Mediastinal restaging: EUS-FNA offers a new perspective

Jouke T. Annema a,*, Maud Veselićb, Michel I.M. Versteeghc, Luuk N.A. Willemsa, Klaus F. Rabe a

a Department of Pulmonology C3 P, Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden University Medical Center, Leiden, The Netherlands
b Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands
c Department of Cardio-thoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands

Received 28 March 2003; received in revised form 16 June 2003; accepted 17 June 2003

SUMMARY

Study objective: We hypothesized that transoesophageal endoscopic ultrasound guided fine needle aspiration (EUS-FNA) has the potential to be a valuable and accurate new diagnostic technique for mediastinal restaging in non-small cell lung cancer (NSCLC) after induction chemotherapy. The current restaging modalities either have a low diagnostic accuracy (computed tomography (CT) scan of the thorax) or they are invasive, can be technically difficult and are therefore not commonly performed (remediastinoscopy).

Methods and patients: Nineteen consecutive patients with NSCLC and proven ipsilateral or subcarinal lymph node metastases (N2 disease) who had been treated with induction chemotherapy underwent mediastinal restaging by EUS-FNA. Patients had either a partial response (n = 14) or stable disease (n = 5) based on sequential CT scans of the thorax. Interventions: EUS-FNA was performed in an ambulatory setting with biopsy of mediastinal lymph nodes (LN). No complications occurred. When EUS-FNA restaged the mediastinum as no regional lymph node metastasis (N0), surgical resection of the tumour with lymph node sampling or dissection was performed.

Results: The positive predictive value, negative predictive value, sensitivity, specificity and diagnostic accuracy of EUS-FNA in restaging mediastinal LN were 100, 67, 75, 100 and 83%, respectively.

Conclusions and significance: EUS-FNA qualifies as an accurate, safe and minimally invasive diagnostic technique for the restaging of mediastinal lymph nodes after induction therapy in NSCLC. In the future EUS-FNA might play an important role in the mediastinal restaging in NSCLC, particularly to identify the subgroup of down staged patients who benefit most from further surgical treatment.

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1. Introduction

Mediastinal restaging in non-small cell lung cancer (NSCLC) after induction chemotherapy remains a major problem. Computed tomography (CT) of the thorax has a low accuracy of only 58% and often overestimates the degree of local tumour regression [1]. Mediastinoscopy has a diagnostic accuracy of 80 respectively, 85% as shown in two small studies (n = 24, n = 27) [1,2], however, a high number of incomplete procedures (40%) due to technical difficulties [3]. The current controversy about the effectiveness and implementation of mediastinoscopy in daily practice stimulates the search for alternative restaging methods [4].

Recent studies reported that NSCLC patients with ipsilateral lymph node metastases (IIIA-N2 disease), who were down-staged with induction chemotherapy [no regional lymph node metastasis] had a significantly prolonged survival after surgical resection compared to those with persistent N2 disease [5—7]. These studies demonstrate that patients without a pathological complete response after induction chemotherapy usually do not benefit from a surgical resection. Although an optimal treatment strategy for IIIA-N2 NSCLC with ipsilateral or subcarinal lymph node metastases is still under investigation, there is increasing evidence that multimodality treatment with induction chemotherapy significantly improves survival [8—10]. Considering the high prevalence of lung cancer and the poor overall survival of stage IIIA-N2 as a whole, it is a challenge to identify the subgroup of patients who are down-staged by induction chemotherapy to a complete pathologic response. After surgical resection these patients have a 4-year survival of 50% [7]. In addition, unnecessary surgical resection in patients with persistent N2 disease should be avoided. Restaging is important but the current available technique of mediastinoscopy is controversial.

Recently, the minimally invasive technique of transoesophageal endoscopic ultrasound guided fine needle aspiration (EUS-FNA) has become clinically available for the analysis of mediastinal lymph nodes (LN). An ultrasound transducer incorporated on top of an endoscope enables the investigator to visualize and puncture mediastinal LN under real-time ultrasound guidance. The procedure is well tolerated, safe and has a high diagnostic accuracy (89—95%) for the analysis of mediastinal LN [11—14]. So far, no complications of EUS-FNA in the analysis of mediastinal LN have been reported [11—14]. The advantages of this technique are multiple: tissue samples are obtained (in contrast to the imaging technique of CT) and the procedure itself is minimally invasive, is performed in an outpatient setting and can be repeated a number of times without technical difficulties (in contrast to mediastinoscopy).

In this preliminary study, we performed restaging of mediastinal lymph nodes with EUS-FNA in 19 patients with NSCLC and proven N2 disease (stadium IIIA) who had been treated with induction chemotherapy. Patients who were restaged by EUS-FNA to N0, underwent surgical resection of the tumour containing lobe or lung and LN sampling or dissection in order to confirm the complete pathologic response. We hypothesized that EUS-FNA has a high diagnostic accuracy in mediastinal restaging and that it is suitable and well tolerated in these patients.

2. Materials and methods

2.1. Patients

Nineteen consecutive patients with NSCLC and proven stadium IIIA-N2 disease who had been treated with induction chemotherapy were referred to the Department of Pulmonology of the LUMC for mediastinal restaging by EUS-FNA between February 2001 and March 2003. All patients were accepted regardless of the localisation of the initial lymph node metastasis. Twelve of the 19 patients had previously undergone a mediastinoscopy for staging purposes during the initial lung cancer staging. The induction chemotherapy consisted of three cycles of a cisplatin-based agent. After completion of the induction chemotherapy all patients were re-evaluated with a CT scan of the chest and upper abdomen. The patients in this study had either radiological stable disease (n = 5) or a partial response (n = 14). Conventional response definitions were used for this CT scan-based clinical response measurement [15]. A partial response was defined as a reduction of 50% or more of the product of the largest diameters from primary tumour and enlarged mediastinal lymph nodes. A reduction of less than 50% or progression less than 25% was classified as stable disease.

2.2. EUS-FNA

The EUS examination was performed with a Pentax FG 34 UX echo-endoscope with an electronic curved linear array ultrasound transducer with an adjustable ultrasonic frequency of 5, 7.5 or 10 MHz in combination with a Hitachi EUB 6000 ultrasound scanner. EUS-FNA was performed on an outpatient
basis with the patient under conscious sedation using midazolam. Previous to the investigation informed consent was obtained. All EUS-FNA inves-
tigations were performed in a standardised way in order to examine all N2/N3 lymph node stations which are accessible from the oesophagus [16]. Af-
ter the introduction, the echo-endoscope was ad-
vanced into the distal oesophagus and then slowly withdrawn while making circular movements. Anatomical landmarks such as inferior vena cava, right and left atrium, azygos vein, main pulmonary artery and aorta were identified. Lymph nodes were identified according to the International Staging System (ISS) [17]. As ultrasound features alone are not reliable to make a distinction between benign and malignant LN [18], we routinely biopsied medi-
astinal LN above 5 mm with the exception of those that were elongated or oval in shape with vague borders. Biopsies where taken under real-time ul-
trasound guidance from the oesophagus with a 22-gauge needle using suction (GIP/MEDI-Globe, type Hancke/Vilmann). The aspirated material was examined on site by the investigator whether a rep-
resentative sample was obtained, and afterwards judged by a cytopathologist. The investigator, a pulmonologist, was trained by a cytopathologist to assess the aspirates for adequacy.  

2.3. Study design

If EUS-FNA detected viable tumour tissue in medi-
astinal lymph nodes, patients were considered as having persistent N2 disease and were referred for palliative radiotherapy. Those patients restaged by EUS-FNA as N0, underwent thoracotomy with attempted curative resection with unilateral medi-
astinal sampling or dissection of the lymph node stations. All technically accessible mediastinal lymph nodes, for left sided lung tumours lymph node stations 2L, 4L, 5–9 and for right sides lesions 2R, 4R, 7–9 were sampled or resected and classified according to the regional lymph node classification for lung cancer staging [17]. In those patients restaged by EUS-FNA as N0, the material obtained by thoracotomy provided the final diagnosis. The ethical committee of the Leiden University Medical Center approved this study.  

3. Results

3.1. Patients

Nineteen patients (6 female, 13 male), mean age 58 years (range 34–73) were included in the study. The primary tumours were predominantly located in the right lung; RUL (n = 7), RLL (n = 5), LUL (n = 2) and LLL (n = 5). The various tumour types were: squamous cell carcinoma (n = 9), adenocarcinoma (n = 7), large cell carcinoma (n = 2) and adenoacanthoma (n = 1). The initial IIIA-N2 disease was established by mediastinoscopy (n = 8), EUS-FNA (n = 9), by both diagnostic tech-
niques (n = 1) or during explorative thoracotomy (n = 1). After induction chemotherapy, patients had either radiological stable disease (n = 5) or a partial response (n = 14) as defined by sequential CT scans of the thorax (Fig. 1). Eleven of the 19 patients had CT-stage N2/N3 as defined by a en-
larged mediastinal lymph nodes (short axis >1 cm) the remaining eight had normal sized LN. Of the 14 patients with a partial response as defined by CT, six had CT-stage N0.  

3.2. EUS-FNA

All nineteen patients underwent EUS, in two pa-
tients no biopsies were taken, in eight a single LN station and in nine patients two different LN stations were biopsied. Hyperechoic "white dots" were observed in the lymph nodes of 7 of the 19 patients. Three of the 10 patients in whom both the initial staging as well as the restaging was per-
fomed by EUS developed the "white dot" pattern after chemotherapy (Fig. 2). From each lymph node biopsies were taken under ultrasound guidance. Per lesion, 1–3 needle passes were performed with an average number of 4 needle passes per proce-
dure (range 0–6). The procedure lasted on average 20 min and no complications, such as bleeding or fever, occurred. In eight patients EUS-FNA proved persistent N2 disease, in one patient (10) a highly suspected right paratracheal lymph node was seen but it was technically not possible to biopsy it safely due to an aberrant position of the pulmonary artery. Based on the EUS findings a right parastra-
chnal mediastinotomy was performed by which mali-
gnancy was proven. These nine patients were classified as having persistent N2 disease and were referred for palliative radiotherapy. The 10 pa-
tients who were restaged by EUS-FNA as N0, were scheduled for surgical resection of the lung tumour and mediastinal lymph node sampling/dissection in order to verify the EUS-FNA results.  

3.3. Surgical resection

The scheduled lobectomy for patient 1 was can-
celled because a skin metastasis was discovered just before the operation and this patient was not in-
cluded in the analysis.
Fig. 1  Chest CT scan before (A) and after induction chemotherapy (B) (patient 7). T, tumour; LN, lymph node; partial response as defined by CT scan of the chest. Restaging by EUS-FNA: persistent tumor metastasis.

Fig. 2  Image of an endoscopic ultrasound guided biopsy of a subcarinal lymph node. Note the white dots, a feature observed in several LN after chemotherapy. OE, oesophagus; LN, lymph node; N, needle; LA, left atrium.

Of the remaining nine patients whom EUS-FNA restaged as N0, seven underwent lobectomy and two a pneumectomy with resection of the lung tumour and extensive mediastinal lymph node sampling (Table 1). Six of the initially 18 patients (33%) were histological down staged to pN0 after induction chemotherapy. In three patients residual tumour metastasis was found in the mediastinum. In patient 2, two small (<1 cm) LN’s at position 4L were removed during thoracotomy one with and one without tumour. In patient 9, a 1 cm sized paraoesophageal LN with tumour breaking trough the capsula was assessed. In patient 16, a small (<1 cm) right paratracheal LN contained tumour, in addition there were two small subcarinal LN’s both necrotic, one containing small islands of tumour cells.

3.4. Analysis

On ethical grounds, patients in whom EUS-FNA established persistent LN metastasis where not subjected to undergo an explorative thoracotomy to verify the positive EUS-FNA results. In all eight patients the aspirates clearly demonstrated LN metastases and in none of the cases the aspirated LN was adjacent to the primary tumour making a biopsy from the tumour instead of the LN highly
Table 1 Patient characteristics and results

<table>
<thead>
<tr>
<th>Nr/sex/age</th>
<th>Lobe/PA</th>
<th>pn2/tool</th>
<th>CTnr</th>
<th>EUS</th>
<th>Treatment</th>
<th>tPA/st</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/62</td>
<td>RUL/ad</td>
<td>2R/MS</td>
<td>PR</td>
<td>−/4L</td>
<td>None</td>
<td>m1 (skin)</td>
</tr>
<tr>
<td>2/F/61</td>
<td>LLL/sq</td>
<td>4L/EUS</td>
<td>SD</td>
<td>−/2, 4L</td>
<td>Pneumectomy</td>
<td>+/4L</td>
</tr>
<tr>
<td>3/M/61</td>
<td>RUL/ad</td>
<td>7/MS</td>
<td>SD</td>
<td>+/7</td>
<td>RT</td>
<td>−/4L</td>
</tr>
<tr>
<td>4/F/63</td>
<td>LLL/sq</td>
<td>4L/MS</td>
<td>PR</td>
<td>−/4L, 7</td>
<td>Lobectomy</td>
<td>−/7</td>
</tr>
<tr>
<td>5/M/65</td>
<td>LLL/sq</td>
<td>7/MS</td>
<td>PR</td>
<td>−/5, 7</td>
<td>Lobectomy</td>
<td>−/7</td>
</tr>
<tr>
<td>6/M/58</td>
<td>LUL/ns</td>
<td>4L/EUS</td>
<td>PR</td>
<td>−/4L, 7</td>
<td>Mediastinoscopy</td>
<td>−/4L, R, 7</td>
</tr>
<tr>
<td>7/M/73</td>
<td>RUL/sq</td>
<td>4R/MS</td>
<td>PR</td>
<td>+/4R, 7</td>
<td>RT</td>
<td>−/4R</td>
</tr>
<tr>
<td>8/M/70</td>
<td>RLL/sq</td>
<td>4R/EUS</td>
<td>PR</td>
<td>−/FNA−</td>
<td>Lobectomy</td>
<td>+/8L</td>
</tr>
<tr>
<td>9/M/34</td>
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<td>7/EUS</td>
<td>PR</td>
<td>−/7</td>
<td>Mediastinotomy</td>
<td>+/4R</td>
</tr>
<tr>
<td>10/M/56</td>
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<td>SD</td>
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<td>+/4R</td>
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<tr>
<td>11/F/54</td>
<td>LUL/ad</td>
<td>5, 7/EUS</td>
<td>SD</td>
<td>+/5, 7</td>
<td>RT</td>
<td>−/7</td>
</tr>
<tr>
<td>12/M/65</td>
<td>RLL/sq</td>
<td>7/EUS</td>
<td>PR</td>
<td>+/7</td>
<td>RT</td>
<td>−/7</td>
</tr>
<tr>
<td>13/M/54</td>
<td>RUL/sq</td>
<td>4R,7/MS</td>
<td>SD</td>
<td>+/7</td>
<td>Mediastinoscopy</td>
<td>2R, 4R, 4L, 7</td>
</tr>
<tr>
<td>14/F/55</td>
<td>RUL/ad</td>
<td>4R/EUS</td>
<td>PR</td>
<td>−/FNA−</td>
<td>Mediastomy</td>
<td>2R, 4R, 4L, 7</td>
</tr>
<tr>
<td>15/M/52</td>
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<td>7/MS</td>
<td>PR</td>
<td>+/7</td>
<td>Lobectomy</td>
<td>−/2R, 4L, 7</td>
</tr>
<tr>
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<td>7/Thor</td>
<td>PR</td>
<td>−/5, 7</td>
<td>Lobectomy</td>
<td>+/2R, 7</td>
</tr>
<tr>
<td>17/F/54</td>
<td>RLL/ns</td>
<td>7/EUS</td>
<td>PR</td>
<td>+/7</td>
<td>Lobectomy</td>
<td>−/4R, 7, 8</td>
</tr>
<tr>
<td>18/M/44</td>
<td>RUL/adq</td>
<td>4R/MS</td>
<td>PR</td>
<td>−/4R, 7</td>
<td>Lobectomy</td>
<td>−/4R, 7, 8</td>
</tr>
<tr>
<td>19/M/70</td>
<td>LLL/sq</td>
<td>7/EUS</td>
<td>PR</td>
<td>+/7</td>
<td>Lobectomy</td>
<td>−/4R, 7, 8</td>
</tr>
</tbody>
</table>

nr, study patient nr; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; PA, histology of the primary tumour; PN, pathology of LN station as established by thoracotomy; sq, squamous cell carcinoma; ad, adenocarcinoma; adsq, adenosquamous carcinoma; ns, undifferentiated large cell carcinoma; pn2, the tumour containing ipsilateral or subcarinal lymph node station; tool, the diagnostic technique used to prove N2 status; MS, mediastinoscopy; *, mediastinoscopy also performed but negative; CTnr, response determined by computed tomography of the chest; PR, partial response; SD, stable disease; −, no tumour in lymph node present; +, tumour in lymph node present; FNA−, no EUS guided fine needle aspiration was performed; $, EUS highly suspect for malignancy, no biopsy possible; RT, radiotherapy; st, mediastinal lymph node station according to Naruke; m1, distant metastasis.

Table 2 EUS-FNA results

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>pn2</th>
<th>pn0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>phN2</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>phN0</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

Comparison of the EUS-FNA results of mediastinal N2 restaging and the final diagnoses.

4. Discussion

We found that in patients with IIIA-N2 disease, EUS-FNA restaged the mediastinal lymph nodes after induction chemotherapy with a diagnostic accuracy of 83%. This is the first report of the concept using EUS-FNA for mediastinal restaging.

There were 3/18 false negative results (Tables 1 and 2). In patient 2 a sampling error must have been occurred as adequate material was aspirated by EUS-FNA from the lower paratracheal station. In patient 9 tumour was found during pneumectomy in a parasaophagéal structure which was not detected by EUS. In patient 16 viable tumour was detected at LN station 2R and 7. Station 2R is often beyond reach of EUS-FNA, the multiple biopsies that were taken by EUS from LN station 7 showed lymph node tissue without tumour, obviously a sampling error. A limitation of our study is the small number of study

likely. Based on this, we assumed that there where no false positive EUS-FNA results in this study. The positive predictive value, negative predictive value, sensitivity, specificity and diagnostic accuracy of EUS-FNA for mediastinal restaging post induction chemotherapy were 100, 67, 75, 100 and 83%, respectively.
patients, a fact that is also applicable for the few studies on remediastinoscopy and positron emission tomography (PET) on this subject. Both sensitivity (75%), and diagnostic accuracy (83%) of EUS-FNA are slightly lower compared to those found in the studies of EUS-FNA in non-chemotherapy pre-treated mediastinal LN (sensitivity 83–94% and diagnostic accuracy 88–94%) [11–14]. An explanation could be that 42% of the patients had normal sized LN, whereas the other studies are performed in selected patients with enlarged LN. Furthermore, the presence of necrosis and haematisation observed in several of the lymph nodes, as can be seen after chemotherapy, made the judgement of the biopsies more difficult. The specificity of EUS-FNA in our study was high (100%). EUS-FNA of mediastinal LN has limitations regarding the target area. Air in the trachea and main bronchi often obscure the visualisation of the upper paratracheal stations (2L and 2R), and it is frequently difficult to find the lower paratracheal station on the right (4R). So far EUS-FNA of upper paratracheal lesions (level 2) [19,20] and the right lower paratracheal area (level 4R) [20] only have been reported in enlarged lesions. LN stations that can be reached are the lower paratracheal left (4L), subaortic or aorto pulmonary window (5), subcarinal (7), para oesophageal (8) and those at the pulmonary ligament (9). Contra indications for EUS-FNA investigations are oesophageal strictures. A major advantage of biopsying lymph nodes from the oesophagus by EUS-FNA is the real-time controlled biopsy where the tip of the needle is visible during the complete biopsy procedure. So far it has not been possible to perform real-time endobronchial ultrasound (EBUS) guided transbronchial needle aspiration (TBNA). With the current available technique the ultrasound probe has to be removed before the actual needle aspiration [21].

The diagnostic accuracy of EUS-FNA presented in this study (63%) is comparable to that of remediastinoscopy (83–85%) [1,2]. In all but one patient (patient 10) it was possible to visualize the target LN stations and perform a biopsy when indicated. This in contrast to a study of repeat mediastinoscopy where in 40% of the cases the procedure was judged as inadequate due to fibrosis or adhesions [3]. No complications were observed during or after EUS-FNA. Bleeding complications have been described in patients who underwent a mediastinoscopy [2].

EUS-FNA has a diagnostic accuracy, which exceeds that of the CT scan of the thorax by far (85 versus 58%). Of the thirteen patients in our study with a radiological partial response, seven (54%) were down-staged to N0 whereas six (46%) still had N2 disease, demonstrating that CT is of no value identifying these two subgroups. On the contrary, all five patients with radiologically stable disease after induction chemotherapy proved to have persistent N2 disease. Our preliminary data suggest that only patients with at least a radiological partial response qualify for mediastinal restaging.

So far, the few studies which investigated the accuracy of positron emission tomography for mediastinal restaging show inferior results compared to the EUS-FNA study. In one Boston-based study of 26 NSCLC patients with stadium III who were treated with induction chemoradiotherapy, PET had a sensitivity of 58% and a specificity of 93% in restaging mediastinal LN [22]. An Australian study in which 34 NSCLC patients were restaged after induction chemotherapy, PET appropriately down-staged 10 of the 16 patients who were initially planned for palliative therapy [23]. There is also a serious limitation for the applicability of PET when the primary tumour is located near the mediastinum.

A recurrent remarkable ultrasound finding was the presence of "white dots" in several LN after induction chemotherapy (Fig. 2), a feature which was new and was not observed during the initial lung cancer staging. Possibly, these white dots could represent fibrous tissue or necrosis.

There is increasing awareness that staging and restaging is of vital importance in the optimal treatment of NSCLC. Several studies have demonstrated that the subset of patients with IIIA-N2 NSCLC which are down-staged with induction chemotherapy to N0, and are successively treated with surgical resection, are long survivors [5–7]. The 3-year survival of successfully down-staged N2 disease was 59% compared to 0% of the patients who still had persistent N2 disease 6. In another study the 4-year survival of resected patients with persistent N2 disease was 15% in contrast to 50% in those patients who were down-staged to N0 [7]. In the future we expect a shift in how NSCLC staging algorithms will be organised. EUS-FNA showed in a small prospective study the same diagnostic accuracy as mediastinoscopy [24]. Both techniques, however, are complementary in their reach of different mediastinal N2 stations.

EUS-FNA has shown to be particular useful in the analysis of lesions in the aortopulmonary window (station 5), the subcarinal area (station 7) the lower paraoesophageal LN (station 8) and those in the ligamentum pulmonale (station 9) whereas mediastinoscopy provides access to the upper and lower paratracheal areas (stations 2 and 4) and the anterior part of the subcarinal region (station 7). Studies will have to define how new less invasive staging modalities such as PET and EUS-FNA compare with
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In terms of invasiveness we hypothesize that patients will prefer a minimally invasive endoscopic procedure such as EUS-FNA above an operation such as repeat mediastinoscopy. In addition, EUS-FNA does not require hospital admission nor does it require operation facilities in contrast to repeat mediastinoscopy.

In conclusion, we have shown that transoesophageal endoscopic ultrasound guided fine needle aspiration has the potential to be a valuable tool in the restaging of mediastinal lymph nodes in NSCLC patients after induction therapy. Based on the data in this preliminary study, EUS-FNA could qualify as the diagnostic tool of choice to identify patients who might benefit from surgical treatment. We hypothesize that IIIA-N2 NSCLC patients which have a partial response on the CT scan after induction chemotherapy should be restaged with EUS-FNA. In this way the subgroup of patients who are likely to benefit most from surgical resection are identified. In addition in patients with persistent N2 disease, in which a surgical resection does not lead to an improved survival, the morbidity and mortality of a futile thoracotomy can be prevented. Ongoing and further studies have to confirm our results and should concentrate on the development of new (re)staging strategies.

Appendix A

The following definitions were used in order to calculate the diagnostic values for EUS-FNA.

Positive predictive value (PPV):
true positive EUS-FNA diagnoses/total number of positive EUS-FNA diagnoses

Negative predictive value (NPV):
true negative EUS-FNA diagnoses/total number of negative EUS-FNA diagnoses

Sensitivity:
true positive EUS-FNA diagnoses/total number of positive final diagnoses

Specificity:
true negative EUS-FNA diagnoses/total number of negative final diagnoses

Diagnostic accuracy:
true positive EUS-FNA diagnoses + true positive EUS-FNA final diagnoses/total number of final diagnoses

Positive:
contains tumour

Negative:
does not contain tumour

References


