The Impact of Endoscopic Ultrasonography on the Management of Suspected Pancreatic Cancer—A Comprehensive Longitudinal Continuous Evaluation

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Objectives: Between 1997 and 2001, a single-center chart review demonstrated significant impact of endoscopic ultrasonography (EUS) in evaluating suspected pancreatic cancer (PCA). Repeating and comparing this review with that from 2001 to 2004 was performed to determine whether increased use of EUS results in more patients being accurately chosen for curative versus palliative procedures, and for surgical versus nonsurgical oncotherapy.

Methods: The complete systematic review was made up of electronic files from the gastroenterology, oncology, and pathology departments of patients presenting with suspected PCA. Results were compared with those obtained in 1997–2001.

Results: From 2001 to 2004, 72 patients had PCA. Seven tumor types were identified. Forty-seven percent (34/72) of patients with suspected PCA were preoperatively staged by EUS; 24% (17/72) of all patients underwent surgery. Comparatively, from 1997 to 2001, only 32% (20/62) of patients were evaluated by EUS ($P = 0.056$) and 45% (28/62) of all patients underwent surgery ($P < 0.01$). The EUS detected a tumor in 32 of 34 cases. The EUS-guided fine-needle aspiration cytology identified PCA in 14 of 18 cases. F-18-deoxyglucose–positron emission tomography and magnetic resonance imaging were not used. Endoscopic retrograde cholangiopancreatography was performed in 29% (21/72) of patients, with 15 stents inserted.

Conclusions: Increased EUS use for diagnosing and staging PCA resulted in fewer patients undergoing futile surgery. The EUS plays a pivotal role in the management of patients with PCA.

Key Words: pancreatic cancer, EUS, staging, outcomes studies

(*Pancreas* 2007;35:130–134)

Pancreatic cancer (PCA) is a devastating disease with an incidence that continues to rise. In the year 2000, an estimated 216,400 new cases were diagnosed worldwide.[1] That same year, the global death rate from PCA totaled 213,500.[1] By 2003, 30,000 new cases were diagnosed in the United States alone, and 97% of these patients are expected to die as a result of the disease.[2] United States projections for 2004 are even worse, with 31,860 new cases anticipated and an expected death rate of 31,270.[1]

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States.[3,4] Historically, clinicians have made a concerted effort to detect and treat this disease as early as possible. However, as its mortality rate is alarmingly similar to its incidence,[3] the current reality is that PCA is almost universally fatal. Most studies demonstrate a dismal overall 5-year survival rate of between 3% and 5%.[1,4,5] Advances in staging may lead the way to most appropriate management. As PCA therapies have improved, it is imperative that patients diagnosed as having PCA undergo appropriate staging to most effectively direct their case management.

The management of PCA patients involves the use of a wide range of modalities for diagnosis and staging, and these procedures are under extensive review in the literature.[6–8] Endoscopic ultrasonography (EUS) and EUS-guided fine-needle aspiration (FNA) are reported to be among the most sensitive and specific procedures for diagnosis and staging of PCA.[9] The EUS/EUS-guided FNA was reported to be the single most important test for the diagnosis and staging of PCA.[9] In recent years, several studies have also demonstrated EUS' ability to prevent, by as much as 75%, needless diagnostic surgery when compared with computed tomographic (CT) scanning.[9] The EUS has even been found to be capable of identifying premalignant conditions, as demonstrated by Kimmey et al[10] in a study that screened family members with suspected PCA.

The EUS is also thought to be among the most effective modalities for the diagnosis of particularly small pancreatic masses (<2–3 cm) and for discovering involvement of the local vasculature.[9,11,12] This contributes to its effectiveness in obviating unnecessary surgeries, which frequently take place because small secondary or vascular invasive lesions are easily missed by other diagnostic methods. The EUS is shown to be greater than 90% sensitive at detecting vascular invasion and can therefore be successfully used to predict surgical success.[12] A study by Mertz et al[13] showed that in the hands of an experienced operator, EUS was 80% sensitive at

Received for publication June 16, 2006; accepted March 13, 2007.

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diagnosing PCA, and moreover, was superior to CT scan in the detection of vascular invasion.

In light of the reality that PCA is almost universally fatal, physicians must endeavor to ensure that patients maintain, for the often short remainder of their lives, the greatest quality of life possible. This frequently involves primarily offering palliative care, which may be either surgical or nonsurgical. For PCA patients, the decision whether to perform surgery is often difficult to make. Selection of patients with appropriately resectable tumors is crucial. Unnecessary exploratory operations or, worse yet, failed resections due to undiagnosed regional metastasis are best avoided as the risks and costs (in health, and emotional costs, as well as financial burdens) are enormous.

MATERIALS AND METHODS

After receiving approval from the institutional review board to perform this retrospective study, intensive review was made of the electronic records of all patients presenting to the Western Galilee Hospital with the final diagnosis of PCA. Records from the departments of gastroenterology, oncology, and pathology for the years 2001–2004 were reviewed, and results were then compared with those of the period 1997–2001. In total, from 2001 to 2004, 72 patients were diagnosed as having PCA.

Diagnoses were confirmed cytologically or histologically. Fifty-two patients were diagnosed either by EUS-guided FNA, endoscopic retrograde cholangiopancreatography, or during surgery performed with intent to cure. The remaining 20 patients underwent palliative operations either when CT scan clearly showed inoperable tumors or when CT scan suggested an operable tumor that, during surgery, was determined to have been understaged by CT scan and converted to a palliative procedure.

Records were scrutinized, with emphasis placed on patient demographics, risk factors, initial clinical presentation, imaging modalities used, operations performed, and surgical outcome. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software and reviewed by a professional statistician. Particular interest focused on the number of patients staged by EUS before surgery and whether the use of EUS was successful at preventing unnecessary surgery.

Flourodeoxyglucose Positron Emission Tomography (FDG-PET) and magnetic resonance imaging (MRI), 2 relatively expensive modalities routinely used in the diagnosis and staging of PCA, were not used in any of these patients. Twenty-nine percent (21/72) of all patients underwent endoscopic retrograde cholangiopancreatography, and 15 stents were placed. Computed tomographic scan was performed in 92% of cases. In 66% of cases, carbohydrate antigen 19-9 was measured, whereas in 62% of cases, carcinoembryonic antigen was quantified.

RESULTS

From 1997 to 2001, we identified 62 patients with PCA at our institution. Of these, 32% (20/62) were preoperatively evaluated by EUS. Forty-five percent (28/62) of all patients with PCA underwent surgery with curative intent (Table 1).

Comparatively, during the period 2001–2004, we identified 72 patients with PCA. During these later years, 47% (34/72) of patients were preoperatively staged by EUS ($P = 0.056$). Only 24% (17/72) of all patients with PCA underwent curative-intent surgery ($P < 0.01$) during this period, a decrease of 21% from the preceding 4 years (Table 1).

Of the 34 patients with PCA in whom EUS evaluation was performed, a tumor was detected in 32 (94%) cases. Cytological EUS-guided FNA sampling was performed in 18 patients, from which PCA was positively identified in 14 patients (sensitivity, 78%).

Eight tumor types were identified: adenocarcinoma (n = 63), neuroendocrine tumors (n = 2), metastatic tumors (n = 2), pancreatic lymphoma (n = 1), gastrointestinal stromal tumor (n = 1), pseudopapillary tumor (n = 1), adenosquamous carcinoma (n = 1), and undifferentiated cancer (n = 1). The average time from presentation of relevant first symptoms until a confirmed diagnosis of PCA was 7 months. Mean age at diagnosis was 72 years. Male-to-female ratio was 55:45. Twenty-nine percent of patients admitted to current tobacco use, and all patients denied excessive alcohol consumption. No patient had a history of chronic pancreatitis. Six of 72 patients previously had another cancer type: colon (n = 1), breast (n = 1), prostate (n = 1), chronic lymphocytic leukemia (n = 1), lymphoma (n = 1), or bladder (n = 1). A positive family history for any cancer was present in 17% of patients. Although patient clinical presentation varied, many similarities were observed, most conspicuously, abdominal pain (92%), weight loss (76%), weakness (70%), diabetes mellitus (40%), jaundice (38%), and depression (4%).

Computed tomographic scan was performed in 92% of patients. Of these, 7% were read as negative, not showing the presence of a pancreatic tumor. The quality of CT scan included multidetector fine-slice CT scans, with triple-phase imaging using contrast intravenously in all, but 2, patients, who had no contrast used. Subsequent EUS testing of patients with negative CT scan but persistent symptoms clearly demonstrated the presence of a mass lesion later proven to be PCA.

Fifty percent of our patients underwent transabdominal ultrasonography (TUS), which was successful in diagnosing tumors in only 50% of the 36 cases. In the other 50%, the pancreas on TUS was documented as being normal, unremarkable, or not well imaged because of abdominal gas. It should be noted that at our institution, as is common practice throughout Israel, patients with a clinical presentation that is highly suggestive of PCA are sent by their physicians directly for CT scanning. Therefore, it is not unusual for a patient to bypass TUS in favor of more sensitive detection modalities.

TABLE 1. Pancreatic Cancer Patients—Comparison of Eras

	1997–2001	2001–2004	*P*
% undergoing EUS	32	47	<0.56
% undergoing surgery	45	24	<0.01

TABLE 2. Summary of Clinical Data of PCA Patients

Patient demographics	
Mean age (yrs)	71
Male-to-female ratio	55:45
Reported risk factors (%)	
Smoking	29
Family history of cancer	17
History of other cancer	12
Chronic pancreatitis	2
Alcohol consumption	0
Reported signs and symptoms (%)	
Abdominal pain	92
Weight loss	76
Weakness	70
Diabetes mellitus	40
Jaundice	38
Depression	4
Diagnostic tests performed (%)	
CT	92 (false negative, 7%)
TUS	50
CA19-9	66 (>37 in 50%)
CEA	62 (elevated in 24%)
EUS	47

CA19-9 indicates Carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

Carbohydrate antigen 19-9 was greater than 37 in only 50% of the PCA cases. Carcinoembryonic antigen was abnormally elevated in 24% of the cases (Table 2).

DISCUSSION

A multitude of studies have demonstrated that EUS is a highly sensitive and specific modality for the detection of pancreatic tumor. The EUS is also the preferred tool for the evaluation of locoregional metastases and for vascular invasion.[12] This is particularly relevant to PCA because, more than in some other cancers (for example, colon cancer), the presence of even minute metastases will play an important role in deciding whether to perform surgery and in directing future treatment options.

Our hospital has been performing EUS for almost 10 years, with approximately 2500 EUS procedures completed. It was therefore felt to be important to perform a periodic self-review to determine whether continued use of EUS by 1 experienced operator at our institution would improve diagnostic yield and accuracy in trying to categorize patients with PCA as operative or not for surgery with curative intent. Results from our 1997–2001 survey were compared with our later results. We hypothesized that with greater EUS use and experience, we would now more accurately identify and stage cases of suspected PCA. Longitudinal comparative studies of this nature are rarely performed within a single center, and in light of the present results, we would strongly encourage others to perform a similar study.

Adding EUS-guided FNA to basic diagnostic EUS examinations offers the further benefit of being able to perform a cytological analysis of suspect masses, without the need for exploratory surgery. In our study, EUS-guided FNA successfully detected PCA in 14 (sensitivity, 78%) of 18 patients, with no incident of procedure-related complications.

The EUS-guided FNA is particularly useful in patients with known chronic inflammatory conditions such as chronic pancreatitis who, even when evaluated by an experienced EUS operator, present a diagnostic challenge.[11] According to Voss et al,[14] histological diagnosis before performing surgery in resectable tumors is essential to differentiate between malignant and inflammatory masses. Although the yield of EUS-guided FNA for early PCA in cases in which chronic pancreatitis is lower than in the absence of pancreatitis, this series included 2 anecdotal successes in this area. Our emphasis on avoiding a Whipple procedure only to discover a benign inflammatory process seems to justify continuing this application of EUS. Studies examining the number of pancreatoduodenectomies performed in patients with inflammatory conditions mistaken for malignancy indicate that this occurs in approximately 5% to 13% of cases, especially those in which the lesion is in the pancreatic head.[15,16] Thus, in addition to identifying cases of inoperable/advanced cancer, EUS-guided FNA can prevent inappropriate, highly aggressive operations in a second way, by identifying nonmalignant conditions such as chronic pancreatitis.

Because EUS is still a rapidly evolving field of study, maximal benefit from its use has been attained only at centers with experienced operators. Our study clearly demonstrates that over time, at the same institution, and with all other factors being equal, increased use of EUS significantly reduces the number of unnecessary surgeries. Our expertise in EUS enhances our capability to preoperatively diagnose very small tumors and local metastases such as those in the celiac region or liver, which, once detected, obviate the need for curative surgical intervention. Therefore, the sooner physicians become proficient in EUS evaluation, the sooner the number of failed curative procedures performed at their institutions will decrease.

There is both an enormous local and international disparity in the distribution of qualified endosonographers. The shortage of necessary equipment and skilled staff prevents this proven technique from being effectively used at many centers or, worse yet, in some parts of the world altogether. Some large countries with otherwise modern health care systems have only a handful of capable endosonographers. For example, in India, there are an estimated 7 physicians qualified in EUS evaluation, whereas in Israel, a country that is a tiny fraction of India's size, there are 20 EUS centers with trained and practicing endosonographers.[17] This discrepancy means that until all centers reach the level of proficiency in EUS established by the best centers in the world, an unnecessarily high number of patients will be misdiagnosed and/or will undergo futile surgeries. The efficiency of EUS found in the current study may help motivate others in EUS-scarce regions to begin such a practice. Considering that the average patient with PCA dies within 4 to 6 months of diagnosis,[9] any time spent recovering from a useless surgery is too much time.

Our study demonstrates that when used properly, EUS alone, in the absence of other advanced diagnostic modalities such as FDG-PET or MRI, can determine which patients

would most benefit or not from surgery for local tumor resection. Computed tomographic scans continue to be essential for M-staging and for ruling out distant nonlocoregional metastases, which also exclude patients from expecting benefit from attempts at curative resections. Based on the currently accepted data regarding the local accuracy of EUS, it is our belief that, when judiciously used, there is little, if any, need for adding MRI and/or FDG-PET scanning to the staging regimen of patients with suspected PCA. Recent studies have demonstrated that, along with CT scanning, in the hands of an experienced operator, EUS yields comparable results to both MRI and/or FDG-PET and is among the most cost efficient initial investigative modalities for PCA detection.[7,12]

The 7-month average time from first appearance of symptoms related to PCA to making the diagnosis presents a challenge to clinicians. Although some patients appear with painless jaundice and are quickly diagnosed as having PCA within several days, far too many patients encounter critical time-consuming delays in diagnosis. Shortening this delay depends on the local availability of medical facilities, more importantly, on the level of suspicion among their primary care physicians, and on appropriate application of sensitive procedures to make the diagnosis.

As the genetic component of PCA is elucidated, emerging strategies to screen first-degree relatives of PCA patients are needed.[10] Beginning with a good family medical history and an awareness of the genetic propensity toward PCA is vital. Pancreatic cancer screening recommendations for first-degree relatives have not yet been formulated by consensus groups. Thus, we feel justified in encouraging grassroots efforts to evaluate various screening modalities, including the appropriate use of EUS to this effect.

The complex association of non–insulin-dependent diabetes mellitus (NIDDM) and PCA has previously been examined. Although minimal pancreatic reserve is generally considered sufficient to prevent the onset of hyperglycemia, we found that 40% of our patients with PCA have associated NIDDM. This value is consistent with other studies that obtained similar results.[18] Interestingly, DiMagno's[18] study results indicated that patients presenting with new-onset diabetes and PCA had a greater percentage of surgically resectable tumors when compared with those with newly diagnosed PCA without diabetes mellitus. We hypothesize that PCA may cause a paraneoplastic diabetes. Late-onset diabetes may be an early marker for PCA, and increasingly, the relevant literature advocates increasing suspicion for PCA in patients with late-onset NIDDM, along with the judicious use of pancreatic imaging studies in select cases. Therefore, based on EUS' ability to detect very small lesions, it may prove to be a useful tool in the evaluation of patients with late-onset DM in whom PCA can be reasonably suspected.

As can be noted by the number of patients with suspected PCA managed at our medical center during the 4-year period, Western Galilee Hospital may be considered a low-volume institution. Low-volume medical centers that perform few operations are associated with poorer operative results, including both increased perioperative and long-term (5-year) mortality.[19] For the purpose of EUS evaluation, being a 700-bed medium-sized regional hospital may be considered one of the strengths of the present study. Most hospitals in the world are similarly low volume. As we are not a large tertiary care center with a sizable referral base of patients with suspected PCA, our findings are relevant to most practitioners throughout the world, including those in community centers, who account for a significant proportion of the medical community. Furthermore, this study is not intended to address the question of surgical success rates or the morbidity associated with operations for PCA, but rather to evaluate the success of preoperative staging and diagnosis of PCA.

Most patients are initially seen in small- to medium-sized medical centers. Clinicians in this setting should be capable of evaluating cases of suspected PCA and of providing proper guidance for future management. The EUS can be used to assess a patient's surgical candidacy, thus saving the patient from the burden of unnecessary travel, which, in many parts of the world, can be excessively long and taxing. It can also direct palliative therapies, which can be performed in many small- to medium-sized facilities.

The impact of EUS was most evident in 2 situations: (1) when patients had a negative TUS and/or CT scan but suspicious clinical presentation, tumors discovered by EUS in these patients were most likely to be resectable for cure; and (2) when used to preoperatively stage PCA and arterial encasement or metastases identified the PCA as advanced, therefore sparing the patient a futile surgical intervention. Thus, the more EUS was chosen by surgeons for preoperative staging, the fewer futile procedures were attempted.

Pancreatic cancer is optimally treated by a collaborative multidisciplinary medical staff. Continued use of EUS for suspected PCA seems likely, based in these data, to spare patients unnecessary, futile, and high-risk procedures. In conclusion, EUS seems to be an increasingly effective tool for directing patients with PCA toward optimal, stage-appropriate therapy.

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