lymph node, 1–4 needle passes per lesion were performed. The aspirated material was examined on site, by the EUS examiner, to judge the sample for its adequacy. When the investigators judged, based on the onsite cytology, that a MLN had been proven to contain metastatic disease, the procedure was stopped, and no further analysis of other PET positive lesions was performed. After the procedure all cytological specimens were examined by a cytopathologist using a Giema staining. Patients were observed for 2h after the procedure. They were instructed to phone the hospital in case of chest discomfort or complaints.

2.4. Mediastinoscopy/thoracotomy

Patients with negative EUS-FNA underwent mediastinoscopy (if the MLN was within reach of mediastinoscopy) and/or thoracotomy. At thoracotomy, sampling was performed of mediastinal lymph nodes which were classified according to the regional lymph node classification for lung cancer staging [14]. Pathological examination of resected MLN was done according to standard procedures (sliced once in the midline and stained with HE).

2.5. Data analysis

All (suspected) NSCLC patients included in this study had a PET scan suspicious for N2 and/or N3 MLN metastases, mediastinal staging by EUS-FNA and surgical staging if EUS-FNA did not assess MLN metastases. The final diagnosis was either based on the surgical-pathologic examination (pN) at thoracotomy and MLN sampling/dissection in case EUS-FNA (and in selected cases mediastinoscopy as well) did not detect MLN metastasis, or defined as a EUS-FNA biopsy with a proven MLN metastasis. A patient was considered PET positive independent of the number of PET positive N2/N3 MLN. Based on the final diagnosis, the proportion of EUS-FNA positive biopsies was calculated versus the total number of evaluated patients.

3. Results

3.1. EUS-FNA

The total number of PET positive MLN was 57. EUS guided biopsies were taken from the following forty MLN stations: 2L \(n=1\), 4L \(n=2\), 4R \(n=3\), 5 \(n=13\), 7 \(n=19\), 8L \(n=1\) and 8R \(n=1\). EUS-FNA confirmed N2/N3 metastases in 27 patients who were subsequently staged as IIIA-N2 \(n=23\), IIIB-N3 \(n=1\) or as SCLC \(n=1\) (Table 1). Example case: A 76-year old male with an adenocarcinoma of the left upper lobe (Figs. 2–5). In 26 patients one MLN station and in 7 patients two
Analysis of PET positive mediastinal lesions by EUS-FNA

Fig. 3 Transversal $^{18}$FDG PET scan demonstrating FDG uptake in a LN in the aortopulmonary window (LN) and the tumor (T).

different LN stations were biopsied. The median number of needle passes was three per patient (range 0–6). In three patients no EUS guided biopsies were performed. The EUS-FNA procedure itself took on average 20 min and no complications, such as bleeding or fever, were recorded. In one patient the EUS findings were highly suspicious for a MLN metastasis but it was not possible to perform a safe biopsy due to the interposed aorta, which was confirmed at subsequent mediastinotomy. Mediastinoscopy was performed in 2/11 PET positive but EUS-FNA negative patients with sampling of stations 4R, 4L and 7, revealing no MLN metastases.

3.2. Surgical resection

Of the remaining 10 patients, six underwent a lobectomy, one a bilobectomy and three a pneumonectomy, all with lymph node dissection or sampling. Seven patients were finally staged as pN0, one as pN1 and two as pN2 (Table 1). In the seven patients staged as pN0, reactive LN were found at histopathological examination.

3.3. Accuracy

In 25 of the 36 PET positive patients EUS-FNA revealed N2/N3 metastases (69%). EUS-FNA correctly identified 25 of the 28 patients (89%) with clinically verified N2/N3 disease, EUS was highly suspicious in one and false negative in two. In 8 of the 36 PET positive patients (22%) no N2/N3 MLN metastases were established after EUS-FNA, mediastinoscopy (two patients) and thoracotomy (Table 1). In true sense, predictive values and accuracy cannot be determined while not all LN stations were surgically

![Image](image1.png)

**Fig. 4** EUS guided FNA of the lymph node in the aortopulmonary window. LN, lymph node; AP, arteria pulmonalis; N, needle; ES, esophagus.

**Table 1** EUS-FNA results

<table>
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<th>Final diagnosis</th>
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<th>N1</th>
<th>N0</th>
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<td>—</td>
<td>—</td>
<td>1</td>
</tr>
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<td>10</td>
<td>36</td>
</tr>
</tbody>
</table>

Comparison of the MLN status as assessed by EUS-FNA in patients with (suspected) NSCLC and PET positive N2 or N3 mediastinal lesions, with the final diagnosis.

1. One patient was diagnosed with a SCLC.
2. One patient: EUS suspicious for a MLN metastasis, no safe biopsy possible.
examined in all patients and tumor positive EUS-FNA results were not surgically verified. However, as none of the LN metastases were located adjacent to the primary tumour (making a sampling error of EUS-FNA highly unlikely) we assumed that there were no false positive EUS-FNA results. Bearing these limitations in mind, the PPV, NPV, sensitivity, specificity and accuracy of EUS-FNA in analysing PET positive MLN were 100, 80, 93, 100 and 94% respectively.

4. Discussion
This study shows that the yield of a strategy of FDG PET guided EUS-FNA in terms of tumour positive MLN biopsies is considerable. The specificity of $^{18}$FDG PET for MLN staging is 89% (95% CI 83–93%) [4] as calculated from a recent meta analysis of 1045 patients. In the present study, a guideline was implemented in which we refrained from preoperative MLN staging in case of a negative FDG PET scan. This follows from the high sensitivity of PET in MLN staging for FDG avid primary tumours [4]. In our current practice of PET, ancillary findings [3] have been translated into a strategy which accounts for the limited anatomical resolution of PET. This involves an advice of invasive preoperative mediastinal staging in case of presumed hilar uptake at PET, and in case the primary tumour cannot be separated from MLN. In the present study EUS-FNA confirmed N2/N3 disease in 25 of the 36 patients (69%) with (suspected) NSCLC and a $^{18}$FDG PET scan result which was suspect for N2 or N3 metastases according to the above mentioned definitions. Of note, in 8 of 26 patients (31%) (25 patients with a LN metastasis proven by EUS-FNA and one with a highly suspicious EUS) the MLN metastases were located outside the reach of mediastinoscopy; this might be due to the fact that referring physicians were more likely to refer patients with PET positive lesions located outside reach of mediastinoscopy. In one patient the EUS findings were highly suspicious for a MLN metastasis but it was not possible to perform a safe biopsy due to the intervening aorta. In one patient EUS-FNA and mediastinoscopy, did not confirm the PET positive subcarinal LN metastasis despite biopsies of the affected station on both occasions. In another patient a subcarinal LN metastasis was assessed after lobectomy, this LN station was PET negative and not detected by EUS. In terms of patient management performing a surgical resection in such a patient with a so called "minimal N2 disease" is justifiable [15]. In seven patients (19%) no MLN metastases and in one patient (3%) a N1 MLN was established by either EUS-FNA, mediastinoscopy or thoracotomy. False positive PET scans in NSCLC in the literature are described between 9 and 13% [2,3,7], up to 39% in a recent study of 102 patients where 47 of the 122 PET positive LN stations turned out to be false positive [6]. In the latter study results are described on nodal station level. Our results underline the current opinion that tissue confirmation of PET positive mediastinal lesions is obligatory in order to secure correct staging and deny patients a potential curative surgical resection [2,3,6] Thus, in this selected population of NSCLC patients, EUS-FNA proved to be a accurate diagnostic tool in correctly classifying clinical stage based on MLN involvement in patients with a $^{18}$FDG PET scan suspect for N2 or N3 metastases.
The accuracy of EUS-FNA in the analysis of MLN in our study is 94%. It should be noted however that not all LN stations are biopsied in all patients (the PET positive LN station always was) and positive EUS-FNA results were not surgically verified. Our results are in line with other studies [8–12] for which the present paper is consistent with the safety record of MLN analysis by EUS-FNA, no complications were recorded in this study. To our knowledge, this is the first study to evaluate the yield of FDG PET instigated by EUS-FNA. Our results compare favourably with those obtained by mediastinoscopy analysing PET positive MLN. In a recent study, four cases of false negative mediastinoscopy in NSCLC patients with PET positive MLN are described [7]. Although a sensitivity of mediastinoscopy of 87% has been reported [16], in another study a sensitivity of only 49% was recorded, with half of the mediastinoscopies being false negative in majority of the cases due to unreachable nodes [17]. An advantage of EUS-FNA is its diagnostic reach in areas which are not or difficult to reach by mediastinoscopy. The retrotracheal station (3), the left paratracheal station (4L), the aortopulmonary window (station 5), the subcarinal station (nr 7), and the lymph nodes in the lower mediastinum (stations 8–9) are well within the reach of EUS-FNA (Fig. 1). A limitation of EUS-FNA is its restricted value in the upper paratracheal areas (station 2) and lower paratracheal region on the right (4R) where air from the trachea and main bronchi intervene with the ultrasound images making it sometimes difficult or impossible to visualize the lymph nodes. However, in the present study, we observed one patient with a solitary high paratracheal PET positive lymph node (station 2L) which could be easily identified and biopsied by EUS-FNA. In addition, the three PET positive right lower paratracheal stations (4R) could all be correctly analysed by EUS-FNA. Several other such cases are described in the literature [11,12]. Large prospective studies comparing EUS-FNA and mediastinoscopy in the staging of NSCLC are not yet available in the literature. The current small retrospective [18] and prospective [19] studies suggest that both techniques share a high diagnostic accuracy and are complementary in their diagnostic reach. For the detection of MLN metastases PET is more accurate than EUS (imaging without FNA) [4]. The combination of CT and PET has a similar accuracy as EUS-FNA as shown in one prospective study [12]. Rising costs of health care and waiting list problems focuses the attention on cost-effectiveness of different staging strategies in NSCLC. Relying on its high negative predictive value, PET may contribute to a marked decrease in surgical staging procedures [7]. Poncelet et al. concluded that staging costs would have been reduced with 23%, comparing the conventional staging including mediastinoscopy to the staging with PET combined with mediastinoscopy in PET positive cases. A decision analysis model [20] postulates that EUS-FNA was more cost effective compared to mediastinoscopy in mediastinal staging. Therefore, in a setting which involves FDG PET as routine procedure prior to mediastinal staging [5] we hypothesize that application of EUS-FNA instead of mediastinoscopy staging, at least in cases with lymph nodes outside the realm of the latter, will be cost-effective, as EUS-FNA is performed ambulant and does not require clinical admission nor time in the operating theatre as required by mediastinoscopy.

Furthermore, the number a futile thoracotomies due to inaccurate staging of NSCLC patients should be reduced. We expect a dramatic change in the way NSCLC will be staged in the near future with the increasing availability of FDG PET scanning and EUS-FNA. A CT scan of the chest is still a mandatory diagnostic test in clinical NSCLC staging. Mediastinoscopy, PET and EUS-FNA each have their specific advantages and limitations and are partly complementary to another in their diagnostic reach. Further studies should concentrate on different staging strategies with diagnostic accuracy, reduction of futile thoracotomies, patient preference and cost effectiveness as outcomes. A staging strategy that combines 18FDG PET with EUS-FNA as reported here may well qualify as an accurate and minimally invasive way to correctly stage NSCLC and at the same time reduce the need for invasive diagnostic procedures and reduce the number of futile thoracotomies which are still performed today.

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