

The Impact on Clinical Practice of Endoscopic Ultrasonography Used for the Diagnosis and Staging of Pancreatic Adenocarcinoma

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ABSTRACT

Context Endoscopic ultrasonography is considered a highly accurate procedure for diagnosing small pancreatic tumors and assessing their locoregional extension.

Objective To evaluate the impact of endoscopic ultrasonography on the management of pancreatic adenocarcinoma in clinical practice.

Patients Sixty-four consecutive patients (mean age 70.5±11.9 years) hospitalized for staging or diagnosis of pancreatic adenocarcinoma were retrospectively (from January 1995 to November 1997) or prospectively studied (from December 1997 to August 1999).

Setting Group 1 consisted of 52 patients with pancreatic adenocarcinoma which was discovered using computerized tomography scanning and/or ultrasound. Endoscopic ultrasonography was utilized for staging purposes only in patients who were considered to be operable and the tumor to be resectable based on computerized tomography scanning criteria. Group 2 consisted of 12 patients who were diagnosed as having a pancreatic adenocarcinoma using endoscopic

ultrasonography whereas computerized tomography scanning and ultrasound was negative.

Main outcome measures The impact of endoscopic ultrasonography was analyzed on the basis of the number of patients requiring endoscopic ultrasonography as a staging procedure (Group 1) and by evaluating the performance of endoscopic ultrasonography in determining resectability (Groups 1 and 2) based on the surgical and anatomopathological results.

Results Endoscopic ultrasonography was performed in 20 out of 64 patients (31.3%): 8/52 in Group 1 (15.4%) and all 12 patients of Group 2. Endoscopic ultrasonography correctly assessed an absolute contraindication to resection in 11 cases. Resection was confirmed in 8 of the 9 cases selected by endoscopic ultrasonography. The positive predictive value, negative predictive value and overall accuracy of endoscopic ultrasonography for determining resection were 89%, 100%, and 95%, respectively.

Conclusions The impact of endoscopic ultrasonography seems especially relevant for the detection of pancreatic tumors after

negative computerized tomography scanning, and for the prevention of unnecessary laparotomies as complementary staging after ultrasonography and computerized tomography scanning.

INTRODUCTION

With a 0-5% survival at 5 years, the prognosis of pancreatic adenocarcinoma (PA) remains dim and is dramatically affected by a delayed diagnosis and a low resection rate [1, 2]. The situation has not significantly changed over the past 20 years despite the improvement of surgical procedures and the introduction of new imaging techniques such as computerized tomography scanning (CT-scan) [3]. Endoscopic ultrasonography (EUS) is considered the most accurate imaging procedure for the diagnosis of small tumors of the pancreatic area [4] and is usually indicated after ultrasonography (US) and CT-scan to complete locoregional staging and to confirm the resectability of PA [5, 6]. However, the role and influence of EUS in decision-making has not been clearly elucidated in clinical practice. The aim of this study was to evaluate the impact of EUS both as a diagnostic and as a staging procedure in the management of a consecutive series of patients with PA.

METHODS

From January 1995 to August 1999, 64 consecutive patients hospitalized in our unit for PA were retrospectively (from January 1995 to November 1997: n=37) and then prospectively (from December 1997 to August 1999: n=27) evaluated. Retrospectively, the study included only patients in whom PA had been demonstrated after surgical biopsy or fine-needle aspiration. In the prospective part of the study, the selection was based on the association of a clinical course consistent with pancreatic malignancy, elevation of CA19.9 greater than 300 U/mL and the presence of a hypodense (spiral CT-scan) or hypoechoic (US-EUS) heterogeneous, poorly delimited pancreatic tumor where adenocarcinoma was suspected in the absence of any history of chronic pancreatitis [6, 7, 8, 9]. Thereafter, only patients with histologically proven PA, as defined above, were definitively included. Patients with ampullary carcinoma or those referred for palliative management of the PA were excluded. No significant differences were noted in clinical characteristics between the retrospectively (n=37) and the prospectively (n=27) studied cases (Table 1). Patients were followed for a minimum of 6 months or until death.

EUS was indicated in our unit either for staging PA (Group 1) or for screening for pancreatic tumors (Group 2). EUS was performed as a complementary staging procedure (Group 1)

Table 1. Comparison of retrospectively and prospectively studied patients with pancreatic adenocarcinoma with regard to of the different clinical parameters. No significant statistical difference was observed for the different parameters.

	Retrospective (n=37)	Prospective (n=27)	P value
Age (mean±SD)	70.9 ± 12.0	69.9 ± 12.1	0.744
Gender			0.545
Males	22 (59.5%)	14 (51.9%)	
Females	15 (40.5%)	13 (48.1%)	
Tumor localization			0.118
Head	27 (73.0%)	24 (88.9%)	
Other	10 (27.0%)	3 (11.1%)	
Resection rate	3 (8.6%)	5 (18.5%)	0.247
Median survival time (months)	2.5	2.5	-
1-year survival (%)	7.1	4.6	0.930

only in operable patients and in the case of a resectable tumor as defined by US-color Doppler and enhanced spiral CT-scan examinations [10]. EUS was performed as a screening procedure for pancreatic tumors (Group 2) in all patients with symptoms compatible with a pancreatic tumor, after US and spiral CT-scan examinations were interpreted as normal.

All EUS procedures (Olympus EUM 20) were performed under general anesthesia (midazolam, propofol) by the same operator. During examination, the following items were carefully described: location and size of the tumor, invasion of locoregional organs and vascular axis, existence and location of lymph nodes suspected to be malignant, existence of left liver metastasis and signs of peritoneal carcinomatosis, based on recognized criteria [6, 11].

Surgical resection was judged inappropriate in the case of visceral metastasis, distant lymph node metastasis, arterial involvement (celiac trunk, common hepatic artery, superior mesenteric artery and splenic artery) or visible neoplastic thrombus of the venous axis (portal vein, superior mesenteric vein, splenic vein). Suspicion of parietal invasion of the venous axis constituted a relative contraindication to resection and was discussed with the surgeon.

We analyzed the number of tumors which were considered unresectable according to EUS criteria and which were then confirmed at

laparotomy. These cases were defined as potentially unnecessary laparotomies (i.e. laparotomies that could have been avoided) except in the situation of duodenal involvement in which palliative surgery was indicated.

Definitive staging of the tumor was assessed histologically (curative resection), cytologically (US-guided needle biopsy of a liver metastasis or peritoneal carcinomatosis) or operatively (palliative surgery) according to the AJCC 1997 classification (Table 2) [12]. Resection was considered complete when tumor margins were free of neoplasia and no lymphatic or perivascular invasion was visualized histologically.

The impact of EUS on the management of PA was determined by the following criteria: the percentage of all patients with PA requiring EUS, the percentage of patients with PA requiring EUS as a staging procedure, the number of tumors diagnosed by EUS only and the number of unnecessary laparotomies. Furthermore, a possible benefit of EUS in diagnosing small tumors was evaluated by comparing the proportion of curative resections and number of survivors in Group 2 to Group 1 patients.

ETHICS

Data were collected by the usual methods used in clinical practice.

Table 2. UICC-TNM classification of pancreatic adenocarcinoma.

T1	Tumor limited to the pancreas, less than or equal to 2 cm at its maximum diameter		
T2	Tumor limited to the pancreas, greater than 2 cm at its maximum diameter		
T3	Tumor extending directly into the duodenum, bile duct, or peripancreatic tissue		
T4	Tumor extending directly into the stomach, spleen, colon or adjacent large blood vessels		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M0	No distant metastasis		
M1	Distant metastasis-hepatic metastasis or peritoneal dissemination		
Stage I	T1-2	N0	M0
Stage II	T3	N0	M0
Stage III	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	T1-4	N0-1	M1

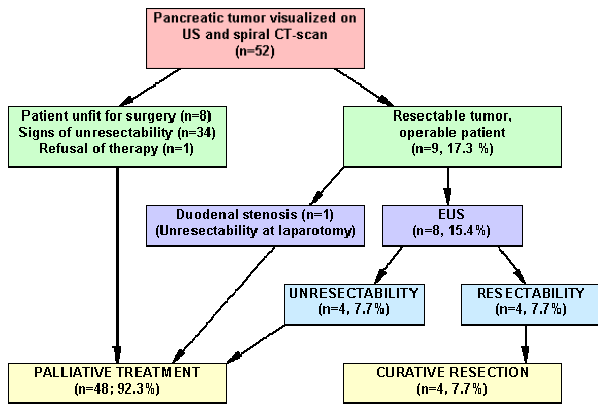


Figure 1. Management of patients with pancreatic adenocarcinoma in Group 1 (tumor visualized on US and CT-scan).

STATISTICAL ANALYSIS

Data are reported as mean±SD. Survival analysis was performed by the Kaplan-Meier method and the groups were compared using the log-rank test. The chi-squared and the Student’s t-tests were applied to compare proportions and age, respectively. Two-tailed P values less than 0.05 were considered significant. Statistical analysis was performed by means of the SPSS/PC+ statistical package.

RESULTS

Patients

During the study period, PA was diagnosed in sixty-four patients (mean age 70.5±11.9 years; 36 men and 28 women). The tumor was located in the pancreatic head in 51 cases (79.7%), in the body in 6 patients (9.4%) and in the tail in 7 patients (10.9%). PA was diagnosed by US or CT-scan in 52 cases (Group 1, 81.3%), and by EUS alone in 12 cases (Group 2, 18.8%). Eight patients (12.5%) underwent curative surgery. The median survival time and the one-year survival rate in all patients were 2.5 months and 6%, respectively.

Endoscopic ultrasonography

EUS was indicated in 30 cases (46.9%), but was carried out in only 20 cases (31.3%) due to

the poor general condition of the patient (n=8, Group 1), patient refusal (n=1, Group 1), or duodenal stenosis (n=1, Group 1).

The 20 EUSs were performed in 8 out of the 52 patients of Group 1 (15.4%) and in all 12 patients of Group 2.

Figure 1 shows the management of the 52 Group 1 patients and the number of EUS carried out as a staging procedure. After US and CT-scan, the tumors were classified as follows: stage I (none), stage II (n=16, 30.8%), stage III (n=3, 5.8%), stage IVA (n=10, 19.2%), and stage IVB (n=23, 44.2%). The 8 EUS examinations (15.4% of Group 1 cases) were performed in 5 patients with stage II tumors and 3 patients with stage III tumors on initial US/CT-scan. Celiac involvement was visualized by EUS in the 3 tumors initially classified as stage III and in 1 tumor initially classified as stage II (n=4, 7.7% of Group 1 patients, and 50.0% of EUS performed in this group), and this was confirmed upon surgical exploration thus determining the non-resectability of the tumor. EUS confirmed the staging of the 4 remaining cases (stage II). Resection was considered feasible in these 4 patients and this was confirmed at laparotomy and anatomopathology.

Figure 2 shows the management of the 12 patients with PA diagnosed only by EUS (Group 2). The procedures were motivated by the following circumstances: unexplained abdominal pain (n=2, 16.7%), acute pancreatitis of unknown origin (n=1, 8.3%), unexplained

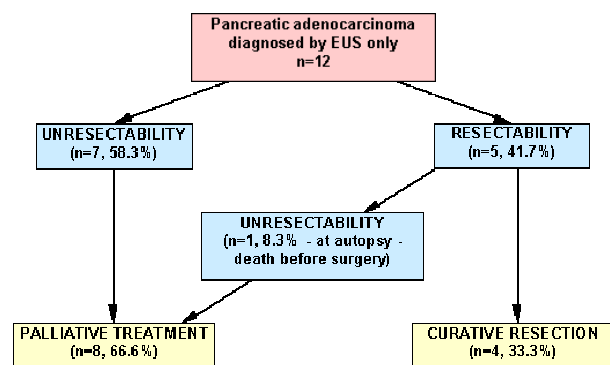


Figure 2. Management of patients with pancreatic adenocarcinoma in Group 2 (tumor diagnosed by EUS only).

jaundice (n=5, 41.7%), increasing pain or deterioration of general status in patients with known chronic pancreatitis (n=4, 33.3%). In these 12 patients, the tumor size on EUS was 2.3±0.8 cm and tumor staging was the following: 4 EUS stage II, 1 EUS stage III, 4 EUS stage IVA, and 3 EUS stage IVB tumors (signs of peritoneal carcinomatosis: n=3; left liver metastasis not visualized at US or with CT-scan: n=1). At laparotomy, 4 patients were found to be resectable (33.3% of the patients in Group 2; 3 EUS stage II and the EUS stage III tumors) and this was confirmed histologically. Seven patients were found to be unresectable (the 4 EUS stage IVA at laparotomy and the 3 EUS stage IVB after US-guided cytology). The last patient (EUS stage II tumor) died of myocardial infarction before laparotomy, but was finally classified as stage IVB at autopsy (liver metastasis).

On the whole, EUS correctly assessed an absolute contraindication to resection in 11 cases (17.2% of all patients, 55.0% of all EUS examinations), 4 cases in Group 1 and 7 cases in Group 2. Resectability was confirmed in 8 of the 9 cases selected by EUS. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of EUS in determining resection were 88.9%, 100%, 100%, 91.7%, and 95.0%, respectively. PA management could have been modified by EUS in 16 patients (25.0% of all patients, 80.0% of all endoscopic ultrasonography examinations).

The proportion of resectable tumors was significantly higher (P=0.015) in Group 2 (i.e., diagnosed only by EUS: 4/12, 33.3%) than in Group 1 (i.e., diagnosed by US or CT-scan: 4/52, 7.7%). In this subgroup of patients, the one-year survival was superior to that of other patients, although not reaching statistical significance (18.1% versus 2.7%, P=0.17).

DISCUSSION

This study is one of the attempts to evaluate the impact of EUS on clinical practice in the management of a homogeneous series of patients with PA [13, 14, 15]. According to our

criteria, EUS was indicated in nearly half of the patients either for staging or for making the diagnosis, and it was eventually performed in about one-third of the patients. Overall, EUS influenced decision-making in 80% of these selected cases. In our study, the impact of EUS on the management was therefore much higher than the 26% to 45% found by other authors in their series [15]. The discrepancy between these results may be explained by the differences in the criteria applied for performing EUS. The study by Nickl *et al.* [15] pools data from several centers, where indications for EUS and PA management may be heterogeneous. Furthermore, criteria for pancreatic neoplasia and for confirming EUS results are not clearly defined. Finally, EUS was only indicated as a complementary examination after initial US and CT-scan, which excluded all PAs diagnosed only by EUS. In our study, we selected only patients with histologically or cytologically confirmed PA, including patients with pancreatic tumors diagnosed only by EUS and we restricted the use of EUS as a staging procedure only to those patients having tumors considered to be resectable after CT-scan criteria. We therefore believe that the selection process of our patients more precisely reflects the clinical reality.

In our study, the major impact of EUS lies in the detection of pancreatic tumors (more than 50% of all EUS procedures). In fact, EUS is considered the most sensitive technique for diagnosing pancreatic tumors, permitting the detection of tumors smaller than 1 cm [4, 6]. The resection rate (50%) is significantly higher in patients with PA diagnosed only by EUS as compared to other patients. The absence of significant improvement in one-year survival was probably due to the insufficient number of patients in our study. However, patients with non-invasive tumors at presentation represent only a small minority of all PAs and their life expectancy remains poor despite favorable management conditions [16]. An accurate determination of patients at risk for PA is the first step in improving early screening by EUS [17].

Unlike earlier series [13], our study confirms that, since the development of spiral CT-scan, the role of radial EUS as a staging technique of PA is relatively limited. Recent studies report a 90% prediction of non-resectability by US and spiral CT-scan used as first intention techniques [18, 19, 20]. Since locally advanced or metastatic disease constitutes nearly 80% of PAs, EUS as a second intention staging procedure is subsequently indicated in a minority of patients. However, the impact of EUS is evident in these highly selected patients as reflected by the detection of local invasion and non-resectability criteria in 50 % of cases deemed resectable by CT-scan. The use of EUS in the staging of PA could benefit from the development of EUS-guided fine-needle biopsy which enhances the diagnostic value of lymph node staging from 60% (without fine-needle biopsy) to more than 85% [21, 22].

Our study demonstrates that EUS is performed in about one-third of all patients with PA in our clinical practice. Its impact lies essentially in the detection of pancreatic tumors. As a staging procedure, EUS may help to prevent unnecessary laparotomies, but its influence is limited by the usual invasive presentation of the disease at diagnosis. These results are likely to be modified by the development of EUS-guided fine-needle aspiration which allows tumor staging and histological confirmation of the cancer during the same examination. This procedure appears particularly attractive in neo-adjuvant therapy since it limits the risk of tumor dissemination, as seen by means of US- or CT-scan-guided cytology and restricts the use of surgical biopsies [21, 22, 23].

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Key words Carcinoma, Pancreatic Ductal; Disease Management; Laparotomy, Neoplasm Staging, Surgical Procedures, Operative

Abbreviations CT-scan: Computerized Tomography Scanning; EUS: Endoscopic Ultrasonography; PA: pancreatic adenocarcinoma; US: Ultrasonography

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