

## Mediastinal Endoscopic Ultrasound-guided Fine Needle Aspiration

a report by

**Peter Vilmann, MD, DSc**

Consultant Surgeon and Head of Endoscopy, Department of Surgical Gastroenterology,  
Gentofte University Hospital

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Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) biopsy was originally developed for gastrointestinal (GI) diseases. However, it soon became apparent that a considerable part of the mediastinum can be reached and tissue sampled using this method. EUS-FNA can be used either to obtain a diagnosis from an unknown primary lesion in the mediastinum or to sample tissue from mediastinal lymph nodes (LNs) in order to stage lung cancer (LC) or to differentially diagnose other diseases involving LNs of the mediastinum. EUS-FNA is therefore relevant for the evaluation of a variety of different mediastinal lesions.

LC is the most common cancer-related cause of death in the Western world. Non-small-cell lung cancer (NSCLC) accounts for 80% of lung cancers. The prognosis of NSCLC is poor and is closely related to the stage of disease. NSCLC usually metastasizes first to hilar and mediastinal LNs. Subsequently, hematogenous metastasis to distant sites may occur. For staging of NSCLC, the TNM classification has been developed, in which T stands for local tumor extension, N for LN metastasis, and M for distant metastasis. The treatment of NSCLC is highly stage-dependent, and is generally either surgical resection, provided no spread outside the lung is found (stage I and II), or induction chemotherapy followed by resection in patients with ipsi-lateral mediastinal LN metastases (stage IIIA) or chemo/radiotherapy alone, provided that contralateral mediastinal or distant metastases are present (stage IIIB and IV). Up to 10% of operations for NSCLC result in explorative thoracotomies without tumor resection, and an additional 25–35% of the operations are unsuccessful because of post-operative recurrent disease. Surgery may therefore be regarded as futile or unnecessary in up to 45% of patients operated on, apparently because the stage of the disease is more advanced than pre-operatively expected. This, combined with the stage-dependent multimodality treatment of NSCLC, underlines the importance of exact staging of the disease.

### LN Staging of LC

LNs in the mediastinum are classified according to the Mountain/Dressler classification; mediastinal LN staging can be divided into imaging and sampling.

Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) may be used to image mediastinal LNs.

Chest CT and MRI are not recognized as proof of advanced disease because of the inadequate accuracy of these examinations. PET has a high sensitivity in detecting advanced disease. However, its specificity is too low to finally exclude patients from surgery (false positive diagnoses). A pathological diagnosis of mediastinal tumor spread, obtained by an invasive staging method, is therefore necessary to avoid the unjustified rejection of patients from curative surgery.

Pathologic sampling of suspicious lesions can be performed by mediastinoscopy (MS), thoracoscopy, trans-thoracic FNA, and 'blind' transbronchial FNA (TBNA). MS is considered the gold standard method for invasive mediastinal staging, and recent guidelines recommend MS before all LC resections with curative intention. MS is performed in the operating room (OR) under general anesthesia with a complication rate of 2–3%. However, the accessible area of MS is limited to the anterior part of the mediastinum and in 10–15% of patients undergoing thoracotomy after a negative MS N2–N3 disease is nevertheless ascertained.

The other tissue sampling methods all have variable sensitivities and are mainly used in selected patients. Consequently, there is a need for a safer and more accurate diagnostic procedure in patients suspected of mediastinal tumor growth.

### EUS-FNA

EUS-FNA was first described in 1992 by the author's group. Since then, several studies have been published and it has been demonstrated that, generally, all lesions outlined by EUS may be punctured and even small lesions down to the size of 5mm may be diagnosed. However, there are large fluctuations in the diagnostic values depending on the site of puncture and on the nature of the lesion.

Trans-esophageal EUS gives an excellent overview of mediastinal structures, including access to the para-



Peter Vilmann, MD, DSc, is Consultant Surgeon and Head of Endoscopy in the Department of Surgical Gastroenterology at Gentofte University Hospital, Copenhagen, Denmark. He is also Associate Professor of Surgery at the same university. Dr Vilmann is Past-Chairman of the Danish Society of Endoscopy and a board member of the Scandinavian Association of Digestive Endoscopy (SADE). He is also Associate Editor of the *Scandinavian Journal of Gastroenterology and Endoscopy* and is co-author or author of 14 medical books on endoscopic ultrasonography or laparoscopic ultrasonography. He is internationally recognised as a pioneer on endoscopic ultrasound (EUS) with linear transducer, as well as on EUS guided diagnostic and therapeutic interventions, and has had approximately 80 publications accepted in international peer-reviewed medical journals. Dr Vilmann gained his MD in 1981 and a DSc in 1998.

oesophageal space, the aortico-pulmonary window, the sub-carinal region, and the region around the left atrium. EUS can assess mediastinal LNs at most levels, particularly at levels 4 (left), 5, 7, 8, and 9, as well as metastasis in the left adrenal gland. Levels 1, 2, 3, and 4 (right) are not always assessable, because of interference by air in the larger airways. When enlarged LNs are present, detection is easier.

More than 40 studies reported sensitivities of 0.61–1.00 (median 0.90) and specificities of 0.71–1.00 (median 1.00). The majority of the studies are retrospective and present the results of EUS-FNA performed in LC patients selected by CT.

### EUS-FNA and TBNA Biopsy

'Blind' TBNA of subcarinal LNs has a variable yield. A single retrospective study in 14 patients has tried to assess the diagnostic accuracy of EUS-FNA in the analysis of enlarged subcarinal LNs previously staged tumor-negative by TBNA. Subcarinal LN metastases were assessed by EUS-FNA in 10 of 14 patients (71%). The sensitivity, specificity, and diagnostic accuracy of EUS in analyzing TBNA-negative LNs was 100% in all. These data suggest that for the analysis of the subcarinal LNs the realtime controlled technique of EUS-FNA is superior to the 'blind' technique of TBNA. However, blinded controlled studies should be initiated for firm conclusions to be drawn.

### EUS-FNA and MS

MS and EUS-FNA are often considered to be complementary; MS covering the anterior- and EUS-FNA the posterior mediastinum. However, no studies have actually compared the two methods in a controlled and blinded design; whether one of the methods may obviate or reduce the need for the other is unknown. Both methods can reach the para-tracheal and subcarinal regions.

Serna et al. compared MS with EUS-FNA in a retrospective study using different patient groups and reported a sensitivity of EUS-FNA of 86% and 100% for MS. This is in contradiction with the author's experience in a cohort of 60 patients with NSCLC considered for surgery who underwent both procedures. The diagnoses were confirmed by either open thoracotomy or clinical follow-up. MS and EUS-FNA was conclusive for para-tracheal or subcarinal mediastinal disease in six and 24 patients, respectively (sensitivity 24%/96%). These results suggest that MS is significantly inferior to EUS-FNA for the staging of NSCLC patients.

In a paper by Eloubeidi the value of EUS-FNA after a negative MS was studied. Of the 35 patients who had a

prior negative MS, 13 patients (37.1%) had malignant N2 or N3 LNs. Accuracy of EUS-FNA (98.1%) was significantly higher than that of CT (41.5%;  $p < 0.001$ ) and PET (40%;  $p < 0.001$ ). The authors concluded that starting with EUS-FNA would preclude MS in more than one-third of the patients with NSCLC and combined anterior-posterior (AP) LNs.

Annema et al. investigated the additional value of EUS-FNA to MS in a prospective, non-randomized multi-center trial in 107 consecutive patients with potential resectable NSCLC. The patients underwent thoracotomy with tumor resection if MS was negative. The combination of EUS-FNA and MS identified more patients with tumor invasion or LN metastases (36%) compared with either MS alone (20%), or EUS-FNA (28%) alone. This indicated that 16% of thoracotomies could have been avoided by using EUS-FNA in addition to MS; however, 2% of the EUS-FNA findings were false positive.

### EUS-FNA in CT-negative Patients

In the author's experience EUS-FNA is able to demonstrate mediastinal LN metastases in a number of patients without enlarged mediastinal LNs by CT. This impression is supported by limited experience from two studies in which EUS-FNA demonstrated mediastinal malignancy in 10 of 24 (42%) and in four of 18 (22%) CT-negative patients, respectively. In addition, Wallace evaluated EUS-FNA in a study with 69 patients with NSCLC and LNs less than 1cm by CT. A sensitivity of 61% and a specificity of 98% for advanced LC was found by EUS-FNA. EUS detected advanced disease in 25% (17/69) of the CT-negative patients (nine N-2-3, one M-1 and one T-4).

If these preliminary results can be reproduced in randomized studies, EUS-FNA might be recommended for all LC patients as a routine staging method.

### EUS-FNA and PET

A study by Annema has evaluated EUS-FNA in 36 patients with NSCLC suspected of mediastinal involvement (N-2/N-3 disease) by PET. EUS-FNA confirmed mediastinal involvement in 25 of the patients (69%). EUS-FNA correctly identified 25 of the 28 patients (89%) with clinically verified N2/N3 disease, EUS was suspicious in one and false negative in two patients (sensitivity 93%), and PET was false positive in eight of the 36 PET positive patients (22%). In another study by Kramer a total of 81 patients with MS activity by PET were enrolled. All patients were investigated by EUS and EUS-FNA. A positive diagnosis of malignancy was achieved in 50 of 81 (62%) patients using EUS-FNA alone. The remaining patients underwent an additional surgical staging procedure. A negative or

inconclusive EUS-FNA result did not reliably exclude malignancy as 68% (19/31) of these patients were found to have LN involvement when staged by additional methods. The authors concluded that if EUS-FNA was used routinely to stage patients with PET-positive mediastinal LNs, 62% of these patients could avoid an MS or an explorative thoracotomy.

In a blinded comparative study of EUS-FNA, PET and CT in 79 patients with NSCLC, EUS-FNA, and PET had a comparable sensitivity (63%/68%) but EUS-FNA had a superior specificity. Both methods had a sensitivity superior to that of CT (43%). False positive inoperable diagnoses were found by PET, CT, and EUS-FNA in nine of 36, three of 20, and none in 25 patients; EUS-FNA was therefore the most reliable method.

Another study of 33 patients with NSCLC considered for surgery compared CT, PET, EUS, and EUS-FNA. The authors concluded that CT and EUS-FNA in combination was the most successful approach in the management of patients with NSCLC being assessed for operative resection.

The largest study to date included 104 consecutive patients with suspicious nodes on PET or CT. The reference standard included thoracotomy with complete lymphadenectomy in patients with LC or if EUS-FNA was benign, repeat clinical imaging, or long-term follow-up. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EUS-FNA were 92.5%, 100%, 100%, 94%, and 97%, respectively. EUS-FNA was more accurate and had a higher PPV than the PET or CT ( $p < 0.001$ ) scan in confirming cancer in the posterior mediastinal LNs. More studies are needed before final conclusions can be drawn; however, it seems that EUS-FNA will have an important role to confirm or exclude a PET suspicion of mediastinal disease in patients with NSCLC.

### Clinical Impact Studies

A number of clinical impact studies have been published. A study published by the author's group, including 84 patients selected for EUS-FNA by CT, evaluated the clinical impact of EUS-FNA. A board of thoracic specialists was asked to decide the further course for the patient if EUS-FNA had not been available—this diagnostic strategy was compared with the actual clinical course after EUS-FNA. EUS-FNA demonstrated a sensitivity of 92%, specificity of 100%, PPV of 100%, NPV of 80%, and an accuracy of 94%, for cancer in the mediastinum. In 18 of 37 patients (49%) a thoracotomy/scopy was avoided as a result of EUS-FNA. In 28 of 41 patients (68%) an MS was avoided. According to Hunerbein et al., EUS-FNA made an unexpected diagnosis in 30% of the procedures.

In a randomized study from the author's group with 104 patients, 53 patients were randomly assigned to routine EUS-FNA and 51 patients to a conventional work-up (CWU) strategy including EUS-FNA if CT demonstrated enlarged LNs in the mediastinum. EUS-FNA was performed in 50 patients (94%) in the routine EUS-FNA group, and in 14 patients (27%) in the CWU group. In the routine EUS-FNA, group five patients (9%) had a futile thoracotomy, compared with 13 (25%) in the CWU group ( $p = 0.03$ ), indicating that the routine use of EUS-FNA in LC staging significantly reduces the number of futile thoracotomies when compared with a conventional staging strategy. These results argue very strongly for a standard staging strategy with EUS-FNA in all NSCLC patients.

In a study by Annema in 242 consecutive patients with suspected ( $n = 142$ ) or proven ( $n = 100$ ) LC and enlarged ( $> 1\text{cm}$ ) mediastinal LNs at chest CT, the goal was to assess to what extent EUS-FNA could prevent surgical intervention. EUS-FNA prevented 70% of scheduled surgical procedures because of the demonstration of LN metastases in NSCLC (52%), tumor invasion (T4) (4%), tumor invasion and LN metastases (5%), SCLC (8%), or benign diagnoses (1%). The sensitivity, specificity, and accuracy for EUS in mediastinal analysis were 91%, 100%, and 93%, respectively.

### EUS-FNA after Induction Chemotherapy

EUS-FNA seems to be indicated for downstaging evaluation after induction chemotherapy. In a study of 19 consecutive patients with NSCLC and proven ipsilateral or subcarinal LN metastases, who had been treated with induction chemotherapy and underwent mediastinal restaging by EUS-FNA, the patients had either partial response or stable disease based on sequential CT scans of the thorax. When EUS-FNA restaged the mediastinum as no regional LN metastases (N0), surgical resection of the tumor with LN sampling or dissection was performed. The PPV, NPV, sensitivity, specificity, and accuracy was 100%, 67%, 75%, 100%, and 83%, respectively, qualifying EUS-FNA as an accurate method for the restaging of mediastinal LNs after induction chemotherapy in NSCLC, and it seems to be able to identify the subgroup of downstaged patients, who may benefit from further surgical treatment.

### EUS-FNA of the Left Adrenal Gland in Patients with Thoracic Malignancies

The diagnostic yield and safety of trans-gastric EUS-FNA of the left adrenal gland is currently not well defined. In a study by Eloubeidi of 31 patients with a focal lesion of the left adrenal gland, EUS-FNA demonstrated metastatic disease in nine of the 15 LC patients (sensitivity of 100%); further studies are required.

### Cost-effective Studies

In three studies with decision-analysis models, EUS-FNA was shown to be cost-effective. In one of these studies EUS-FNA was less expensive compared with MS for the assessment of the entire mediastinum or for subcarinal LNs only. Kramer has calculated a cost reduction from US\$3,514 to US\$2,101 per patient if a staging algorithm with EUS-FNA was used. Aabakken calculated a cost reduction from US\$2,411 to US\$1,729 in patients with NSCLC and enlarged LNs by CT if EUS-FNA was used instead of MS. The advantage conferred by EUS remained even when the NPV of EUS-FNA was as low as 22%. In a recent study in 35 patients, initial EUS-FNA resulted in average costs per patient of US\$1,867 (SD +/- US\$4,308) while initial MS cost US\$12,900 (SD +/- US\$4,164.40). If initial EUS-FNA is utilized rather than initial MS, an average cost saving of US\$11,033 per patient would result.

### EUS-FNA in Non-LC Disease

A number of studies have demonstrated that other diagnoses from mediastinal lesions can be obtained by EUS-FNA. Most of these studies are a mixture of patients from retrospective studies. The diagnoses obtained are tuberculosis (TB), lymphoma, sarcoidosis, histoplasmosis, and metastases from other primary tumors such as renal cancer, breast cancer, gynecological cancer, esophageal cancer, gastric cancer, and pancreatic cancer.

A few studies have evaluated EUS-FNA in sarcoidosis. Bronchoscopy with transbronchial lung biopsy is non-diagnostic in 30% of patients with suspected sarcoidosis. Fritscher-Ravens found a sensitivity of 94% of EUS-FNA in 19 patients suspected of sarcoidosis. Another study by Mishra found a sensitivity of 86% in seven patients. Annema included 51 patients with suspected sarcoidosis stage I and II. Thirty-six patients (71%) previously underwent a non-diagnostic bronchoscopy. All patients were clinically followed (median 18 months) and surgical-pathological verification occurred in those patients with EUS aspirates that contained unrepresentative material. EUS-FNA demonstrated non-caseating granulomas without necrosis in 41 of 50 patients (82%) with the final diagnosis of sarcoidosis.

Wildi et al. showed 35 cases of granulomas (group 1) by EUS-FNA in 124 patients with mediastinal lymphadenopathy; in the other 89 cases (group 2) no granulomas were detected. The definite diagnoses in group 1 were sarcoidosis (n=25), indefinite (n=7), and no sarcoidosis (n=3). The definite diagnoses in group 2 were sarcoidosis (n=3), indefinite (n=9), and no sarcoidosis (n=77). Of the 77 cases with no sarcoidosis, 44 were diagnosed with other diseases. The other 33 showed non-specific changes in the FNA and sarcoidosis was excluded by negative

non-EUS pathology (n=17) and clinical presentation. The sensitivity and specificity for EUS-FNA were 89% (95% confidence interval (CI) 82 to 94), and 96% (95% CI 91 to 98), respectively, after exclusion of the indefinite cases in both groups. EUS-FNA seems to be an accurate method for diagnosing sarcoidosis in an unselected group of patients with mediastinal lymphadenopathy.

### Complications

EUS-FNA is generally considered to be a safe method; most complications reported are case studies. Barawi prospectively studied the incidence of complications associated with EUS-FNA. In 842 mediastinal EUS-FNA procedures, one infection, two hemorrhages, and one inexplicable transient hypotension were reported. FNA of a cystic mediastinal lesion should be avoided or, when necessary, be preceded by prophylactic antibiotics.

### Limitations and Perspectives

Most of the presented studies are retrospective, not consecutive, and include selected patients only. However, controlled and randomized studies have begun to arise. Currently, no blinding has been performed when comparing EUS-FNA with MS and TBNA. Most of the published results are from expert centers. If EUS-FNA is taken up by all groups involved in LC staging, the question arises of how this would affect the diagnostic yield. However, substantial evidence speaks in favor of EUS-FNA as a safe and minimally invasive tissue sampling method in patients with enlarged mediastinal LNs outlined by CT.

Currently, MS is still considered complementary to EUS-FNA because EUS-FNA cannot visualize structures anterior to the air-filled trachea and main bronchi. Endoscopic trans-bronchial realtime ultrasound guided biopsy (EBUS)-TBNA performed via the trachea and main bronchi seems to be an obvious solution. Use of a prototype EBUS-TBNA bronchoscope in approximately 500 patients has shown promising results (unpublished data). The author has recently published preliminary results of EUS-FNA and EBUS-TBNA, in combination, for the diagnosis of mediastinal cancer in 33 patients. An accuracy of 100% (95% CI;83-100%) was found with the combined method. According to the author's experiences, EUS-FNA and EBUS-TBNA appear to be complementary methods. A combined approach with both EUS-FNA and EBUS-TBNA may be able to replace more invasive methods for evaluating LC patients with suspected hilar or mediastinal metastases, as well as for evaluating unclear mediastinal or hilar lesions. ■

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