RESULTS AND CLINICAL IMPACT OF EUS-FNA. RESULTS OF 11 YEAR EXPERIENCE IN MORE THAN 1500 PATIENTS.

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ABSTRACT

Background:
Endoscopic ultrasonography (EUS) is an established method for staging gastrointestinal malignancies. EUS in conjunction with fine needle aspiration (FNA) may overcome some of the specificity problems associated with EUS in distinguishing benign from malignant lesions. To date, a large prospective evaluation has not been reported describing the accuracy and the safety of EUS-FNA.

Methods:
A total of 1544 patients patients who had undergone EUS-FNA over a 11-year period were prospectively included in the study. In all patients the results of the biopsies were later confirmed by surgical exploration or laparoscopy, or by clinical follow up of the patient. All complications from the procedure were recorded.

Results:
The sensitivity, specificity, positive predictive value, negative predictive value and the accuracy of EUS-FNA for the diagnosis of a malignancy were 84.6%, 98.4%, 99.6%, 54.7% and 86.9% respectively. EUS-FNA allowed a diagnosis and avoided invasive techniques such as mediastinoscopy, laparoscopy or laparotomy in 43.9% of patients. Overall, EUS-FNA modified therapeutic decision in 70.1% of patients. Complications occurred 15 patients (0.97%).

Conclusions:
These results suggest that EUS-FNA is highly accurate in diagnosing suspected malignancy. EUS-FNA is a relatively safe technique. In more than two-thirds of the patients EUS-FNA modified the therapeutic decision.
INTRODUCTION

Endoscopic placement of the ultrasound transducer immediately adjacent to the area of interest has allowed higher ultrasound frequencies to be used permitting greater spatial resolution. This in turn has provided anatomical detail that can not be obtained with standard transabdominal ultrasound and CT scan. As an extension of this imaging, several case series have described employing EUS in conjunction with FNA to sample lesions within and adjacent to the gastrointestinal tract (1-10). This promising technique allows cytologic confirmation of suspected malignancy. Moreover, in several of these described cases, biopsied lesions were not identified by CT scanning. This added ability to perform FNA under EUS guidance may overcome some of the specificity problems associated with EUS in distinguishing benign from malignant lesions (e.g. lymph nodes, pancreatic masses, and gastric ulcers. This report details a large, single center experience of patients undergoing EUS-FNA for primary diagnosis, staging and/or follow-up purposes.

PATIENTS AND METHODS:

Patients:
A total of 1544 patients (904 male, 640 female) had one or more EUS-FNA between November 1991 and September 2002. The age of the patients ranged from 17 to 88 years (median: 67.2) The EUS-FNA indications were the following: 534 patients with Pancreatic mass, 363 with mediastinal mass or mediastinal lymph nodes, 245 with celiac lymph nodes, 121 with peri-rectal masses or lymph nodes, 104 with hepatic metastases, 63 with large gastric folds with negative endoscopic biopsies, 68 with pleural effusion or ascitis, 32 with sub-mucosal tumors, 11 with left adrenal gland masses and 3 with gall-bladder tumors. Eighty two percent of these exams were performed on an out patient basis.

Equipment:
Although it is possible to perform EUS-FNA with both types of equipment (radial or linear, sector-based), the technique of biopsy with the radial system is technically more difficult and more dangerous, as it is impossible to completely follow the biopsy needle as it comes out of the operator channel and to guide it into the lesion.
Linear sector-based endoscopic ultrasound scope comes equipped with a small diameter convex electronic probe. This is a fibre optic device with a 60° field of vision and depending on the particular instrument, has an operating channel diameter ranging from 2 to 3.8 mm. through which accessories can be passed. It is possible to carry out guided biopsies with this type of sector-based probe. This is done by following the biopsy needle at the exit of the operator channel and guiding it into the lesion. This is possible because the ultrasound beam is emitted parallel to the axis of the endoscope and not perpendicularly as in radial ultrasound endoscopes.
There are now 2 series of linear electronic ultrasound endoscopes that can be used to perform FNA.

A/ PENTAX-HITACHI

Several devices are available: the FG 34-X (2 mm working channel)[Fig 1], the FG 38-X (3.2 mm operating channel); these 2 devices are equipped with the same ultrasound probe. FG 36 X (2.4 mm working channel) and EG 38UT[fig 2] (3.8 mm working channel) also equipped with an elevator which is very convenient for difficult EUS guided biopsy (as in the uncinate process of the pancreas) or for therapeutic procedures (as pancreatic pseudocyst drainage). This probe is sector-based and operates at 3 frequencies (5, 7.5 and 10MHz) connected with the 6500 Hitachi-US Machine. It is also possible to use a colour doppler or an angio-doppler imager with this type of probe.

B/ OLYMPUS

Olympus has developed 2 linear electronic ultrasound endoscope (GF UC30P with a 2.7 mm working channel) fitted with a 7.5 and 12.5 MHz frequency probe and a colour Doppler imager, but the absence of lower frequencies inhibits the penetration of the ultrasound deeper and may render biopsies more
difficult, particularly for deep seated lesions such as some small lymph nodes. The second EUS scope is an interventional device (GF UCT30) with a large working channel of 3.7 mm and an elevator.

The NEEDLE

Several types of needle of different lengths and calibre have been used: 25 gauge/5 cm, 22-gauge/5 cm, 22 gauge echo-tip/6 cm (adjustable). The common problem with all these first prototypes was the risk of perforation of the operating channel. Two types of needle are now commercially available that no longer carry this risk. These are the Vilmann-Hancke needle (11) manufactured by Mediglobe Company (Gassau-Germany) and the Wilson-Cook needle. Both these needles are made from a Teflon-coated shaft partly made of metal. Their particular feature is a manual control screwed onto the endoscope, which has a brake preventing any manipulation of the needle when it is being inserted into the operating channel. They take 22 gauge needles of between 8 and 12 cm in length. The advantage of the Wilson-Cook needle is that it is entirely disposable while the metal reinforced shaft and the needle control of the GIP are reusable. But after it has been used several times, the metal reinforced channel has a tendency to get longer (the metallic spirals stretch) and cause the needle to penetrate when performing a biopsy across the wall of the digestive tract, which could lead to a risk of the needle being stuck in the lesion. Recently, Mediglobe manufactures a new disposable 19 and 22 Gauge needles. Wilson-Cook company offers more variety in terms of size of the needle (19, 22 and 25 gauge) and different sheaths (metallic or Teflon). More recently a core-biopsy needle (Quick-Core needle) has been approved by FDA.

Technique:

EUS-FNA was performed after a detailed EUS examination while the patient lying down on their left side. All the procedures were performed under conscious (midazolam - pethine combination) or deep (propofol) sedation. The FNA was done in the following sequence: The lesion is positioned on the needle's exit path.

Then stylet is withdrawn and the needle is inserted into the tumour (Fig 3). The operator can visualize the tip of the needle by ultrasound enabling its correct position in the lesion to be aspirated. The sample is obtained by aspirating with the aid of a 20 ml suction syringe as the needle makes to-and-fro movements within the tumour. One to three passages are usually necessary in order to obtain an adequate sample. It is currently possible to obtain micro-fragments of tissues (Fig 4) in about 90% of cases with the Vilmann-Hancke type of needle, which is 22 gauge and 12 cm long. The micro-biopsies were retrieved in the following manner: a) the entire sample contained within the needle is withdrawn using a foam stylet that is introduced into the needle. b) the sample is then placed in formaldehyde or Cytolit then completely enclosed in paraffin wax.

In contrast to american teams, we do not routinely administer antibiotics except for trans rectal EUS-FNA and cystic pancreatic lesions. At the end of the examination, patients were monitored for at least three hours. Relative contraindications for the FNA were the size of lesion below 5 mm, depth of the lesion >6-7 cm compared with the probe and a blood clotting problem (PT < 60%, platelets < 80,000/mm³)

RESULTS

The main indications for the EUS-FNA are on table 1. In all patients the results of the biopsies were later confirmed by surgical exploration or laparoscopy, or by clinical follow up of the patient. The sensitivity, specificity, positive predictive value and negative predictive value EUS-FNA for the diagnosis of malignancy were respectively 84.6 %, 98.4 %, 99.6 %, 54.7 %. The overall accuracy of EUS-FNA was 86.9 % (Fig 5).

In sub-groups analysis, EUS-FNA yielded a diagnosis in 489 out of a total of 534 patients with solid lesions of the pancreas (cystic lesions of the pancreas were not included in the current study).
Among the 489 patients who had a positive FNA, 331 patients had adenocarcinoma, endocrine tumor in 76 cases, pancreatic metastasis in 28 cases, pancreatic abscess in 17 cases, pancreatic sarcoma in 4 cases, a primitive pancreatic lymphoma in 5 cases and a squamous cell carcinoma of the pancreas in 3 cases. For the solid tumors of the pancreas, the sensitivity, specificity, accuracy of EUS-FNA were respectively 89.8 %, 98.8 % and 90.1 % (Fig 6). Finally, EUS-FNA was not contributory in 45 patients and were surgically explored. The pathologic examination of the resected specimen showed adenocarcinoma in 28 cases, endocrine tumor in 3 cases, pancreatic sarcoma in 1 case and in 13 cases a nodule of chronic pancreatitis.

A total of 729 patients had undergone EUS-FNA for variety of lesions, which included mediastinal or celiac lymph nodes or peri-rectal masses. The overall sensitivity, specificity and accuracy of EUS-FNA for the diagnosis of malignancy were respectively, 92.8 %, 100 % and 91.8 %. The submucosal tumors and large gastric folds which represented a total of 85 patients were sub-divided into the following groups- large gastric folds with negative endoscopic biopsy (63 patients), esophageal submucosal tumor (16 patients), gastric submucosal tumor (10 patients). Sensitivity, specificity and accuracy for the diagnosis of malignancy of these lesions, were respectively 71.8 %, 100 % and 62.3 %.Finally, for hepatic lesions, EUS guided FNA was diagnostic in 98 out of a total of 104 lesions.

Overall, EUS-FNA was diagnostic in 678 out of 1544 patients (43.9 %) and avoided a more invasive diagnostic procedure such as mediastinoscopy, laparoscopy or laparotomy. Therapeutic decision-making was modified by EUS-FNA in 161 patients with malignancy of the esophagus, the stomach, the rectum or the pancreas. It was in that case about lymph nodes situated at distance in sites considered as metastases according to the TNM classification; or of the discovery of small secondary hepatic metastasis unnoticed on CT scan.

EUS-FNA results influenced the treatment decisions in 242 patients with pancreatic lesions found on other imaging modalities. Ninety-one were found to have adenocarcinoma that was not diagnosed on CT or MRI and in 151 who had pancreatic masses, EUS-FNA ruled out adenocarcinoma (76 endocrine tumors, 28 metastases, 25 chronic pancreatitis, 17 abscess, 4 sarcomas, 5 lymphomas and 3 squamous cell carcinomas). Overall, EUS-FNA has modified diagnosis and/or therapeutic decision in 1081 patients of the total 1544 cases (70.1 %).

Complications occurred in 15 patients (0.97%): fever in 9 patients, acute pancreatitis in 5 and one had bleeding. Only one of the 5 patients who developed pancreatitis required hospitalization for more than a week and was complicated by the formation of a pseudo-cyst. All the febrile episodes responded to empiric antibiotic therapy (combination of amoxicillin with clavulinic acid and Ciprofloxacin). Finally, bleeding consisted of wirsungorrage after EUS-FNA of a pancreatic tumor. The patient had no hemodynamic compromise, required no blood transfusion and stopped spontaneously.

DISCUSSION

The most important question is to know if performing EUS-FNA will modify the therapeutic and diagnostic decision-making. The best results were obtained for lymph nodes, anastomotic recurrences, extrinsic wall compression and pancreatic tumors. Interestingly, for the solid lesions of pancreas, the yield of EUS-FNA is best for lesions measuring < 4 cm in diameter. This may be due to the fact that more voluminous cancers are necrotic and/or with fibrosis resulting in lower diagnostic yield.

The initial works concerning esophageal cancers (14,15) have shown that it was important to obtain a lymph node biopsy guided under EUS when the node was a distant lymph node (cervical or celiac LN). The histologic confirmation of metastasis in the LN will then result in upstaging of the tumor and surgery could be avoided, as it will not improve survival. EUS-FNA seems indispensable for pancreatic tumors, notably for those only visible on EUS. In addition, the transgastric or transduodenal approach will decrease the risk of seeding and for tumors of the head of the pancreas the
The site of puncture will be resected during the Whipple procedure. Finally, the confirmation of an anastomotic recurrence, often visible only on EUS, appears promising particularly for anastomotic recurrences of colorectal cancers (3). The confirmation of this recurrence implies often an aggressive therapeutic approach (radiation therapy ± chemotherapy followed most often by surgery (abdomino-perineal resection or sub-total colectomy). On the other hand, this aggressive approach is not to apply ipso facto on anastomotic recurrences of esophageal or gastric cancers.

The obtaining of a «micro - biopsy» allows a histologic diagnosis more precise and a precise tissue characterization in approximately 80% of cases for the diagnosis of malignancy. Furthermore, some teams recommend the presence of a pathologist in the endoscopic room so as to insure the good quality of the specimen.

Results of the literature show a global sensitivity of the technique varying between 76 and 91%, a specificity of 84 to 100% and an accuracy of 78 to 94%. Results of a prospective study (12) regrouping 457 patients from 4 centers (Indianapolis, Copenhagen, Marseilles and Orange in California) (Table II) have been published. In this study, the sensitivity of the puncture was significantly better for lymph nodes (94%) and extra - luminal masses (86%) compared to parietal lesions (sub-mucosal tumors and large gastric folds) (61% p<0.001). On the other hand, there was no difference in specificity in these 3 groups of lesions. Another multicenter study (13) published by the same center regarding the EUS-FNA of pancreatic tumors. This study included 164 patients, the average diameter of the lesion varied between 28.5mm and 41.3 mm. The sensitivity, the specificity, the positive predictive value and the negative predictive value for the diagnosis of cancer of the pancreas were respectively 83%, 90%, 100% and 80% with accuracy of 85%.

For solid pancreatic masses, the impact of the EUS on the therapeutic decision is now well established in the literature (16,17,18,19,20). Nevertheless, in our series, we show that this impact is rather important because it concerns 268 of 534 patients presenting a pancreatic mass, notably by showing an other histology than adenocarcinoma (endocrine tumor, pancreatic metastasis), but especially, it allowed to confirm the diagnosis of pancreatic cancer in 91 patients whose tumor had not been diagnosed with the conventional techniques (Ct and MRI).

In our experience, EUS-FNA appears to be very safe (5 minor complications in 1554 biopsies, of which 3 were directly attributable to the puncture: 2 episodes of fever which promptly responded to antibiotic treatment and 1 hemorrhage due to the puncture of a cyst of the pancreas) and is less invasive compared to mediastinoscopy or a thoracotomy, for the diagnosis of mediastinal masses or lymph nodes of unknown origin. This technique is an obvious alternative to diagnostic laparoscopy for celio-mesenteric lymph nodes not accessible to a biopsy under CT-scan or US guidance.

It seems so today that EUS guided biopsy is the best technique to obtain a cytological specimen of a pancreatic mass and that it also has a important impact on the therapeutic decision, notably in case of adenocarcinoma not seen on other imaging modalities. Being this at present mattering because of the development of preoperative protocols of radio-chemotherapy for resectable tumors.

In conclusion, EUS-FNA is a simple and safe technique once proficiency in linear sector-based EUS is achieved. At present, it is possible to obtain an adequate sample in 80 to 85 % of the cases allowing a tissue characterization. The best indications are the mediastinal lymph nodes and masses, celiac lymph nodes, pancreatic masses and extrinsic compression of the GI wall, as well as the small lesions of the left lobe of the liver. Nevertheless, before performing this invasive procedure, it is always necessary to ask the same question- will the EUS-FNA change the therapeutic decision-making?
REFERENCES


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TABLE 1: INDICATIONS FOR EUS-FNA.

A. Main Indications:

- Mediastinal masses and lymph nodes
- Celiac lymph nodes (< 3 cm)
- Extrinsic compression of the gastrointestinal wall
- Pancreatic masses (< 4 cm)
- Anastomotic recurrence

B. Miscellaneous Indications:

- Submucosal tumours (using 19G needle)
- Large gastric folds with negative endoscopic biopsies

TABLE 2: EUS GUIDED BIOPSY OF PANCREATIC MASSES: REVIEW OF THE LITERATURE

<table>
<thead>
<tr>
<th>AUTHORS/YEAR</th>
<th>Ref.</th>
<th>Nb Pts</th>
<th>ACCURACY</th>
</tr>
</thead>
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<tr>
<td>Giovannini (1995)</td>
<td>4</td>
<td>43</td>
<td>79.1%</td>
</tr>
<tr>
<td>Chang (1996)</td>
<td>13</td>
<td>164</td>
<td>83%</td>
</tr>
<tr>
<td>Buthani (1998)</td>
<td>1</td>
<td>57</td>
<td>85%</td>
</tr>
<tr>
<td>Wiersema (1997)</td>
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<td>124</td>
<td>90%</td>
</tr>
<tr>
<td>Williams (1999)</td>
<td>10</td>
<td>144</td>
<td>85%</td>
</tr>
<tr>
<td>Giovannini (1999)</td>
<td>17</td>
<td>231</td>
<td>92.6%</td>
</tr>
<tr>
<td>Palazzo (2000)</td>
<td>20</td>
<td>100</td>
<td>93%</td>
</tr>
</tbody>
</table>
Figure 1: FG 34X and Wilmann Needle

Figure 2: EG 38UT with a large working channel of 3.8 mm

Figure 3: EUS guided biopsy of a pancreatic mass

Figure 4: Micro-core obtained using EUS guided biopsy of pancreatic adenocarcinoma

Figure 5: Accuracy, Sensitivity, specificity, positive predictive value and negative predictive value of EUS-FNA of 1544 patients.

Figure 6: Results of EUS guided biopsy of 542 pancreatic solid masses
FIGURE 5

<table>
<thead>
<tr>
<th>Sensibility</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>84.8</td>
<td>98.6</td>
<td>99.6</td>
<td>54.8</td>
<td>87.1</td>
</tr>
</tbody>
</table>

Accuracy, NPV, PPV, Specificity, Sensibility
FIGURE 6: T sousmuqueuses + Gros plis gastriques