CONTRIBUTION OF ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION IN THE WORKUP OF MEDIASTINAL LYMPH NODES

Performance diagnostique des ponctions sous échoendoscopie des adénopathies médiastinales

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Summary
Background and aim. — The aim of this retrospective study was to assess endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), a minimally invasive technique, to determine its diagnostic accuracy and morbidity in the etiological diagnoses of mediastinal lymph nodes.

Methods. — A total of 84 patients underwent EUS-FNA biopsy of the mediastinal lymph nodes, and were classified as either malignant disease, inflammatory disease or incidental diagnosis, according to the suspected clinical condition. To evaluate the diagnostic accuracy of EUS-FNA in each group, a comparison of the cytological results obtained with 19- and 22-gauge needles was performed.

Results. — All 84 procedures were carried out between January 2004 and June 2008. Six patients were excluded because of non-contributory results. On analyzing the results of EUS-FNA in the malignant group (n = 41), the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 93, 100, 100 and 85%, respectively. In the inflammatory (n = 20) and incidental diagnosis (n = 17) groups, the sensitivity, specificity, PPV and NPV were 85, 100, 100 and 75%, and 80, 100, 100 and 77%, respectively. There was no significant difference between the FNA results with the 19-gauge (20/78 patients) versus 22-gauge (58/78 patients) needles (P = 0.55). Also, no complications were reported either during the procedure or after the 6-month follow-up.

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Conclusion. — EUS-FNA is a safe and accurate diagnostic procedure for the study of mediastinal lymph nodes not only for malignancy, but also for inflammatory diseases and incidental diagnoses. In addition, there is no difference in diagnostic accuracy whether FNA is carried out with a 19-gauge or 22-gauge needle.

Résumé

Objectif. — La ponction sous échoendoscopie est une technique diagnostique peu invasive utilisée dans le bilan étiologique des adénopathies médiastinales. Son impact thérapeutique est majeur et sa morbidité faible.

Méthodes. — Les données des 84 patients adressés pour bilan échoendoscopique d’adénopathies médiastinales ont été recueillies rétrospectivement. Les patients étaient divisés en trois groupes : maladie néoplasique, maladie inflammatoire ou diagnostic fortuit. La performance diagnostique des ponctions sous échoendoscopie dans les trois groupes de patients a été évaluée. Une comparaison entre les ponctions par aiguille de 22-gauge et 19-gauge a été faite.

Résultats. — Entre janvier 2004 et mai 2008, l’examen a été réalisé chez 84 patients. Six patients ont été exclus de l’étude du fait de résultats histologiques non contributifs. L’analyse des groupes montre une sensibilité, spécificité, valeur positive prédictive et valeur négative prédictive de 93, 100, 100 et 85 % pour le groupe néoplasique (41 patients) ; 85, 100, 100 et 75 % pour le groupe inflammatoire (20 patients) et 80, 100, 100 et 77 % pour le groupe des diagnostics fortuits (17 patients). Il n’y avait pas de différence significative entre les ponctions par aiguille à 19-gauge et 22-gauge (p = 0,55). Aucune complication lors de l’examen et après un suivi d’au moins six mois n’a été rapportée.

Conclusion. — La ponction sous échoendoscopie d’adénopathies médiastinales est un examen précis et sûr, non seulement dans un contexte néoplasique mais également dans le diagnostic d’atteintes inflammatoires. Il n’y a pas de différence significative entre les ponctions par aiguille de 22-gauge et 19-gauge.

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Mediastinal EUS-FNA

Introduction

Mediastinal lymph nodes are involved in both benign and malignant pathologies, and are usually asymptomatic, but can cause dysphagia because of extrinsic compression of the esophagus. Lymph nodes can be visualized on thoracic radiography and on computed tomography (CT) during staging of previously known cancer or while searching for the cause of non-specific symptoms (such as weight loss, fever or chronic cough).

The main problem encountered with mediastinal lymph nodes is how difficult it is to access this area for histological analysis. Endoscopic ultrasound (EUS) is a procedure that allows direct visualization of most of the mediastinal lymph nodes and the possibility of fine-needle aspiration (FNA) for obtaining biopsy samples, which can help patients to avoid more invasive investigations such as thoracotomy.

The main indications for EUS-guided biopsy in the mediastinum are staging of a known cancer with mediastinal adenopathy, diagnosis of lymph node changes of unknown etiology, and diagnosis of inflammatory disorders with mediastinal involvement such as sarcoidosis, tuberculosis and histoplasmosis.

The present study aimed to assess the diagnostic accuracy of EUS-FNA in mediastinal lymph nodes. As our institution is a reference endoscopic center for chest cancer and internal medicine departments, it was essential to investigate the contribution of EUS-FNA in the diagnostic workup of mediastinal adenopathies and their clinical outcomes.

Materials and methods

Patients

This was a retrospective evaluation of all patients referred to our center for EUS-FNA of the mediastinal lymph nodes. As a retrospective study, no patient’s consent was necessary, although the study was approved by the local ethics review board. From January 2004 to May 2008, 84 EUS-FNA biopsies of mediastinal lymph nodes were carried out, comprising 44 male patients and 40 female patients, aged 19 to 86 years (mean: 56.2 ± 13; median: 58). All were referred because of mediastinal lymph node findings on CT scans, and were categorized according to the diagnostic circumstances as either known or suspected tumor, known or suspected inflammatory disease, or an incidental diagnosis.

Instruments

All procedures were performed at our center by one of three experts in EUS (F.P., G.R., L.M.). A linear-array transducer (Olympus GF-UCT140, Olympus Optical; Hamburg, Germany) was used, and either a 19- or 22-gauge needle (EchoTip; Cook Endoscopy, Winston-Salem, NC, USA) was used for the FNA, introduced through the working channel.

Technique

All procedures were carried out under general anesthesia after informed consent had been obtained. With the patient in a left-lateral position, the EUS channel was introduced at...
the level of the celiac axis and withdrawn from this point to obtain an adequate evaluation of the posterior mediastinal region. After localization of an enlarged mediastinal lymph node, the needle was introduced through the working channel. Under direct ultrasonographic visualization, the needle was introduced into the nodal mass, the stylet withdrawn and a 10-mL syringe attached to apply suction. Back-and-forth movements were used to obtain material for cytological evaluation. The needle was then pulled back into the sheath, and the entire system withdrawn via the working channel. Between one and five needle passes were made, and all material thus obtained was gently flushed with a small amount of 9% saline in a 5% formaldehyde solution before being sent away for anatomicopathological evaluation, as neither the pathologist nor cytologist was present on site. Specimens were fixed and analyzed after Papanicolaou staining. Patients were then followed-up for at least 6 months after the procedure.

A true-positive result was defined as the detection of malignant cells in the cytological evaluation of patients with known malignancy or who were subsequently diagnosed on clinical follow-up. The presence of a caseating or non-caseating granuloma, or a positive culture for infectious disease (tuberculosis), was also classified as a true-positive result in patients investigated for an inflammatory disease. The diagnosis of sarcoidosis was based on clinical suspicion, the presence of a non-caseating granuloma and a negative culture test for fungal or mycobacterial infection, while the diagnosis of tuberculosis was made on the basis of clinical suspicion, caseating granuloma and/or a positive culture.

A false-negative result was obtaining a normal lymph node tissue result after FNA cytological analysis, with a subsequent positive result (malignant or inflammatory) after surgical mediastinoscopy or thoracotomy. A non-contributory result was defined as a hemorrhagic FNA result with either no cells or insufficient lymph node material to determine whether it was malignant, inflammatory or normal.

### Results

Of the 84 patients referred for EUS-FNA of the mediastinal lymph nodes, six were excluded because of non-contributory results on FNA cytological analysis. Of the 78 patients included in the final analysis, the global sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of EUS-FNA for cytological diagnosis of the mediastinal lymph nodes were 88, 100, 100 and 92%, respectively. The results of the intention-to-treat (ITT) and per-treatment analyses are presented in Tables 1 and 2.

Patients were divided into three groups according to the suspected clinical condition: known or suspected tumor; known or suspected inflammatory disease; or incidental diagnosis. In the group with known or suspected malignancy (41/78 patients), the sensitivity, specificity, PPV, NPV and accuracy were 93, 100, 85 and 95%, respectively (Table 2). All of the diagnosed tumors were metastatic, with a final diagnosis of lung cancer (24/28 patients), gastric cancer (1/28 patients), neuroendocrine tumor (1/28 patients), cholangiocarcinoma (1/28 patients) and bladder carcinoma (1/28 patients).

In the group with known or suspected inflammatory disease (20/78 patients), the sensitivity, specificity, PPV, NPV and accuracy were 85, 100, 75 and 90%, respectively (Table 2). Of the patients with a true-positive diagnosis (12/20 patients), all had an inflammatory final diagnosis. Eight were diagnosed and treated as sarcoidosis, and four were considered tuberculosis (caseating granuloma and/or positive culture), with normal or reduced lymph nodes after at least 6 months of follow-up.

The final group comprised 17/78 patients who needed evaluation because of an incidental mediastinal lymph node diagnosis. The sensitivity, specificity, PPV, NPV and accuracy were 80, 100, 77 and 88%, respectively (Table 2). Of these patients, eight had true-positive results, mostly an inflammatory diagnosis (6/8 patients), although two had new neoplastic diagnoses — specifically, lung cancer and lymphoma — that had not been clinically suspected. Fig. 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diagnostic accuracy rates of EUS-FNA in the workup of mediastinal lymph nodes (intention-to-treat analysis).</th>
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<tbody>
<tr>
<td>Group (n/n patients)</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>Total (84/84)</td>
<td>82</td>
</tr>
<tr>
<td>Malignant (43/84)</td>
<td>87</td>
</tr>
<tr>
<td>Inflammatory (21/84)</td>
<td>80</td>
</tr>
<tr>
<td>Incidental (20/84)</td>
<td>66</td>
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<td>PPV: positive predictive value; NPV: negative predictive value.</td>
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<th>Table 2</th>
<th>Diagnostic accuracy of EUS-FNA in the workup of mediastinal lymph nodes (per-treatment analysis).</th>
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<tbody>
<tr>
<td>Group (n/n patients)</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>Total (78/78)</td>
<td>88</td>
</tr>
<tr>
<td>Malignant (41/78)</td>
<td>93</td>
</tr>
<tr>
<td>Inflammatory (20/78)</td>
<td>85</td>
</tr>
<tr>
<td>Incidental (17/78)</td>
<td>80</td>
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<tr>
<td>PPV: positive predictive value; NPV: negative predictive value.</td>
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</tbody>
</table>
Figure 1  Final diagnoses for the mediastinal lymph nodes following EUS-FNA. *All results were done with a 22-gauge needle; 
three patients with non-contributory results, followed-up because of low clinical suspicion, showed no evidence of lymph node
enlargement after at least 6 months of follow-up; PTES: patients.

presents all of the final diagnoses (malignant and inflammatory) obtained by EUS-FNA.

Patients with a negative EUS-FNA result were followed-up with mediastinoscopy or thoracotomy to clinch the diagnosis. However, no patients were sent for a second EUS-FNA after a negative or non-contributory result. There was also a group of patients who were only clinically followed-up because of a low clinical suspicion of inflammatory or malignant disease (most of them from the incidental group).

Of the six patients excluded because of non-contributory results, three were followed for 6 months because of incidental lymph node findings with low clinical suspicion of either inflammatory or malignant disease; follow-up revealed no lymph node enlargement or other signs of disease. The other three patients underwent mediastinoscopy to obtain samples for histological examination. Their final diagnoses were mesothelioma, lung cancer and sarcoidosis, respectively.

In addition, the results were analyzed according to the size of needle used (19- or 22-gauge) to determine whether or not there was a difference in diagnostic performance between them. A total of 20 biopsies had been done with a 19-gauge needle, and 58 with a 22-gauge needle. The sensitivity, specificity, PPV, NPV and accuracy were 94, 100, 100, 80 and 95%, respectively, for the 19-gauge needle, and 87, 100, 100, 80 and 92%, respectively, for the 22-gauge needle (Table 3). There was no statistically significant difference between the two needle sizes (P = 0.55). As for the six patients excluded because of non-contributory results, all had been done with the finer, 22-gauge needle. There were no immediate or late complications after 6 months of follow-up.

Discussion

Given the short distance between the esophagus and mediastinum, EUS is a highly accurate technique for exploring the region, not only including the posterior mediastinum, but also the subcarinal region, aortopulmonary window and inferior paraesophageal region.

In addition, the diagnostic accuracy of EUS has improved since the advent of FNA, as lymph node morphology visualized by EUS alone cannot determine the etiology [1]. The typical features of rounded shape, diameter greater than 1 cm at the widest point, hypoechochogenicity and well-demarcated rim are non-specific; they can predict malignancy in only 80% of cases. Also, it is important to remember that all four features are present in less than 20% of cases [2].

<table>
<thead>
<tr>
<th>Needle size (n/n patients)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-Gauge (20/78)</td>
<td>94</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>22-Gauge (58/78)</td>
<td>87</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>92</td>
</tr>
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</table>

PPV: positive predictive value; NPV: negative predictive value (P = 0.55).
The "gold-standard" technique for analysis of mediastinal lymph nodes is mediastinoscopy, although the area accessible by this procedure is limited to the anterior mediastinum [3]. It has a sensitivity and specificity of 87 and 100%, respectively [4]. However, it is costly and invasive, with a reported morbidity of up to 16% [5].

CT is widely available, and useful for the primary diagnosis and staging of mediastinal lymph nodes, but is not a good method for detecting lymph nodes less than 1 cm in diameter, and has only moderate sensitivity and specificity—around 43 to 81% and 44 to 94%, respectively—for lung cancer [6]. CT-guided needle aspiration is limited to small lesions and the "skin-to-lesion" path of the needle is generally considered unsafe [7].

Bronchoscopy and transbronchial needle aspiration offer another approach to mediastinal lymph nodes, albeit with the disadvantages that the needle has to be advanced blindly, using landmarks identified on CT, and is limited to areas adjacent to the trachea and bronchi (lower paratracheal, right upper paratracheal and subcarinal parts) [4,6,8]. However, the problem of blindness can be resolved by endoscopic transbronchial real-time ultrasound-guided biopsy [3], an examination that is complementary to transoesophageal EUS-FNA for staging non-small-cell lung cancer [9]. The sensitivity, specificity, PPV and NPV with such a combination have been reported to be 95, 100, 100 and 90%, respectively [10].

On the other hand, EUS-FNA can access most of the mediastinal lymph nodes except for the right paratracheal area and pretracheal space [4]. The method has a sensitivity of 90% and specificity of 97 to 100% for lung cancer staging [11–16], and a reported complications rate of less than 1%, of which very few are major [17,18]. Ideally, the procedure should be carried out with cytopathological feedback, which can increase the yield by 10 to 15% [7]. If such feedback is not available, then three or four passes resulting in lymphocytes with no malignant cells are deemed sufficient to exclude malignancy [8].

In comparison to mediastinoscopy, EUS-FNA is considered superior for mediastinal disease in the paratracheal and subcarinal lymph nodes [19,20], and is also more cost-effective. In comparison to CT and positron emission tomography (PET) scans, the sensitivity for metastatic involvement is 53 and 73%, respectively, versus 94% for EUS-FNA, with a specificity of 74, 83 and 100%, respectively [6].

To our knowledge, this is the first study to compare EUS-FNA diagnostic accuracy in malignant, inflammatory and incidental mediastinal lymph nodes, grouped according to the suspected clinical condition. In the present study, EUS-FNA proved to be accurate in making etiological diagnoses, with figures similar to those of other reported studies. Indeed, the diagnostic accuracy was adequate not only for the diagnosis of malignant lymph nodes, but also for the differential diagnosis of inflammatory disease and a positive diagnosis of incidental mediastinal lymph nodes.

The potential of EUS is well known for lung cancer staging. The American College of Chest Physicians recommends invasive staging with tissue confirmation of suspected metastatic lymph nodes to determine a treatment schedule [21]. EUS helps to avoid unnecessary surgical procedures in 70% of cases [22,23], and improves staging in patients sent for surgical treatment on the basis of only a CT scan result, which is well recognized as unable to detect lymph nodes that are less than 1 cm in diameter [24,25].

The present study demonstrates that EUS-FNA is a highly accurate diagnostic procedure for the evaluation of malignant mediastinal lymph nodes not only in lung cancer, but also in other malignant diseases with a risk of mediastinal lymph node metastases.

Comparable results were found in patients referred for evaluation with suspected inflammatory disease. Some patients had a history of autoimmune disease and immunosuppressant therapy, thus increasing the risk of opportunistic infections, while other patients had an inflammatory syndrome with fever, elevated C-reactive protein (CRP), joint swelling and mediastinal lymph nodes that might be associated with sarcoidosis. Out of 20 patients, 60% were newly diagnosed cases of sarcoidosis or tuberculosis that led to adequate and specific treatment with a good response after 6 months of follow-up.

EUS-FNA is a useful diagnostic procedure with low morbidity and high diagnostic accuracy that renders more invasive procedures unnecessary [26]. As the presence of clustered, well-demarcated, homogeneous, isoechoic lymph nodes with hyperechoic strands is only suggestive, and not specific, of sarcoidosis, it is essential to obtain histological material to make a definitive diagnosis [27]. The reported sensitivity and specificity of EUS-FNA ranges from 82 to 100% and 96%, respectively, in the literature [28–30], which is consistent with our present results.

Incidental mediastinal lymph nodes are a difficult diagnostic challenge. The presence of enlarged lymph nodes with no other clinical symptoms suggests a benign disease, but it is nevertheless important to rule out any treatable malignant or inflammatory condition. Of these diseases, one of the most serious is lymphoma, so it is essential to obtain histological samples for analysis. It is also useful to request flow cytometry and immunocytochemistry to confirm the diagnosis of lymphoma [31]. Given the difficulty of classifying lymphomas on cytology alone, Yasuda et al. [32] have recommended the use of a 19-gauge needle to allow an adequate diagnosis. Their diagnostic accuracy for EUS-FNA of mediastinal lymph nodes with changes of unknown origin was 89 to 90%, comparable to our present results [32,33].

Another aim of the present study was to determine whether or not there was a difference between results obtained with the standard (22-gauge) versus larger (19-gauge) needle. This issue has previously been investigated in other, non-randomized studies [34,35], and found no differences between the two types of needle. The present study also found no statistically significant differences between the two sizes (19-gauge vs 22-gauge), but it should be borne in mind that the two groups were not homogeneous (58 vs 20 patients), and that all the patients with non-contributory results had EUS-FNA using the 22-gauge needle. A prospective, blinded, comparative study of mediastinal lymph nodes is required to settle the question.

In terms of safety, it is well known that EUS-FNA carries a low procedure-related risk of morbidity and a risk of complications of around 1 to 2% [36,37]. Most of the reported complications were the consequence of FNA of pancreatic cysts, with the most common complication being pancreatitis [38–40]. In the mediastinum, the most serious risk is...
mediastinitis following FNA of cystic lesions, not the lymph nodes [41,42].

Conclusion

We conclude that EUS-FNA is a safe and accurate diagnostic procedure for the evaluation of mediastinal lymph nodes not only for malignancy, but also for inflammatory diseases and incidental conditions. Although there is no significant difference in FNA diagnostic accuracy with 19-gauge versus 22-gauge needles, it may be worthwhile to consider the use of a 19-gauge needle when there is a risk of non-contributory results that would expose the patient to either a second procedure or more aggressive intervention.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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