State of the art lecture: Mediastinal EUS

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Introduction

Endoscopic ultrasound guided fine needle aspiration biopsy (EUS-FNA) was originally developed for gastrointestinal diseases [1]. However, it very soon became apparent that a considerable part of the mediastinum can be reached and tissue sampled by this method [2]. Trans-esophageal EUS guided biopsy of lesions in the mediastinum is a minimal invasive diagnostic method which can spare patients from much more aggressive and risky methods. At present both cytology as well as histology can be obtained by EUS guidance which has broadened the range of applications for EUS even further. The main indications of EUS guided biopsy in the mediastinum is at present staging of non-small cell lung cancer (NSCLC), diagnosis of lymph nodes of unknown nature, staging of a wide range of cancers if CT has demonstrated enlarged mediastinal lymph nodes and differentiation between specific cancers or lymphomas for accurate diagnosis (EUS guided histology).

The aim of the following is to present the status of EUS guided biopsy of the mediastinum based on a literature survey.

Lymph node staging of lung cancer

Non-small-cell lung cancer (NSCLC) accounts for 80% of lung cancers. The treatment of NSCLC as well as the prognosis is highly stage dependent (TNM-stage) [3].

Lymph nodes in the mediastinum are classified according to the Mountain/Dressler classification [4]. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are frequently used to image mediastinal lymph nodes [5].

However, lymph nodes detected by CT and MRI are not recognized as proof of advanced disease, because of inadequate accuracy of these examinations [6]. PET has a high sensitivity in detecting advanced disease. However, its specificity is too low to finally exclude patients from surgery (false positive diagnoses) [7]. Therefore a pathological diagnosis of mediastinal tumor spread, obtained by an invasive staging method, is necessary to avoid unjustified rejection of patients from curative surgery.

Mediastinoscopy (MS) is considered the "gold standard " for invasive mediastinal staging [8]. 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 [5]. Consequently, there is a need for a more safe and accurate diagnostic procedure in patients suspected of mediastinal tumor growth.

Endoscopic ultrasound guided fine needle aspiration biopsy

Trans-esophageal EUS gives an excellent overview of mediastinal structures, including access to the para-oesophageal space, the aortico-pulmonary window, the sub-carinal region and the region around the left atrium [9 – 11]. EUS can assess mediastinal lymph nodes at most levels, particularly at levels 4 left, 5, 7, 8, and 9, as well as metastases in the left adrenal gland. Levels 1, 2, 3, and 4 right are not always accessible.

More than 50 studies on EUS-FNA have reported sensitivities of 0.61–1.00 (median 0.90), and specificities of 0.71– 1.00 (median 1.00).

EUS-FNA and transbronchial needle aspiration biopsy

"Blind transbronchial needle aspiration (TBNA) of subcarinal lymph nodes has a variable yield. A single retrospective study in 14 patients has found a diagnostic accuracy of EUS-FNA of 100% in the analysis of enlarged subcarinal lymph nodes previously staged tumor negative by TBNA [12]. In a recent study [13] in 20 patients trans-bronchial needle aspiration with rapid on-site cyto-pathologic evaluation was performed and if unrevealing EUS-guided FNA was added in the same session. The diagnostic yield for TBNA and EUS-FNA alone was 65% and 86%, respectively. This single-session approach provided a yield of 90%, with no complications. It therefore seems that TBNA and EUS-FNA may complement each other. However, blinded controlled studies should be initiated for firm conclusions to be made.

EUS-FNA and mediastinoscopy

MS and EUS-FNA are often considered as complementary, MS covering the anterior- and EUS-FNA the posterior mediastinum [14,15]. However, no studies have actually compared the 2 methods in a controlled and blinded design.

Serna et al. [15] compared mediastinoscopy with EUS-FNA in a retrospective study using different patient groups and reported a sensitivity of EUS-FNA of 86% and 100% for mediastinoscopy. This is in contradiction with our own experience [16] in a cohort of 60 patients with NSCLC considered for surgery who underwent both procedures. Mediastinoscopy and EUS-FNA was conclusive for para-tracheal or subcarinal mediastinal disease in 6 and 24 patients, respectively (sensitivity 24%/96%).

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In a paper by Eloubeidi [17] the value of EUS-FNA after a negative mediastinoscopy was studied in 35 patients. The accuracy of EUS-FNA (98.1%) was significantly higher than that of CT (41.5%; $p < 0.001$) and PET (40%; $p < 0.001$).

Annema et al. [18] investigated the additional value of EUS-FNA to mediastinoscopy in a prospective multi-center trial in 107 consecutive patients with potential resectable non-small cell lung cancer. The patients underwent thoracotomy with tumor resection if mediastinoscopy was negative. The combination of EUS-FNA and mediastinoscopy identified more patients with tumor invasion or lymph node metastases (36%) compared with either mediastinoscopy alone (20%) or EUS-FNA (28%) alone. This indicated that 16% of thoracotomies could have been avoided by using EUS-FNA in addition to mediastinoscopy. Of concern was that 2% of the EUS-FNA findings were false-positive.

EUS-FNA in CT negative patients

In our own experience EUS-FNA is able to demonstrate mediastinal lymph node metastases in a number of patients without enlarged mediastinal lymph nodes by CT. This impression is supported by limited experience from 2 studies in which EUS-FNA demonstrated mediastinal malignancy in 10 of 24 (42%) and in 4 of 18 (22%) CT-negative patients, respectively [19,20]. In addition, Wallace evaluated EUS-FNA in a study with 69 patients with NSCLC and lymph nodes less than 1 cm by CT [21]. 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 (9 N-2 – 3, 1 M-1 and 1 T-4).

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

EUS-FNA and PET

A study by Annema [22] 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%). PET was false positive in 8 of the 36 PET positive patients (22%). In another study by Kramer [23] a total of 81 patients with mediastinal activity by PET were enrolled. 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 lymph node involvement when staged by additional methods. The authors concluded that, if EUS-FNA was used routinely to stage patients with PET-positive mediastinal lymph nodes, 62% of these patients could avoid a mediastinoscopy 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 [24]. Both methods had a sensitivity superior to that of CT (43%). False positive diagnoses were found by PET, CT and EUS-FNA in 9/36, 3/20, 0/25 patients. Therefore EUS-FNA was the most reliable method.

Another study with 33 patients with NSCLC considered for surgery compared CT, PET, EUS and EUS-FNA [25]. 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 [26] included 104 consecutive patients with suspicious nodes on PET or CT. The reference standard included thoracotomy with complete lymphadenectomy in patients with lung cancer or if EUS-FNA was benign, repeat clinical imaging, or long-term follow-up. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EUS-FNA were 92.5%, 100%, 100%, 94%, and 97%, respectively. EUS-FNA was more accurate and had a higher positive predictive value than the PET or CT ($p < 0.001$) scan in confirming cancer in the posterior mediastinal lymph nodes. 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 few clinical impact studies have been published. A study published by our group [27] including 84 patients selected for EUS-FNA by CT, evaluated the clinical impact of EUS-FNA. In 18 of 37 patients (49%) a thoracotomy/-scopy was avoided as a result of EUS-FNA.

In a randomized study from our group [28] with 104 patients, 53 patients were randomly assigned to routine EUS-FNA and 51 patients to a conventionalt strategy (CWU) including EUS-FNA if CT demonstrated enlarged lymph nodes 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 routinely use of EUS-FNA in LC staging significantly reduces the number of futile thoracotomies when compared to 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 [29] in 242 consecutive patients with suspected ($n = 142$) or proven ($n = 100$) lung cancer and enlarged (> 1 cm) mediastinal lymph nodes at chest CT it was shown that EUS-FNA prevented 70% of scheduled surgical procedures because of the demonstration of LN metastases in non-small-cell lung cancer (52%), tumor invasion (T4) (4%), tumor invasion and LN metastases (5%), SCLC (8%), or benign diagnoses (1%).

EUS-FNA after induction chemotherapy

A study of 19 consecutive patients with NSCLC and proven ipsilateral or subcarinal lymph node metastases, who had been treated

with induction chemotherapy underwent mediastinal restaging by EUS-FNA [30]. When EUS-FNA restaged the mediastinum as no regional lymph node metastases, surgical resection of the tumor with lymph node 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 restaging of mediastinal lymph nodes after induction chemotherapy and it seems to be able to identify the subgroup of down-staged patients, who may benefit from further surgical treatment.

EUS-FNA of the left adrenal gland in patients with thoracic malignancies

The diagnostic yield of trans-gastric EUS-FNA of the left adrenal gland is at present not well defined. In a study by Eloubeidi [31] of 31 patients with a focal lesion of the left adrenal gland, EUS-FNA demonstrated metastatic disease in 9 of the15 lung cancer patients (sensitivity of 100 %). Further studies are needed.

Cost-Effective studies

In 3 studies with decision-analysis models [24,32,33] EUS-FNA was shown to be cost effective. In a recent study [18] in 35 patients it was shown that if initial EUS-FNA is utilized rather than initial mediastinoscopy, an average cost saving of 11,033 dollars per patient would result. More studies are needed.

EUS-FNA in non lung cancer 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 [9,34–38]. The diagnoses obtained are TB, lymphoma, sarcoidosis, histoplasmosis, 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 [39–42]. Fritscher-Ravens found a sensitivity of 94 % of EUS-FNA in 19 patients suspected of sarcoidosis [40].

Annema [41] 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. [42] showed in 124 patients with mediastinal lymphadenopathy 35 cases of granulomas (group 1) by EUS-FNA; in the other 89 cases (group 2) no granulomas were detected. The definite diagnoses in group 1 were sarcoidosis (n = 25), indefinite (n = 7), no sarcoidosis (n = 3). The definite diagnoses in group 2 were sarcoidosis (n = 3), indefinite (n = 9), 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 the clinical course. The sensitivity and specificity for EUS-FNA were 89 % (95 % 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 of the mediastinum is generally considered to be a safe method. Most complications reported are case studies [43,44]. Barawi prospectively studied the incidence of complications associated with EUS-FNA [44]. In 842 mediastinal EUS-FNA procedures, 1 infection, 2 hemorrhages, and 1 inexplicable transient hypotension were reported. FNA of a cystic mediastinal lesion should be avoided, or when necessary be preceded by prophylactic antibiotics [45].

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 show up. At present no blinding has been performed when comparing EUS-FNA with mediastinoscopy and TBNA. Most of the published results are from expert centers. If EUS-FNA is taken up by all groups involved in lung cancer staging, how would this affect the diagnostic yield? Mediastinoscopy 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 real-time ultrasound guided biopsy (EBUS-TBNA) performed via the trachea and main bronchi seems to be an obvious solution. We have recently published our preliminary results of EUS-FNA and EBUS-TBNA, in combination, for the diagnosis of mediastinal cancer in 33 patients [46]. An accuracy of 100 % (95 % CI, 83–100 %) was achieved with the combined method. 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 lung cancer patients with suspected hilar or mediastinal metastases, as well as for evaluating unclear mediastinal or hilar lesions.

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