Transesophageal Endoscopic Ultrasound with Fine Needle Aspiration in the Preoperative Staging of Malignant Pleural Mesothelioma

Kurt G. Tournoy, Sjaak A. Burgers, Jouke T. Annema, Frank Vermassen, Marleen Praet, Marianne Smits, Houke M. Klomp, Jan P. van Meerbeeck, and Paul Baas

Abstract

Purpose: Surgical resection as part of a multimodality approach in malignant pleural mesothelioma (MPM) has a high morbidity and mortality. Because mediastinal lymph node (MLN) metastases are a negative prognostic factor, preoperative staging is of paramount importance. Transesophageal endoscopic ultrasound with real-time guided fine needle aspiration (EUS-FNA) enables accurate MLN staging in lung cancer.

Experimental Design: The feasibility and yield of EUS-FNA in MLN staging were prospectively analyzed in patients with presumed early-stage MPM considered for multimodality therapy. MLN reference pathology was defined by either pathologic staging or the formal demonstration of malignant cells by either EUS-FNA or mediastinoscopy.

Results: Thirty-two consecutive patients (81% males; median age, 61 years) with proven MPM underwent EUS-FNA. In 11 (34%) patients, a negative EUS-FNA or mediastinoscopy was not confirmed by surgical MLN dissection because of clinical deterioration or disease progression. In 21 (66%) patients, a formal pathology of the MLN was obtained and staging with EUS-FNA was positive in 4 (19%). Mediastinoscopy did not result in a greater yield of MLN metastasis as compared with EUS-FNA. Thoracotomy with complete lymph node dissection was done in 17 (81%). The overall prevalence of MLN metastasis was 24%, and the sensitivity of EUS-FNA was 80% (95% confidence interval, 28-99%) with a specificity of 100% (95% confidence interval, 79-100%). One patient had esophageal perforation related to EUS-FNA.

Conclusions: EUS-FNA is feasible and sensitive for MLN staging in patients with MPM who are candidates for multimodality treatment. These data warrant further evaluation.

Malignant pleural mesothelioma (MPM) is a neoplasm arising from the serosal cells of the pleural cavity. In untreated cases, the median survival is 6 to 10 months. Neither chemotherapy nor radiotherapy nor surgery offers cure when used as a single treatment modality. Although improvements in survival have been observed with antifolate-platinum combinations (1, 2), there is keen interest for radical surgery by extrapleural pneumonectomy as a treatment modality for early-stage MPM (3). The primary reason for the poor outcome of MPM patients treated with surgery is a high recurrence rate, even when adjuvant radiotherapy and/or chemotherapy is administered (4, 5). The presence of malignant invasion in the mediastinal lymph nodes (MLN) is, among others (6), an important prognostic factor (7–9). MLN metastases are considered by most experts as an exclusion criterion for extrapleural pneumonectomy. Imaging with computed tomography (CT; ref. 10) and, more recently, with fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT (11) is inaccurate to predict MLN invasion. Invasive staging by mediastinoscopy is hence indicated before considering patients for surgical treatment (12). Schouwink et al. (10) found 11 of 43 patients to have MLN metastasis. He calculated a sensitivity of 60% and 80% for CT scan and mediastinoscopy, respectively, in detecting malignant MLN invasion in MPM patients.

Transesophageal endoscopic ultrasound with fine needle aspiration (EUS-FNA) is a minimally invasive technique that is increasingly implemented in the staging of patients with lung cancer (13, 14). In selected patients, EUS-FNA has a good sensitivity to detect malignant MLN invasion and avoids surgical staging techniques such as mediastinoscopy (15, 16).

The objective of this study was to investigate the feasibility and yield of EUS-FNA in detecting malignant MLN invasion in patients with early-stage/low-volume MPM considered for multimodality treatment including resection.

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The objective of this study was to investigate the feasibility and yield of EUS-FNA in detecting malignant MLN invasion in patients with early-stage/low-volume MPM considered for multimodality treatment including resection.
Materials and Methods

Patients considered for combined modality MPM treatment were referred for EUS-FNA to two centers: the Ghent University Hospital (Belgium) and the Netherlands Cancer Institute (the Netherlands). Patients with histologically proven MPM, WHO-performance score of 0 or 1, and a clinical tumor stage cT1N0M0 (17) or less were eligible for a treatment protocol consisting of induction chemotherapy, extrapleural pneumonectomy, and adjuvant radiotherapy. Other inclusion criteria were resectable tumor mass (judged by the surgeon and based on imaging data including CT and FDG-PET/CT), age <70 y, and fit for all aspects of the multimodality treatment including surgery. Invasive staging of the mediastinum was mandatory, regardless of the imaging findings, because malignant MLN invasion was a formal exclusion criterion for combined modality treatment.

Consecutive patients were included after informed consent. This feasibility study was approved by both local ethics committees (EC-ULG 2005-161 incl Appendix G and M04ZON/E08031 for the respective participating centers).

Imaging. Contrast-enhanced CT scans with slice thickness of 5 mm were done and analyzed according to institutional practices. MLN were considered suspect on CT scan whenever their short axis was at least 10 mm. Integrated FDG-PET/CT was also done according to institutional practices. The MLN were considered suspect on the FDG-PET scan when, by visual correlation with the CT scan, a discrete FDG uptake was done and analyzed according to institutional practices. MLN were removed. Pathologic examination of MLN was done according to the classification for lung cancer staging (20): right-to-extrapleural pneumonectomy. A systematic MLN dissection was performed on site to evaluate the cellular contents of the air-dried smears of the aspirates obtained by EUS-FNA were processed on site to evaluate the cellular contents of the air-dried specimens with a quick staining method (Diff-Quick). Whenever possible, several lymph nodes were sampled. Specimens were categorized as positive (tumor cells), negative (lymphoid but no tumor cells), or not representative (necrosis, no lymphoid cells). Punctures were continued until the cytopathologist was able to make a formal conclusion. In case no FNA was done, the result was classified as inconclusive about MLN metastasis, its result was scored indeterminate.

Transesophageal endoscopic ultrasound. EUS-FNA was done in an outpatient setting under local anesthesia (with or without moderate sedation) with the use of a curved linear scanning ultrasound endoscope (GF-UCT160-0L5, Olympus Co.) connected to the ultrasound unit (ALOKA Co. Ltd. and Biomedic B.V.; ref. 18) with monitoring of heart rate and oxygen saturation (19). The mediastinum was analyzed systematically (transducer frequency range, 5-10 MHz) with screening of paraesophageal, subcarinal, lower left paratracheal, and upper paratracheal MLN as described (19). Punctures were done of those MLN measuring at least 5 mm with a 22-gauge fine needle (EUS-needle, Olympus); the median number of MLN sampled was 1 (range, 0-2); and the subcarinal or paratracheal MLN were biopsied most frequently. Smears of the aspirates obtained by EUS-FNA were processed on site to evaluate the cellular contents of the air-dried specimens with a quick staining method (Diff-Quick). Whenever possible, several lymph nodes were sampled. Specimens were categorized as positive (tumor cells), negative (lymphoid but no tumor cells), or not representative (necrosis, no lymphoid cells). Punctures were continued until the cytopathologist was able to make a formal conclusion. In case no FNA was done, the result was classified as negative (absence of malignant MLN metastasis). In addition to the MLN, the endoscopist also filled in if the primary tumor was observed with ultrasonography and if, based on the endoscopic ultrasound images, a direct mediastinal invasion was thought to be present. Patients were observed for 2 h after the procedure. They were instructed to phone the hospital in case of chest discomfort or complaints.

Surgical staging and treatment. All patients were scheduled for a cervical mediastinoscopy, regardless of the result of EUS-FNA. Biopsies were attempted in a standardized way of at least the upper (2L, 2R) and lower (4L, 4R) paratracheal and subcarinal (station 7) MLN. The median number of MLN sampled was 4 (range, 2-5). Only those patients with a negative mediastinoscopy were treated with induction chemotherapy, and the nonprogressing patients proceeded subsequently to extrapleural pneumonectomy. A systematic MLN dissection was done according to the classification for lung cancer staging (20): right-sided nodes 2, 4, 7, 8, and 9 and left-sided nodes 4, 5, 6, 7, 8, and 9 were removed. Pathologic examination of MLN was done according to standard procedures, and with immunohistochemistry (calretinin). Patients with MLN metastasis at clinical staging or progressive disease after induction chemotherapy received palliative therapy.

Statistical analysis. Patient characteristics are described as numbers and their corresponding rates. The test performance of the different MLN metastasis detection techniques was analyzed only in those patients in whom the clinical staging with either EUS-FNA or mediastinoscopy resulted in a formal proof of malignant MLN metastasis, and in those patients in whom a negative EUS-FNA and a negative mediastinoscopy were confirmed by means of a thoracotomy with systematic MLN dissection. Categorical data were compared with the Fisher exact test. All data were analyzed with SPSS 15.0 (SPSS, Inc.).

Results

From August 2005 to April 2007, 32 patients with presumed early-stage MPM and eligible for the multimodality treatment protocol were referred: 20 (62%) to Netherlands Cancer Institute and 12 (38%) to Ghent. The patient characteristics are shown in Table 1. In all patients, a formal pathologic diagnosis of MPM approved by an expert panel of pathologists was available. The diagnosis was obtained by thoracoscopy or needle core biopsy in 30 (94%) patients and was made on pleural fluid analysis only in 2 (6%) patients. Epitheloid mesothelioma was the most frequent subtype (81%); a biphasic or sarcomatoid subtype was present in 19%.

Staging procedures by imaging and minimally invasive or surgical techniques are shown in Table 1. Based on CT scan, cT1, cT2, and cT3 were assumed in 47%, 34%, and 19% of the cases, respectively, and N2 was suspected based on CT imaging in 7 (22%) patients. With FDG-PET/CT available for 31 patients, the result was indeterminate for MLN invasion in 4 (13%) because of an insufficient spatial resolution between the MPM and mediastinum. A distinct FDG uptake was noted in 6 (19%) patients. The clinical stage distribution based on imaging is shown in Table 1.

Figure 1 shows the patient’s flow through the study. Of the 32 patients investigated with EUS-FNA, 25 (78%) underwent EUS-FNA was done in an outpatient setting under local anesthesia (with or without moderate sedation) with the use of a curved linear scanning ultrasound endoscope (GF-UCT160-0L5, Olympus Co.) connected to the ultrasound unit (ALOKA Co. Ltd. and Biomedic B.V.; ref. 18) with monitoring of heart rate and oxygen saturation (19). The mediastinum was analyzed systematically (transducer frequency range, 5-10 MHz) with screening of paraesophageal, subcarinal, lower left paratracheal, and upper paratracheal MLN as described (19). Punctures were done of those MLN measuring at least 5 mm with a 22-gauge fine needle (EUS-needle, Olympus); the median number of MLN sampled was 1 (range, 0-2); and the subcarinal or paratracheal MLN were biopsied most frequently. Smears of the aspirates obtained by EUS-FNA were processed on site to evaluate the cellular contents of the air-dried specimens with a quick staining method (Diff-Quick). Whenever possible, several lymph nodes were sampled. Specimens were categorized as positive (tumor cells), negative (lymphoid but no tumor cells), or not representative (necrosis, no lymphoid cells). Punctures were continued until the cytopathologist was able to make a formal conclusion. In case no FNA was done, the result was classified as negative (absence of malignant MLN metastasis). In addition to the MLN, the endoscopist also filled in if the primary tumor was observed with ultrasonography and if, based on the endoscopic ultrasound images, a direct mediastinal invasion was thought to be present. Patients were observed for 2 h after the procedure. They were instructed to phone the hospital in case of chest discomfort or complaints.

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Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. patients, N</th>
<th>%</th>
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<tbody>
<tr>
<td>No. patients, N</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Median age (range), y</td>
<td>61 (40-67)</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26 (81)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (19)</td>
<td></td>
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<tr>
<td>Diagnosis of mesothelioma, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracoscopy</td>
<td>25 (78)</td>
<td></td>
</tr>
<tr>
<td>Needle biopsy (CT-guided/Abrams' needle)</td>
<td>5 (16)</td>
<td></td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>2 (6)</td>
<td></td>
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<tr>
<td>Tumor pathology type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epitheloid mesothelioma</td>
<td>26 (81)</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid mesothelioma</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Biphasic mesothelioma</td>
<td>4 (13)</td>
<td></td>
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<tr>
<td>Tumor localization, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>7 (22)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>25 (78)</td>
<td></td>
</tr>
<tr>
<td>Investigations for staging, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>32 (100)</td>
<td></td>
</tr>
<tr>
<td>PET-CT scan</td>
<td>31 (97)</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td>32 (100)</td>
<td></td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>25 (78)</td>
<td></td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>27 (84)</td>
<td></td>
</tr>
<tr>
<td>Clinical stage based on imaging (CT and FDG-PET), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>13 (41)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>8 (25)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>11 (34)</td>
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</table>
FNA, whereas in 7 (22%) the MLN were either not observed or smaller than 4 or 5 mm, impeding a safe puncture. A mediastinoscopy was done in 27 (84%) patients.

In 11 (34%) patients, a negative EUS-FNA (n = 2) or EUS-FNA plus mediastinoscopy (n = 9) was not confirmed because of clinical deterioration or intraoperative irresectability. A formal pathologic MLN staging was hence available in 21 (66%) patients, and the overall prevalence of malignant MLN metastasis was 24%. With EUS-FNA, malignant MLN metastasis was shown in 4 (19%) patients. The pathologist found malignant cells amidst the lymphocyte population characterizing a MLN puncture. Diagnosing MPM solely on the FNA smears was, however, impossible (Fig. 2). With mediastinoscopy, no additional malignant MLN metastasis was found. In addition to the 4 patients in whom clinical staging by means of EUS-FNA showed MLN metastasis, a thoracotomy with MLN dissection was done in 17 (81%) patients. Systematic MLN dissection showed one additional patient with malignant MLN metastasis (station 4R) in whom preoperative mediastinal staging with both EUS-FNA and mediastinoscopy was considered false negative.

The test characteristics for CT scan and EUS-FNA, calculated for the patients in whom formal MLN pathology was available, are shown in Table 2. The sensitivity of EUS-FNA for the detection of MLN metastasis was 80% (95% confidence interval, 28-99%) whereas the specificity was 100% (95% confidence interval, 79-100%). Although the figures suggest a numerical superiority for the test characteristics of EUS-FNA as compared with CT scan, this difference did not reach statistical significance. With regard to FDG-PET/CT, data could be interpreted on only 19 patients because 2 were indeterminate for MLN invasion. An exploratory analysis showed a sensitivity of only 20% (95% confidence interval, 4-48%) and a specificity of 50% (95% confidence interval, 6-93%).

With EUS-FNA the primary tumor was observed in 23 (72%) patients. A formal pT stage was available in 18 of the 19 (95%) patients who underwent thoracotomy. The endoscopist judged that there was a suspicion for T4 based on the ultrasound characteristics in 6 (33%) operated patients. However, this was confirmed in only 3 patients.

In this series, one esophageal perforation related to EUS-FNA occurred. The patient was referred for immediate surgical correction and was discharged from hospital after several weeks.

**Discussion**

The present series is the first to show that EUS-FNA is a feasible and sensitive procedure in MPM patients considered for multimodality treatment. Based on the current data, the accuracy is promising and warrants further clinical evaluation. We found that EUS-FNA has a sensitivity of 80% to detect malignant MLN metastasis, the latter having a prevalence of 24%. This prevalence is similar to previously reported data (7, 9, 10). An initial evaluation of EUS-FNA has recently been reported in a retrospective case series of 6 MPM patients (21). The present data were generated on a selected patient population in whom negative findings of EUS-FNA and
mediastinoscopy were validated by thoracotomy with systematic MLN dissection. This design ensures confirmed data, although selection bias occurs because the patients in whom no surgical pathologic confirmation was done (e.g., due to progressive disease) were not included in the accuracy analysis. The sensitivity of EUS-FNA in this series is comparable to the published sensitivity for staging mediastinoscopy in MPM (10). The microscopic analysis of EUS-FNA smears enables the detection of malignant cell groups. However, without prior knowledge of the primary diagnosis, the pathologist was unable to diagnose MPM based solely on the FNA smears. Suspicious cell groups, although infiltrative, reveal often minute characteristics of malignancy. We speculate that this contributes to the somewhat inferior sensitivity of EUS-FNA in MPM as compared with lung cancer staging, where values of at least 90% have been reported (14).

Although the specificity of EUS-FNA was high, not all patients in whom EUS-FNA showed malignant MLN metastasis were confirmed by mediastinoscopy. As such, the positive predictive value should be cautiously interpreted because during staging (with either EUS-FNA or mediastinoscopy), sampling the primary tumor rather than MLN will result in false-positive findings (22). We believe this was not the case because endoscopic ultrasound generally allows for precise differentiation between sharp-edged MLN and primary tumor as these have different ultrasound characteristics (Fig. 2). In addition, only in a small fraction of the patients was the primary tumor seen with EUS-FNA. Finally, the pathologist documented in the samples not only tumor cells but also numerous lymphocytes, suggesting that the puncture was obtained from a MLN.

An important finding in our study is that mediastinoscopy did not detect any additional metastases in the MLN that were negative by EUS-FNA. The only false-negative EUS-FNA was also missed by mediastinoscopy. It is unlikely that this unexpected MLN metastasis developed during the neoadjuvant chemotherapy. An anatomic miss is an obvious reason because EUS-FNA hardly reaches the right paratracheal MLN.

### Table 2. Test characteristics for the N determinant

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>EUS-FNA</th>
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<tbody>
<tr>
<td>n = 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>60 (14-94)</td>
<td>80 (28-99)</td>
</tr>
<tr>
<td>Specificity</td>
<td>81 (54-95)</td>
<td>100 (79-100)</td>
</tr>
<tr>
<td>PPV</td>
<td>87 (59-98)</td>
<td>94 (71-99)</td>
</tr>
<tr>
<td>NPV</td>
<td>50 (11-88)</td>
<td>100 (39-100)</td>
</tr>
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</table>

NOTE: Data are given as percentages (95% confidence intervals).
Nevertheless, pathologic examination of the resected specimen showed only very discrete infiltration by tumor islets in the MLN, reflecting a sampling miss of both EUS-FNA and mediastinoscopy. It has to be acknowledged that EUS-FNA is a more limited approach than mediastinoscopy to stage the MLN. This has to do with the fact that the number of lymph nodes sampled is smaller with EUS-FNA and is also related to its anatomic reach. It remains to be established whether there is a role for endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) or even for the combination of EUS-FNA with EBUS-TBNA (23–27).

The negative predictive value of EUS-FNA in this series is high. This suggests that EUS-FNA may be the preferential tool to stage the mediastinum in MPN. However, one should be aware that the data are biased by the relatively low overall prevalence of MLN metastasis.

EUS-FNA has been used to describe the T-stage of lung cancer. Although few patients were analyzed, published data showed that this technique is not reliable because of the considerable numbers of both false-positive and false-negative findings (28). In the current series of MPN, discrimination between T2, T3, and T4 extent was also not reliably made by endoscopic ultrasound. First, the primary tumor is often not observed or can be visualized only partially. Second, the ultrasound transducer frequency range does not allow for discrimination of the pleural folds and the adjacent mediastinal margins. Therefore, only a rough estimation can be made on the extent of direct tumor invasion into the mediastinum. The current data at least show that a T-stage based on linear endoscopic ultrasound examination is insufficiently reliable in MPN.

EUS-FNA has been described as a safe procedure (29). Complications of this procedure have been reported infrequently (29, 30). Nevertheless, we noted one serious complication in this limited series. In our opinion, it is unlikely this event was related to the sole fact that the patient had an MPN, although one could argue that MPN-associated pleural fold thickening could relate to a diminished distensibility and increased fragility of the mediastinal structures including the esophagus. Although it would be inappropriate to conclude that EUS-FNA is unsafe based on this unique event, it illustrates that caution is always important, also when so-called minimally invasive techniques are implemented.

In conclusion, we show that EUS-FNA is a valid and reliable minimally invasive procedure to show mediastinal lymph node metastasis in patients with MPN. Further confirmation is, however, warranted in larger series.

Disclosure of Potential Conflicts of Interest

S. Burgers is a member of the speakers’ bureau for Roche Netherlands.

References

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