Clinical Impact of Endoscopic Ultrasound-Guided Fine Needle Aspiration Biopsy in Patients with Upper Gastrointestinal Tract Malignancies. A Prospective Study

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Background and Study Aims: **Several studies have evaluated the accuracy of endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) in the upper gastrointestinal tract, but so far no studies have specifically evaluated the clinical impact of EUS-FNAB in upper gastrointestinal tract cancer patients. In this consecutive and prospective study, EUS-FNAB was only performed if a positive malignant finding would change the therapeutic strategy.**

Patients and Methods: **Between 1997 and 1999, 307 consecutive patients were referred for EUS with a diagnosis or strong suspicion of esophageal, gastric or pancreatic cancer; 274 patients were potential candidates for surgical treatment and had EUS. According to predefined impact criteria, 27 % (75/274) of the patients had EUS-FNAB for staging or diagnostic reasons.**

Results: **The overall clinical impact of EUS-FNAB was 13 %, 14 %, and 30 % in esophageal, gastric, and pancreatic cancer, respectively. The staging-related clinical impact was similar for all three types of cancer (11–12.5 %), whereas the diagnosis-related impact was highest in pancreatic cancer patients (86 %). EUS-FNAB was inadequate in 13 % and gave false-negative results in 5 %. The overall sensitivity, specificity and accuracy for EUS-FNAB were 80 %, 78 % and 80 %, respectively. No complications related to the biopsy procedure were seen.**

Conclusions: **If EUS-FNAB was performed only in cases where a positive malignant result would change patient management, then approximately one out of four patients with upper gastrointestinal tract cancer would require a biopsy. With this approach the actual clinical impact of EUS-FNAB ranged from 13 % in esophageal cancer to 30 % in pancreatic cancer. EUS-FNAB plays a limited, but very important clinical role in the assessment of upper gastrointestinal tract cancer.**

Introduction

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) has been used for evaluating more than 20 different types of lesion in or adjacent to the upper gastrointestinal tract [1]. Observations so far have indicated that EUS-FNAB is a safe procedure, and the reported increased use of EUS-FNAB for both diagnostic as well as therapeutic purposes has further stimulated interest in EUS-FNAB. The major part of EUS-FNAB literature has described evaluation of the ability to diagnose malignant (and benign) tumors and malignant spread to lymph nodes [2–12]. The reported sensitivities and specificities are high, especially for the evaluation of malignant lymph nodes [2, 3, 8, 13]. However, only a few studies have tried to monitor the clinical impact of EUS-FNAB. To our knowledge there has been no series so far, specifically dedicated to evaluating the impact of EUS-FNAB, if biopsies were performed only in patients where a positive finding (i. e. malignant cells) would change the therapeutic strategy.

In this prospective study we report the clinical impact in 307 consecutive cancer patients who underwent pretherapeutic EUS, and in whom EUS-FNAB was carried out only if a positive result would change the therapeutic strategy.

Patients and Methods

Between July 1997 and September 1999, 307 consecutive patients were referred to our department with a diagnosis or strong suspicion of esophageal, gastric, or pancreatic cancer. The patients were referred for pretherapeutic staging and assessment of resectability, by means of endoscopic ultrasonography (EUS). A total of 117 patients with esophageal cancer, 68 patients with gastric cancer and 122

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Table 1 Criteria for performing endosonographic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB)

Criteria for diagnostic EUS-FNAB Cases where repeated endoscopic and/or abdominal ultrasound-guided and/or CT-guided biopsies had been unable to provide a diagnosis of malignancy. Also where the securing of an exact diagnosis was considered relevant for the subsequent treatment
Criteria for staging EUS-FNAB Cases where a suspected metastatic lesion had been located during EUS, and where a biopsy finding of malignancy would change the subsequent treatment. Cases were also included where abdominal ultrasound and/or CT had shown suspected metastatic lesions but could not provide histological proof

patients with pancreatic cancer were scheduled for EUS examination, but 33 patients (10.7%) were excluded because of poor general condition (n = 21), recurrence of upper gastrointestinal tract cancer (n = 9) or a wrong diagnosis (n = 3). Thus, an overall total of 274 patients, with esophageal cancer (n = 109), gastric cancer (n = 64) or pancreatic cancer (n = 101) entered the study.

The assessment of resectability [14], using EUS, was carried out according to the standard written procedure of the Department, and the EUS staging procedure was performed according to the 1997 UICC TNM staging system. EUS-FNAB was carried out only when considered to be clinically relevant according to the departmental routines (Table **1**); thus EUS-FNAB was only attempted in those situations where a positive (malignant) answer would have a clinically relevant impact on the subsequent treatment of the patient.

All EUS examinations were performed using the Pentax FG-36 or FG-38UX echo endoscope, and EUS-FNAB was performed using a 22G dedicated needle system (GiP Medizin Technik, Germany). No cytopathologist was present during EUS-FNAB, and the number of punctures was not recorded. When the endoscopist felt assured that macroscopic cell clusters or tissue had been obtained, the biopsy procedure was ended, reflecting the standard biopsy procedure in our department. No prophylactic antibiotics were given.

Results

Esophageal Cancer

A total of 109 patients (88 men, 21 women; median age 65, range 43–80) with esophageal cancer were evaluated during the study period. Of these, 106 patients had a positive diagnosis of cancer, whereas two patients with esophageal tumors had no definite diagnosis prior to EUS. The EUS examination was incomplete in one patient (0.9%), due to technical problems.

During the EUS examination, in 18 patients (16.5%) one or several metastatic (M1) lesion(s) were suspected. In 14 cases (13%) the lesion was biopsied. With regard to the remaining four cases, two patients were readmitted for abdominal ultrasound-guided biopsies because of obvious and relatively large liver lesions, which had not been suspected during the initial ultrasound. The repeated ultrasound with biopsy confirmed the presence of liver metastases. One patient had no EUS-FNAB as EUS demonstrated concomitant involvement of the aorta. In another patient EUS demonstrated a metastatic lesion located behind the pulmonary artery. The lesion was not accessible by the esophageal route, but computed tomography (CT)-guided biopsy confirmed the metastatic lesion. Table **2** shows the results of the EUS-FNAB in the esophageal cancer patients where a positive biopsy would have had therapeutic implications.

The material aspirated during EUS-FNAB was adequate for analysis in all cases. A total of 12 patients (11%) had EUS-FNAB confirmation of distant malignant spread, two patients (1.8%) had a diagnosis of esophageal cancer and distant spread was correctly ruled out in one patient. One EUS-FNAB from a lymph node at the celiac axis was suspected of malignancy during cytopathological examination, but no definite diagnosis could be made. Surgery revealed a malignant lymph node. EUS-FNAB had an impact on the staging procedure in 12% (13/108) of the patients, and in 100% (2/2) of the patients concerning the malignant diagnosis. If patients who had M1 disease suspected from CT and/or ultrasound were excluded, the impact of EUS-FNAB regarding both staging and diagnosis was 10% (11/108). None of the lesions suspected on CT and/or ultrasound could be histopathologically verified by these modalities.

Table 2 EUS-FNAB results in esophageal cancer patients (n = 16)

	Location	EUS-FNAB result			Suspected on CT and/or ultrasound
		Malignant	Benign	Suspected malignant	
Staging (n = 14)	Celiac axis lymph nodes	6	1	1*	1
	Para-aortic lymph nodes	3	–	–	2
	Liver lesion	2	–	–	–
	Pleural fluid	1	–	–	–
Diagnostic (n = 2)	Esophageal wall	2	–	–	–

CT, computed tomography. * Malignant (surgery).

Table 3 EUS-FNAB results in gastric cancer patients (n = 14)

	Location	EUS-FNAB result			Suspected on CT and/or ultrasound
		Malignant	Benign	Inadequate	
Staging (n = 12)	Mediastinal lymph nodes	3	–	2*	2
	Para-aortic lymph nodes	5	–	–	2
	Ascites	–	1	–	–
	Liver lesion	–	–	1*	–
Diagnostic (n = 2)	Gastric wall	1	1*	–	–

*Malignant (surgery).

Table 4 EUS-FNAB results in pancreatic cancer patients (n = 45)

	Location	EUS-FNAB results		
		Malignant	Benign	Inadequate
Staging (n = 20)	Lymph nodes (n = 13)	6	3 (1*, 2**)	4*
	Liver lesions (n = 5)	4	–	1**
	Ascites (n = 1)	1	–	–
	Retroperitoneal tumor infiltration (n = 1)	1	–	–
Diagnostic (n = 25)	Pancreas (n = 22)	15	5 (2*, 3**)	2 (1*, 1**)
	Duodenum (n = 3)	3	–	–

* Malignant on final evaluation; ** Benign on final evaluation.

There were no false-positive results and no complications of the EUS-FNAB procedure.

Gastric Cancer

A total of 64 gastric cancer patients (39 men, 25 women; median age 64.5, range 36–79) were included in this part of the study, and according to the biopsy criteria (Table **1**) 12 patients (19%) had EUS-FNAB for staging reasons and two patients (3%) for diagnostic reasons. The results are listed in Table **3**.

Eight gastric cancer patients (12.5%) had confirmation of M1 disease by EUS-FNAB, and malignant ascites was correctly ruled out in one patient (1.6%). In one patient (1.6%) a positive diagnosis of gastric cancer was obtained by EUS-FNAB, whereas the second diagnostic EUS-FNAB gave a false-negative result as the patient turned out to have a gastric cancer during surgery. The aspirated material was inadequate for analysis in three cases (21%). Thus, EUS-FNAB had a clinical staging impact in 14% (9/64) of the patients and a diagnostic impact in 50% (1/2). When patients were excluded in whom distant spread was suspected from CT and/or ultrasound findings, the actual clinical impact of EUS-FNAB was 8% (5/64).

None of the lesions suspected during CT and/or ultrasound could be biopsied and verified using these modalities. There was no false-positive EUS-FNAB result and no complications related to the biopsy procedure.

Pancreatic Cancer

During the study period 204 patients were admitted for EUS with diseases related to the pancreas. Pancreatic cancer was the primary diagnosis in 122 of these patients, but as 21 patients (17%) were in a physical condition which was too poor to allow surgery, 101 patients (61 men, 40 women; median age 62, range 36–76) entered this part of the study. EUS was incomplete in one patient (lack of cooperation) (1%), and in one patient (1%) a prior B-2 resection prevented visualization of the pancreatic tumor. In the remaining 99 patients EUS-FNAB was considered relevant in 45 patients (45%). Of these, 25 patients had a diagnostic EUS-FNAB; 22 lesions were located in the pancreas and three lesions in the duodenum. The remaining 20 patients had a staging EUS-FNAB: 13 from lymph nodes, five from liver lesions, one aspiration of ascites and one biopsy from suspected retroperitoneal tumor infiltration. The EUS-FNAB results are listed in Table **4**.

The material aspirated during EUS-FNAB was adequate for analysis in 84% (38/45) of cases. In 12% (12/99) of the patients EUS-FNAB confirmed a metastatic lesion, but failed to do so in 5% (5/99) because of four inadequate biopsies and one false-negative biopsy. EUS-FNAB confirmed a malignant diagnosis in 86% (18/21) within the diagnostic group, whereas three patients were correctly assessed as having a benign condition, based on EUS-FNAB and follow-up. In two cases the EUS-FNAB results were false-negative, and in the two cases of inadequate sam-

pling, one patient turned out to have a malignant tumor and one patient a benign tumor of the pancreas.

The clinical impact of EUS-FNAB for staging purposes was 12% (12/99) and 86% (18/21) for malignant diagnostic purposes. None of the lesions biopsied for staging purposes were visualized during ultrasound or CT.

There were no false-positive EUS-FNAB results and only one minor complication of the biopsy procedure (mild, acute pancreatitis).

Overall Results

The clinical impact of EUS-FNAB in esophageal cancer, gastric cancer and pancreatic cancer is displayed in Table **5**. Based on the criteria for EUS-FNAB (Table **1**), 27% (75/274) of the patients who entered the study had an EUS-FNAB. The overall sensitivity, specificity and accuracy for the EUS-FNAB procedure were 80%, 78% and 80%, respectively.

EUS-FNAB was considered inadequate in 13% (10/75) and to give false-negative results in 5% (4/75).

Discussion

Three important studies including almost 1000 patients have demonstrated high sensitivity and specificity of EUS-FNAB, especially with regard to lymph nodes and extraluminal masses [2,3,8]. The EUS-FNAB procedure seems safe, with a complication rate between 0.3 and 2.0%. The main purpose of these studies was not primarily to assess the clinical impact of EUS-FNAB, but to evaluate the accuracy of EUS-FNAB findings, and secondly to estimate the impact on clinical decision making based on these results. The conclusions in these studies correlate well with the findings of numerous other FNAB studies [4–7,9] indicating that there is sufficient evidence for the safety and feasibility of using EUS-FNAB on a routine basis. However, less information is available regarding issues such as indications and the primary clinical impact of EUS-FNAB [4,9,16]. The variation in treatment strategies, between institutions and between countries, may explain the lack of EUS-FNAB impact studies. An example is the presence of a malignant lymph node at the celiac trunk diagnosed by EUS-FNAB: Although such a lymph node is considered to be M1 disease in mid-esophageal cancers, this finding may not necessarily have an impact on the treatment strategy. If the tumor itself is considered nonresectable, then the lymph node has only limited clinical relevance. Adjuvant treatment protocols, palliative considerations or local surgical preferences may also make the measurement of the clinical impact of EUS-FNAB highly variable and uncertain.

It is generally agreed that EUS-FNAB should not be performed unless the cytopathological or histopathological result of the puncture may influence the diagnostic or therapeutic strategy [9,10,15,17]; i.e. performance of EUS-FNAB is considered to be contraindicated if the result will not affect management of the patient.

In this study we have focused on the ability of EUS-FNAB to provide pathological evidence in selected patients, where such evidence would change patient management. When EUS-FNAB was carried out for staging and diagnostic purposes in these circumstances, the total clinical impact of EUS-FNAB ranged from 13% in esophageal cancer patients to 30% in pancreatic cancer patients. However, if the staging issue only was addressed, then the impact of EUS-FNAB was similar (11%, 12.5% and 12%) for the three different types of cancer patients. The increased "total clinical impact" of EUS-FNAB in pancreatic cancer (Table **5**) was due to the larger number of diagnostic biopsies which partly could be attributed to the need for a specific histopathological diagnosis in pancreatic cancer patients who were potential candidates for neo-adjuvant treatment protocols.

A 15% clinical impact of EUS-FNAB was noted as a maximum in esophageal cancer patients in the present study. Giovannini et al. evaluated the clinical impact of EUS-FNAB in esophageal cancer patients in a study where the conditions resembled those of our study [12]: If a visualized lymph node was considered to be distant, it was biopsied regardless of its size, shape and echo features. In that study the clinical management was altered because of EUS-FNAB in 12% (24/198) of the patients; thus, this was quite similar to the impact figures for esophageal cancer and gastric cancer patients in our study. In a consecutive esophageal cancer study where EUS-FNAB detected malignant celiac lymph nodes in 24% (15/62) the actual impact figure would probably also be similar to ours since

Table 5 Clinical impact of EUS-FNAB in esophageal, gastric, and pancreatic cancer patients with a complete EUS examination (n = 271)

Clinical impact	Esophageal cancer		Gastric cancer		Pancreatic cancer	
	n	%	n	%	n	%
Documented metastatic disease	12/108	11	8/64	12.5	12/99	12
Malignant diagnosis	2/2	100	1/2	50	18/21	86
Total clinical impact	14/108	13	9/64	14	30/99	30
Total clinical impact if all biopsies had been adequate and correct	15/108	14	13/64	20	38/99	38

data concerned a mixture of N1 and M1 disease [10]. As noted earlier, some form of clinical impact was seen in the three large EUS-FNAB studies [2, 3, 8], but because of their design no specific or detailed impact figures were available.

EUS-FNAB of lymph nodes seems to have the highest accuracy and, according to the literature, also the highest impact on clinical decision making. In our material EUS-FNAB confirmation of distant lymph node metastasis was possible in 74% of the patients with M1 disease. A sensitivity of only 55% (6/11) regarding distant lymph nodes in pancreatic cancer patients, and the small number of biopsies, may explain the somewhat lower overall sensitivity found for lymph node biopsies when compared with other studies [2, 3, 8, 13].

EUS-FNAB evaluation of lymph nodes, however, is not without obstacles. In the previously described esophageal cancer study, where the influence of EUS-FNAB in the assessment of celiac lymph nodes was evaluated, the celiac area was accessible in 59 patients and 19 patients had positive findings (presence of lymph node(s) larger than 5 mm) [10]. EUS-FNAB results were positive in 15 out of 17 patients who underwent biopsy, giving a confirmed positivity in 88% of cases. In other words, when EUS alone demonstrated the presence of a positive lymph node in the celiac area, then EUS-FNAB was 88% accurate in the verification of positivity, but as the 19 lymph nodes had already been assessed as "endosonography-positive," then the actual clinical benefit of EUS-FNAB would have been limited and probably did not improve accuracy. Similar findings have been demonstrated by others [8], including in the use of EUS-FNAB in the preoperative staging of non-small-cell lung cancer [7, 8], although the impact of EUS-FNAB detection of malignant lymph nodes within the mediastinum seems very high. In the esophageal cancer study [10] seven patients had positive lymph nodes which had not been detected by EUS (false-negative), and all of these lymph nodes had microscopic tumor foci. If these lymph nodes had been detected by EUS, and EUS-FNAB had been carried out, then the overall EUS-FNAB result might have been worse. This study confirms that EUS-FNAB can verify tumor infiltration in lymph nodes, and if cytological/histological verification is necessary because of a potential change of treatment, then EUS-FNAB can provide the necessary documentation, but micro-involvement may preclude a complete stage assessment, as has been demonstrated in earlier studies where EUS-FNAB was not used.

Thus, all lymph nodes, regardless of size, shape and echo features, with potential clinical impact should be subjected to EUS-FNAB. Theoretically, this would include EUS-FNAB of small lymph nodes (smaller than 5 mm) where the accuracy of biopsy tends to decrease [8], as well as of lymph nodes with only minute foci of malignant cells. This may result in a poorer overall EUS-FNAB accuracy compared with most studies presented so far, but could also result in an improved specificity [2].

It is obvious that a benign result from an EUS-FNAB must be used with great caution, even if the aspirated material is sufficient for analysis and harboring cells from the target. Some studies include the results of true benign biopsies, and the exclusion of a malignant tumor or of malignant spread may indeed have a considerable impact on clinical decisions. In the present study an esophageal cancer patient with a benign celiac axis lymph node as well as the true benign findings in the gastric cancer and pancreatic cancer patients were not included in the calculations ('Total clinical impact,' Table **5**) because the benign finding did not change patient management.

Even with the more tangible clinical question of the presence or absence of malignant cells within a pancreatic mass lesion, there is still room for ongoing debate concerning the clinical value of a positive (i.e. malignant) diagnosis. Some surgeons advocate that a pancreatic mass lesion suspected of malignancy should not be subjected to EUS-FNAB if it is resectable; surgery should be performed immediately, accepting the low "risk" of resecting a tumor consisting of pancreatitis. In addition, large nonresectable pancreatic tumors do not need cytologic diagnosis, since this will not change the therapeutic management in these patients unless they are entering experimental treatment protocols which require histological confirmation of malignancy [4, 17]. The study by Chang et al. evaluating the clinical utility of EUS-FNAB in 44 patients illustrates somewhat the difficulties of pancreatic lesions [5]: the need for further diagnostic tests was avoided in 25 patients (57%), where EUS-FNAB had demonstrated pancreatic cancer. With the above argument in mind, this would not have been considered a clinical benefit at some institutions. On the other hand, in the total of 18 patients (41%) who avoided surgery, this decision was based solely on the EUS-FNAB results in 12 patients (27%) and partly influenced by EUS-FNAB findings in six patients (14%). In 30 of 44 patients (68%) EUS-FNAB results affected the clinical decision and both benign and malignant findings were found to be relevant in this regard. In the present study more than half of the EUS-FNAB procedures in pancreatic cancer patients were diagnostic, but although the diagnostic aspect was greater than the staging aspect of EUS-FNAB, only 25% of the pancreatic cancer patients, who were evaluated by EUS with the focus on resectability and stage assessment, needed a diagnostic biopsy.

Thus, the "pancreatic mass problem" may not be solved by EUS-FNAB, but if a pretherapeutic tissue diagnosis is required, or if malignant invasion of lymph nodes is suspected in an otherwise resectable pancreatic mass, then EUS-FNAB should be considered [4–6, 15]. The issue of false-negative EUS-FNAB findings, the potential risk of complications, and the seeding of malignant cells must also be considered when setting up algorithms for the use of EUS-FNAB in pancreatic masses [2, 3, 16]. The use of lar-

ger needles must still be considered experimental, and their implementation must await further technical developments before any conclusions can be drawn [18].

In conclusion, it seems that the presently available clinical impact data of EUS-FNAB based on strict entry criteria are lower in value than should be expected from previous studies. However, the results of EUS-FNAB are very important for the individual handling of these cancer patients, and future indications, including EUS-FNAB-based staging and treatment of other diseases (e. g. lung cancer) and the early detection of recurrence [19], will further underline the considerable impact of this technique. A very low complication profile, and data suggesting that EUS and EUS-FNAB are cost-effective modalities [7, 14, 20] also contribute to establishing EUS-FNAB as an important investigational tool.

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