Role of Transesophageal Endosonography-Guided Fine-Needle Aspiration in the Diagnosis of Lung Cancer*

Annette Fritscher-Ravens, MD; Nib Soehendra, MD; Lars Schirrow; Parupudi V. J. Sriram, MD; Andreas Meyer, MD; Hans-Peter Hauber, MD; and Almuth Pforte, MD

Study objective: Bronchoscopic methods fail to diagnose lung cancer in up to 30% of patients. We studied the role of transesophageal endosonography (EUS)-guided fine-needle aspiration (FNA; EUS-FNA) in such patients.

Design: Prospective study. The final diagnosis was confirmed by cytology, histology, or clinical follow-up.

Setting: University hospital.

Patients: Thirty-five patients (30 male and 5 female; mean age, 60.9 years; range, 34 to 88 years) with suspected lung cancer in whom bronchoscopic methods failed. Patients with a known diagnosis, recurrence of lung cancer, or mediastinal metastasis from an extrathoracic primary were excluded.

Interventions: EUS and guided FNA of mediastinal lymph nodes.

Results: The procedure was uneventful, and material was adequate in all. The final diagnosis by EUS-FNA was malignancy in 25 patients (11 adenocarcinoma, 10 small cell, 3 squamous cell, and 1 lymphoma) and benign disease in 9 patients (5 inflammatory, 2 sarcoidosis, and 2 anthracosis). Another patient with a benign result had signet-ring cell carcinoma diagnosed on pleural fluid cytology (probably false-negative in EUS-FNA). The sensitivity, specificity, accuracy, and positive and negative predictive values were 96, 100, 97, 100, and 90%, respectively. There were no complications. Reviewing the EUS morphology, the nodes were predominantly located in levels 7 and 8 of American Thoracic Society mediastinal lymph node mapping (subcarinal and parasepahageal region). In seven patients, the punctured nodes were < 1 cm (four malignant and three benign), which are difficult to sample by other methods. The malignant nodes had a hypoechoic, homogenous echotexture.

Conclusions: EUS-FNA is a safe, reliable, and accurate method to establish the diagnosis of suspected lung cancer when bronchoscopic methods fail, especially in the presence of small nodes.

Key words: bronchoscopy; cytology; endosonography; fine-needle aspiration; lung cancer

Abbreviations: ATS = American Thoracic Society; CI = confidence interval; EUS = transesophageal endosonography; EUS-FNA = transesophageal endosonography-guided fine-needle aspiration; FNA = fine-needle aspiration; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer

In the management of lung cancer, the individual therapeutic approach depends on the histologic type of malignancy and tumor staging. In > 70% of patients, the diagnosis can be confirmed by bronchoscopy, including brushings, washings, and transbronchial biopsy.1 In the remaining other methods like CT-guided transthoracic fine-needle aspiration (FNA), mediastinoscopy or thoracoscopic biopsy is required. In the evaluation of the mediastinum, CT is the most preferred imaging technique. However, due to movement and partial volume effect of the

For editorial comment see page 298

*From the Department of Endoscopic Surgery (Drs. Fritscher-Ravens, Soehendra, Sriram, and Mr. Schirrow), and the Department of Internal Medicine, Pulmonology (Drs. Meyer, Hauber, and Pforte), University Hospital Eppendorf, Hamburg, Germany. Manuscript received April 15, 1999; revision accepted September 7, 1999.

Correspondence to: Annette Fritscher-Ravens, MD, Department of Endoscopic Surgery, University Hospital Eppendorf, 2 Martinistrasse, 20246, Hamburg, Germany.
pulmonary vessels, aortic arch, and left atrium, certain regions, such as the aortopulmonary window and the subcarinal and paraesophageal areas, are not always sufficiently imaged. In addition, the sensitivity of CT for lesions < 1 cm is low, and the criteria for diagnosing metastatic involvement of the lymph nodes based on size alone was shown to be less accurate. Transbronchial FNA of subcarinal and paraesophageal nodes has a yield of 50%. Due to the lack of visual guidance, the advancement of the needle is “blind,” and thus targeting is difficult. Transthoracic biopsy has an accuracy of 80 to 95%, but is associated with complications like bleeding and pneumothorax in up to 25 to 35% of cases, while the subcarinal group is inaccessible. Thora-
cotasis, and pneumothorax in up to 25 to 35% of cases,10,11 but is associated with complications like bleeding and pneumothorax in up to 25 to 35% of cases,10,11 and is avoided when the mass is close to major vessels, due to the potential danger of inadvertent vascular puncture. Anterior mediastinoscopy or extended cervical mediastinoscopy is used by few surgeons to access level 5 (aortopulmonary window), which is not inspected by the standard methods. Extended cervical mediastinoscopy has a sensitivity of 83% and diagnostic accuracy of 97% in examining the paraaortic and subaortic lymph node chains, while the subcarinal group is inaccessible. Thora-
coscopy can visualize the inferior mediastinum effectively, but it is limited only up to the level of major bronchi, and the superior mediastinum is out of its reach. Thus, both procedures are selected for tissue sampling on the basis of CT, and are then limited by the sensitivity of CT to detect the nodes in these areas. Moreover, both procedures are invasive and require hospitalization and general anesthesia. Experience with the endobronchial sonography and guided FNA is still limited.

Transesophageal endosonography (EUS) is now an established procedure shown to be superior to CT in the detection of mediastinal lymph nodes in patients with non-small cell lung cancer (NSCLC). In combination with EUS-guided FNA (EUS-FNA), it was used to diagnose mediastinal, perigastric, and pancreatic lesions and in the staging of esophageal, gastric, as well as pancreatic malignancies. Its accuracy for mediastinal masses and lymph nodes is reported to be 83 to 95%, with a sensitivity of 81 to 89%. Compared to the routine use of EUS-FNA in the field of gastroenterology, only a few studies are available using this method in pulmonology. We report our results of EUS-FNA in the diagnosis of suspected lung cancer, when routine bronchoscopic methods were inconclusive.

Materials and Methods

Patients

From November 1997 to November 1998, 283 patients suspected of malignancy on the basis of chest radiography and contrast-enhanced CT underwent bronchoscopy. In 214 patients, the final diagnosis was established by bronchoscopic biopsy, brushings, and washings. In 69 patients in whom EUS and FNA were performed, the results of all the routine investigations were inconclusive. Only those with a suspicion of primary lung malignancy with a demonstrated lung lesion and mediastinal lymph nodes on CT, in whom the bronchoscopy and biopsy, cytology, as well as transbronchial needle aspiration failed to establish the diagnosis, were included. Patients with previous history of malignancy, those with metastatic mediastinal deposits from an extrathoracic primary, and those with esophageal stenosis and bleeding diathesis (coagulopathy or thrombocytopenia) were excluded from the study. We did not examine any immunocompromised patient, so that prophylactic antibiotics were not given. All patients were discharged 2 h after the procedure.

Instruments

A Pentax FG 34 UX echoendoscope with an electronic multielement curved linear array ultrasound transducer (Pentax GmbH; Hamburg, Germany) in combination with the Hitachi EUB 525 ultrasound console (Ecoscan GmbH; Wiesbaden, Germany), or a prototype transducer Olympus UC 30P (Olympus Optical; Hamburg, Germany) with a prototype ultrasound processor (Domier; Germersheim, Germany) were used. EUS-FNA was performed using a 22-gauge Vilmann-Hancke needle (GIP Medizin Technik; Grassau, Germany), introduced through the 2-mm biopsy channel of the echoendoscope.

Technique

After obtaining informed consent, the procedure was performed under IV sedation using midazolam, 5 mg, and nalbuphine hydrochloride, 20 mg, or propofol, 50 to 300 mg (as necessary). The echoendoscope was initially introduced up to the level of celiac axis and gradually withdrawn upwards for a detailed mediastinal imaging. On EUS, the size, location, and EUS morphology of the lesions were recorded on video or thermo prints, and FNA of the suspicious lesions was performed. The location of the lymph nodes was described according to the American Thoracic Society (ATS) mediastinal staging map for lymphadenopathy. If more than one lymph node was detected, FNA was performed on the most suspicious (hypoechoic or inhomogenous and large) and easily accessible nodes. EUS-FNA was performed by introducing the needle through the biopsy channel of the echoendoscope. Since the ultrasound waves are emitted parallel to the long axis of the endoscope, the entire needle could be visualized approaching a target in the sector-shaped sound field. Pulse-wave Doppler ultrasonography imaging was performed, whenever vascular structures were supposed in the pathway of the needle or adjacent to it, to correct the target line if necessary. The needle was advanced through the wall of the esophagus and guided into the target lesion. The 170-mm central stylet was removed, and a special 10-mL syringe attached to the hub of the needle to apply suction as the needle was moved back and forth within the mass. We used a syringe with a self-retaining mechanism to maintain suction (Hepatofix; Fa. Braun; Melsungen, Germany), avoiding the need to manually hold it for the purpose. The suction was released slowly, and the needle assembly removed out of the biopsy channel. One to two needle passes were made to obtain adequate tissue. There was no cytopathologist present, but all the procedures were performed by a single investigator (A.F.R.) who was trained to assess the adequacy of smears. The aspirated material was placed onto at least four glass slides, air dried, stained, and classified. Papainicoelastic staining and light microscopy were done by an independent cytopathologist who was blinded to the details of the cases.
Results

Of the 69 patients who had undergone EUS-FNA, 35 patients (mean age, 60.9 years; range, 34 to 88 years; 30 males and 5 females) were eligible according to the inclusion criteria. The needle could be visualized clearly, and adequate tissue was obtained in all patients (Fig 1, 2). The procedure was uneventful, and there were no complications in any of them.

Confirmation of Diagnosis

A positive cytologic result for malignancy was accepted as evidence enough, and the patients were treated accordingly in case of small cell cancer, since false-positive malignant cytology is very rare. This is an accepted methodology used by other investigators as well. The remaining results were confirmed by histology (n = 17) or a consistent clinical follow-up (n = 8). Wherever surgery was performed, histology of the mass lesion and the nodes were obtained for comparison. In those who did not undergo surgery of the primary for various reasons, findings were confirmed either on histology of the tissue obtained on mediastinoscopy or thoracoscopy, or resected metastasis.

Final Diagnosis

A final diagnosis of malignancy on EUS-FNA was confirmed in 25 patients and benign pathology in 9 patients (Table 1). Positive EUS-FNA for cancer was considered diagnostic in cases that had no further invasive procedures for histologic sampling. In one additional patient with benign findings on EUS-FNA, the diagnosis was considered as probably false-negative. The overall sensitivity of EUS-FNA was 96.2% (95% confidence interval [CI], 77 to 100%); specificity, 100% (95% CI, 67 to 100%); positive predictive value, 100% (95% CI, 80.4 to 100%); negative predictive value, 90% (95% CI, 59 to 100%); and the diagnostic accuracy of EUS-FNA reached 97.1% (95% CI, 85.0 to 100%).

The patient with probable false-negative diagnosis was a 61-year-old man with a right upper lobe mass, pleural effusion, and advanced cardiac disease, who

Table 1—Final Diagnosis of Lesions by EUS-FNA

<table>
<thead>
<tr>
<th>Cytology (n = 35)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Malignancy (n = 25)</td>
</tr>
<tr>
<td>SCLC</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td>Non-Hodgkins lymphoma</td>
</tr>
<tr>
<td>Benign (n = 9)</td>
</tr>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Anthracosis</td>
</tr>
</tbody>
</table>

*Including the patient with signet-ring cell carcinoma on pleural fluid cytology and probably false-negative result on EUS-FNA.
was not operable due to the high surgical risk. His pleural fluid on multiple occasions did not show malignant cells. There were multiple lymph nodes on CT, and bronchoscopic methods to confirm diagnosis failed. EUS revealed two nodes with nonhomogenous echotexture in zone 7 and zone 8 (subcarinal and paraesophageal region), measuring $2.4 \times 3.0$ cm and $1.8$ cm, respectively. However, the EUS-FNA cytology showed only inflammatory cells. Due to the advanced comorbidity, no further attempts were made to confirm the diagnosis. He needed repeated thoracentesis due to breathing difficulty. A repeat pleural fluid cytology on one of the occasions was suggestive of signet-ring cell carcinoma. A pleurodesis was performed subsequently.

**EUS Morphology**

On comparing the EUS location and morphology of lymph nodes in the confirmed benign and malignant lesions, most of them were located in mediastinal groups 7 and 8 (subcarinal and paraesophageal region; Table 2, Fig 3). Malignant lesions were nonhomogenous and echopoor in a majority, whereas 4 out of 10 benign lymph nodes showed hyperechoic features (Table 3). Atypical vessels coursing through the nodes were seen only in two patients with sarcoidosis.

Most of the nodes measured $>3$ cm in malignant as well as in benign lesions. Interestingly, in seven patients (three benign and four malignant cases), the nodes were $\leq 1$ cm, which are impossible to puncture by any other less-invasive procedures (Table 4). The echo features of these small metastatic nodes were homogenous and echopoor in five patients.

**DISCUSSION**

EUS has an important role to play in the evaluation of the mediastinum, due to its inherent ability to image the entire posterior part of it, including the subcarinal node stations and the inferior mediastinum as well as the aortopulmonary window. However, it is of limited value in the pretracheal and partly in the paratracheal regions, due to the intervening air in the trachea. The procedure is safe, less invasive, does not require general anesthesia or hospitalization, and is highly sensitive in the detection of lesions $<1$ cm. The complication rate is extremely low (0.5 to 2.3%), and several studies did not report any complications at all. Lee and coworkers performed EUS preoperatively in 37 patients of lung cancer and detected 65% of the malignant and 44% of the benign lymph nodes, which had a direct implication on the further man-

**Table 2—Locations of EUS-FNA According to ATS Mapping: Benign vs Malignant Lesions (n = 35)*

<table>
<thead>
<tr>
<th>Location</th>
<th>Benign (n = 10)</th>
<th>Malignant (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 right/left</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4 right/left</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>5*</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>10 right</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10 left</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Including the patient with signet-ring cell carcinoma on pleural fluid cytology and probably false-negative result on EUS-FNA.

**Table 3—Morphology of Lymph Nodes Punctured by EUS-FNA (n = 35)*

<table>
<thead>
<tr>
<th>EUS Morphology</th>
<th>Benign (n = 10)</th>
<th>Malignant (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoechoic</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Hyperechoic</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nonhomogenous</td>
<td>2†</td>
<td>10</td>
</tr>
<tr>
<td>Atypical vessels†</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Calcifications</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Including the patient with signet-ring cell carcinoma on pleural fluid cytology and probably false-negative result on EUS-FNA.
†Atypical vessels in addition to echotexture.
agagement. Kondo et al\(^7\) demonstrated the preoperative utility of mediastinal EUS in 132 patients of lung cancer with sensitivity, specificity, diagnostic accuracy, and positive and negative predictive values of 54, 97, 92, 77, and 93\%, respectively. When the right superior mediastinal group of nodes were excluded (which are technically impossible to image by EUS due to the air-filled trachea), the sensitivity was 81\%.\(^7\) Gress et al\(^17\) showed the superiority of EUS (93\%) over CT (43\%) in the detection of metastatic lymph nodes. The additional option of performing FNA for tissue confirmation due to the therapeutic implication of detecting metastatic deposits in nodes now opens new perspectives in the diagnostic work-up for lung cancer.

In a large multicentric study, Wiersema et al\(^24\) showed EUS-FNA to be highly sensitive, specific, and accurate (92, 93, and 92\%, respectively) in the evaluation of 192 patients with enlarged lymph nodes located adjacent to the upper GI wall. In the diagnosis and staging of known or suspected lung cancer, Silvestri et al\(^18\) reported EUS-FNA of enlarged mediastinal nodes in 15 of 27 patients and proved malignancy in all. In 11 patients, EUS was negative, but surgery showed metastatic involvement in 2 patients. The overall accuracy was 89\%. Gress and coworkers\(^17\) gained an accuracy of 96\% in mediastinal nodes in the preoperative evaluation of 24 patients with known NSCLC. EUS-FNA performed in 29 patients with mediastinal malignancy by Hühnerbein et al\(^27\) achieved a sensitivity of 89\% and a specificity of 83\% diagnosing malignancy. We earlier reported the utility of EUS-FNA in 16 patients with undiagnosed mediastinal mass lesions with an overall accuracy of 93.7\% and sensitivity of 90\%.\(^28\)

The present study differs from the earlier reports in the fact that it is a prospective study and only patients with suspected lung cancer whose diagnosis could not be confirmed by bronchoscopic methods were included; patients with a recurrence of lung cancer and mediastinal metastasis from an extrathoracic primary were excluded. In this selected group, EUS-FNA established the diagnosis with a sensitivity of 96\%. Although not comparable, these results are similar to the reported sensitivity in other studies on the use of EUS-FNA. In 16 of the 25 malignant diseases (66.6\%) and 4 of the 10 benign diseases (40\%), further management was altered by the result of EUS-FNA. This demonstrates the particular utility of EUS-FNA in this subset of patients. In addition, it represents an improvement in comparison to the other diagnostic tools.

The two most important advantages of EUS-FNA are the ability to image lesions from 3 to 4 mm onwards and the option to puncture lymph nodes <1 cm,\(^33\) which are too small to be detected by other imaging methods. As they are not seen on CT scan, the disease is often understaged. Arita et al\(^3\) could demonstrate tumor infiltration in 14 of the 19 normal-sized lymph nodes enucleated at thoracotomy. These nodes were not detected on CT scan. Malignant mediastinal nodes may not be larger than the benign lymph nodes.\(^20\) Neither the size nor the echo features can reliably predict malignant infiltration. Although there are some echo features that may suggest malignancy like echopoor structure, size > 1 cm, and sharp margins, Bhutani et al\(^30\) demonstrated that none of them significantly differentiate benign and malignant lymph nodes. In the present study, we could aspirate material for an adequate cytology in seven lymph nodes ≤ 1 cm and four of them showed metastasis.

One major drawback of EUS is its inability to visualize the anterior mediastinum, and thus, it cannot exclude the need for contrast-enhanced CT in the imaging of mediastinum. In presence of pretracheal lymph nodes, mediastinoscopy to access level 2 is still mandatory. Serna et al\(^31\) compared EUS-FNA with mediastinoscopy in a retrospective study and reported a sensitivity of 86\% and 100\%, respectively, with a 100% specificity of both the procedures. Thus, EUS-FNA cannot replace mediastinoscopy, as both these procedures partially target different groups of nodes that are likely to be missed by the other.\(^31–33\)

A reasonable approach for the investigation of suspected lung cancer and mediastinal adenopathy would be an initial thoracic CT followed by bronchoscopy with cytology and biopsy. If this fails to establish the diagnosis, an EUS and guided FNA of the mediastinal nodes avoids further tests in patients with SCLC and in those with NSCLC and contralateral metastasis. These patients are usually treated by chemotherapy and/or radiotherapy. In patients with no evidence of lymph nodes on EUS and those with NSCLC and ipsilateral involvement of nodes, further work-up will be mandatory before surgery (Fig 4).

In conclusion, the diagnosis of suspected lung

| Table 4—Size of Lymph Nodes Punctured by EUS-FNA (n = 35)\(^a\) |
|-----------------|----------------|----------------|
| Size, cm       | Benign (n = 10) | Malignant (n = 25) |
| ≤ 1            | 3              | 4              |
| 1.1–2          | 2              | 4              |
| 2.1–3          | 1              | 7              |
| > 3            | 4              | 10             |

\(^a\)Including the patient with signet-ring cell carcinoma on pleural fluid cytology and probably false-negative result on EUS-FNA.
Cancer is usually successful by bronchoscopy and biopsy in a majority of patients. In cases that could not be diagnosed by the routine methods, histologic confirmation needs invasive procedures like trans-thoracic (CT- or sonography-guided) FNA, mediastinoscopy, or thoracoscopy. EUS and EUS-FNA are useful in the diagnosis of these patients, and are less invasive with negligible complications. Both are especially useful in the presence of small nodes. We advocate the use of EUS-FNA, wherever available, to be the investigation of choice before embarking on to the more invasive techniques. This is especially true in the presence of advanced comorbidity or obvious metastatic disease, where surgery is unlikely to be a therapeutic option.

ACKNOWLEDGMENT: We thank Prof. Dr. Jacob R. Izbicki, Director of the Department of General Surgery, University Hospital, Hamburg, for critical review of the manuscript.

REFERENCES

Figure 4. Potential role of EUS-FNA in the diagnosis of suspected lung cancer.
30 Bhutani MS, Hawes RH, Hoffmann BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc 1997; 45:474–479