Long-term follow-up of patients with clinically indeterminate suspicion of pancreatic cancer and normal EUS

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Background: **EUS often is performed because of a clinical suspicion of pancreatic cancer when the results of other noninvasive diagnostic tests are indeterminate. The aim of this study was to determine the true negative predictive value of a normal EUS in a cohort of patients with an indeterminate suspicion of pancreatic cancer by obtaining long-term follow-up information.**

Methods: **Patients referred for EUS of the pancreas for the following indications were identified: elevated carbohydrate-associated antigen (CA 19-9) without other definitive evidence of pancreatic cancer, subtle abnormalities on CT of the pancreas, and unexplained abdominal pain and/or weight loss. Endoscopy procedure reports, as well as inpatient and outpatient records were obtained. In addition, referring physicians, as well as patients, were contacted to acquire adequate follow-up information.**

Results: **A total of 80 patients were included in the study. Follow-up of at least 6 months was obtained for 76 (95%) patients (mean follow-up 23.9 months). No patient with a normal EUS of the pancreas developed pancreatic cancer or required pancreatic surgery during the follow-up period. One patient in whom a diagnosis of chronic pancreatitis was made by EUS subsequently was found to have pancreatic cancer at surgery.**

Conclusions: **A normal EUS of the pancreas in the setting of subtle radiologic findings, serologic abnormalities, and/or nonspecific symptoms definitively rules out the presence of pancreatic cancer. (Gastrointest Endosc 2003;58:836-40.)**

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related mortality in the United States.[1] The 5-year survival for patients with this malignancy is less than 20%, even for those in whom "curative" resection is possible.[2,3] A known contributing factor to this grim prognosis is the frequent delay in diagnosis.[4] Early in the course of the disease, patients often have non-specific symptoms or are asymptomatic. When symptoms, such as obstructive jaundice, pain, and weight loss appear, the disease often is advanced and not amenable to curative resection.[5] In addition, the only curative treatment for pancreatic cancer, surgical resection, has been associated with a significant morbidity and mortality in some series.[6-8]

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In an effort to diagnose pancreatic cancer at an early stage, the threshold for performing "screening" radiologic and serologic tests has decreased. However, screening tests, such as transabdominal US,[9,10] CT,[11,12] and serum carbohydrate-associated antigen (CA 19-9),[13] have limited sensitivity and specificity for pancreatic cancer. When performed in a patient cohort with a relatively low incidence of pancreatic cancer, indeterminate or inconclusive results often are encountered. In this clinical situation, the difficult choice arises of an operation with significant associated morbidity vs. observation of a patient with a malignancy that is potentially curable. The term indeterminate suspicion of pancreatic cancer is used here to describe this group of patients, many of whom are referred for invasive diagnostic testing. Because of superior imaging of the pancreas, in particular, small tumors, EUS has become the diagnostic test of choice in many institutions in these indeterminate cases.[14,15] Increasingly, EUS is performed for evaluation of indeterminate radiologic findings, elevated CA 19-9 levels, and/or abdominal pain and weight loss of unclear origin. If EUS demonstrates a normal pancreas, surgical exploration is seldom performed. But, because pancreatic cancer can be missed, even by EUS,[16,17] endosonographers must decide whether to recommend follow-up testing in these patients.

The true negative predictive value of EUS in this setting has not been established by long-term follow-up studies. The aim of this study was to define the true negative predictive value of EUS for pancreatic cancer in the setting of subtle radiologic abnormalities, nonspecific GI symptoms/weight loss, and/or elevated CA 19-9 levels.

PATIENTS AND METHODS

The study was conducted at a tertiary referral center where EUS of the pancreas has been performed for over 10 years. Endoscopy reports of all patients, from January 1995 to May 2001, who underwent EUS because of a suspicion for pancreatic disease were reviewed. The examinations were performed by 5 different attending-level endosonographers, often in conjunction with an advanced endoscopy fellow. Two endosonographers had been performing EUS for at least 10 years (one for more than 20 years), and the other 3 had completed specialized training in EUS.

EUS was performed with various radial-scanning echoendoscopes. Curvilinear echoendoscopes were used only for FNA. Standard EUS was performed, the pancreas being examined in 3 stations (descending duodenum, bulb, stomach) for complete evaluation of head, body, and tail. If the EUS findings raised a suspicion that a focal lesion was present, specimens were obtained, at the discretion of the endosonographer, with EUS-guided FNA (EUS-FNA) by using a curvilinear array echoendoscope. All procedures were performed with the patient under conscious sedation by intravenous administration of meperidine and midazolam in titrated doses until a moderate level of sedation was achieved.

Patients were identified who underwent EUS of the pancreas at least 6 months before data collection for one or more of the following indications: elevated CA 19-9 level, with no definitive evidence to support a diagnosis of pancreatic malignancy; chronic abdominal pain; and/or significant weight loss (as determined by the referring physician), without a clear etiology; and indeterminate CT abnormalities (e.g., radiologic reports that included terms such as "enlarged head of pancreas," "heterogenous appearance," "mass cannot be excluded," etc.). Elevated CA 19-9 levels were defined by the reference values from the laboratory in which the test was performed. Patients with obstructive jaundice and/or ductal changes documented by ERCP or MRCP, where the suspicion of a cancer is high, were excluded.

Inpatient as well as outpatient records were reviewed for all patients included in the analysis. In addition, all of the physicians who referred the patients for EUS were contacted to obtain the most recent follow-up information for all patients. Patients no longer under the care of the referring physician were contacted, and data were obtained in a brief telephone interview. Patients were specifically asked the following questions: (1) have you been given any new diagnosis for your abdominal symptoms since the EUS procedure, (2) have you been given any new diagnosis of cancer, (3) have you undergone any operation since the EUS procedure, and (4) has your pain, or any other symptom(s) that led to EUS, resolved. Length of follow-up from the initial EUS was recorded.

EUS findings also were recorded. A normal pancreatic EUS was defined as no evidence of mass/tumor/cyst and no changes of chronic pancreatitis. Differences in the echotexture of the dorsal and ventral portions of the pancreas were noted but did not change the diagnosis of a normal EUS of the pancreas. The following established criteria were used to define chronic pancreatitis: echogenic foci within the parenchyma, focal areas of reduced echogenicity within the gland, increased thickness and echogenicity of the main pancreatic duct wall, accentuation of the lobular pattern of the gland, the presence of a cyst, irregular contour of the main pancreatic duct, and dilatation of the main pancreatic duct.[18] If at least 3 of these features were present at EUS, a diagnosis of chronic pancreatitis was made.

Data were entered into a computer database (Microsoft Access; Microsoft Corp., Redmond, Wash.). Statistical software was used for statistical calculations (Excel; Microsoft). The institutional review board for human investigation at our hospital approved the study.

RESULTS

Eighty patients (50 women, 30 men) who had EUS at least 6 months before initiation of the study were eligible for inclusion. The specified minimum follow-up of 6 months was obtained for 76 (95%) patients, as documented by the referring physician or data obtained during a telephone interview. Two of the 4 patients in whom 6-month follow-up could not be obtained, had normal EUS examinations of the pancreas. For these two patients, respectively, 4-month and 5-month follow-up information was obtained; during follow-up, no new pancreatic diagnosis was made.

Mean follow-up for the study cohort (76 patients) was 23.9 months; the total number of months of follow-up for the entire cohort was 1908. Mean follow-up for patients with a normal EUS of the pancreas was 26.2 months, and, for 76.2% of this subgroup, the length of follow-up was one year or more. Mean patient age was 58.6 years (range 17-91 years). Two patients in the study cohort had at least one first-degree relative with a history of pancreatic cancer.

Twelve patients had abdominal pain and an elevated CA 19-9 level (mean 10,392.8 U/mL, range 33-123,600 U/mL). With the exception of one value of 123,600 U/mL, the highest CA 19-9 value was 330 U/mL, and 8 patients had CA 19-9 levels between 33 and 100 U/mL. Subtle CT findings, which were inconclusive with respect to the presence of a pancreatic mass, were noted in 47 patients. The CA 19-9 level was elevated in 7 of these patients. Twenty-eight patients had abdominal pain of unknown etiology and weight loss with no CT evidence of pancreatic disease and a CA 19-9 that was either normal or not obtained.

Table 1. Clinical outcomes and EUS findings according to clinical presentation

Indication	No. patients (N)	EUS abnormal	Pancreatic cancer diagnosed
Abdominal pain/ weight loss	28	3	0
Elevated CA 19-9	5	2	0
Elevated CA 19-9 and Abnormal CT	7	2	2
Abnormal CT	40	10	0

CA19-9, Carbohydrate-associated antigen 19-9.

Table 2. Patient outcomes according to EUS findings

EUS findings	No. patients (N)	Required pancreatic surgery	Pancreatic cancer diagnosed
Pancreatic mass	4	3	1
Normal	58	0	0
Chronic pancreatitis	13	1	1
Other	6	0	0

EUS findings are summarized in Table 1. Four patients had a pancreatic mass seen on EUS. Three of these patients underwent EUS-FNA of the lesion. EUS-FNA was not performed in one patient because of the intense vascularity of the lesion as documented by Doppler US. Portal vein invasion by a mass was documented by EUS in a second patient. The third patient had known chronic pancreatitis, and EUS revealed a hypoechoic area consistent with a mass vs. focal chronic pancreatitis. Despite 5 needle passes into the mass, evaluation of the cytologic specimens was inconclusive for a diagnosis of malignancy. The patient declined surgical intervention at that time. Surveillance CT has been performed, and there has been no clinical evidence for cancer during follow-up (10 months). The fourth patient had a non-diagnostic EUS-FNA and underwent pancreaticoduodenectomy because of a strong suspicion for undetected malignancy. EUS revealed no evidence for chronic pancreatitis in this patient. No cancer was found in the resection specimen.

Three patients had only one or two EUS criteria for chronic pancreatitis. They were not given a diagnosis of a normal EUS or chronic pancreatitis. No definitive diagnosis of chronic pancreatitis was made in these patients during follow-up. Three patients had other notable EUS findings, including one with changes consistent with pancreas divisum (confirmed by subsequent ERCP). Thirteen patients had at least 3 EUS criteria for chronic pancreatitis. One of these patients also had a pancreatic mass. Fifty-eight patients in the study cohort had a normal EUS examination of the pancreas (Table 2).

There was no documentation of an EUS-related complication in the study group. Six patients died during follow-up. Two died of complications of pancreatic cancer; in the other 4, death was unrelated to any pancreatic diagnosis. No patient with a normal EUS developed pancreatic cancer or required pancreatic surgery during follow-up. One patient with changes of chronic pancreatitis on EUS was referred for pancreaticoduodenectomy because of difficulty in differentiating focal changes of chronic pancreatitis from pancreatic neoplasm and a markedly elevated CA 19-9 (123,600 U/mL). At surgery, a resectable pancreatic cancer was found, but the patient eventually died from complications of recurrent pancreatic cancer.

The negative predictive value of a normal pancreatic EUS for the diagnosis of pancreatic cancer was 100% in the study cohort of patients.

DISCUSSION

The unique and most important conclusion derived from these data is that a normal EUS of the pancreas rules out a diagnosis of pancreatic cancer with a high degree of certainty when there is a clinical suspicion of pancreatic malignancy based on equivocal imaging findings and/or an elevated CA 19-9. This is demonstrated by the absence of any diagnoses of pancreatic cancer or need for pancreatic surgery in patients with a normal EUS for whom follow-up of at least 6 months was available. Given the extremely poor 1-year survival rate for patients with a diagnosis of pancreatic cancer,[19] this follow-up period should be ample time for an occult tumor to become manifest. Thus, if there is confidence that the pancreas has been examined thoroughly at EUS and found to be normal, follow-up imaging studies usually are unnecessary and need not be recommended for patients with indeterminate evidence of pancreatic cancer. However, should there be a persistent strong suspicion for pancreatic cancer and other reasons to consider this diagnosis (e.g., an extensive family history of pancreatic cancer), follow-up EUS and/or other imaging studies may be indicated.

The results of the present study further demonstrate the superiority of EUS compared with other imaging modalities for the purpose of ruling out the diagnosis of pancreatic cancer. EUS increasingly is being used when other imaging studies provide inconclusive evidence for the presence or absence of pancreatic cancer. EUS has been shown to have a higher sensitivity (99%) than CT (77%) and transabdominal US (67%) for the diagnosis of pancreatic tumors,[15] especially tumors less than 2 cm in size.[20]

However, there currently is no published study comparing newer CT imaging technologies with EUS for the detection of pancreatic cancer.

For all imaging modalities, including EUS, pancreatic cancer frequently is difficult to detect in the presence of chronic pancreatitis. The difficulty of differentiating focal chronic pancreatitis and pancreatic cancer by EUS is well documented and remains problematic for endosonographers.[15,21] Chronic pancreatitis was diagnosed by EUS in one patient in the present study who was eventually found to have pancreatic cancer at surgery. This problem in differential diagnosis is compounded by the fact that patients with a history of chronic pancreatitis are at increased risk for the development of pancreatic cancer. The optimal approach to evaluation and management of patients with chronic pancreatitis when a suspicion for pancreatic cancer arises remains uncertain. The efficacy of blind or semi-blind EUS-FNA has not been established. Thus, continued surveillance to include EUS for such patients frequently is the only alternative short of surgical exploration with the potential for an unnecessary pancreatic resection. In the future, immunohistochemical staining and/or analysis for genetic tumor markers by using cytologic specimens obtained by EUS-FNA may be helpful. At present, however, the results of the present study are consistent with the view that EUS cannot rule out pancreatic cancer in the presence of chronic pancreatitis with the same degree of certainty offered by a completely normal EUS.

There are a number of limitations in the present study. CT interpretation and technique are operator and instrument dependent, and results may vary widely between institutions. Helical CT and thin-section imaging techniques through the pancreas were not standard of care for all of the patients included in the study. In addition, subtle changes, such as enlargement or irregular contour of the head of the pancreas, may be interpreted subjectively as a tumor by one radiologist and as a normal variant by another. Thus, some patients may have been included because of CT findings that would be interpreted as normal by a group of expert radiologists. In contrast, all EUS examinations of the pancreas were performed by a single group of experienced endosonographers who used relatively similar examination techniques and diagnostic criteria. This also suggests that the results obtained might not be generally applicable, especially in institutions with lesser degrees of experience with EUS. The patients included in the study were a heterogeneous group, and no effort was made to quantitate the degree of "suspicion" for the presence of pancreatic cancer. The referring physician might have requested EUS for thoroughness, while not being especially concerned that cancer might actually be present. Or, the concern could have been high and EUS requested with the expectation that the diagnosis would be established. Lastly, despite efforts to obtain a minimum follow-up of 6 months, this was not possible for two patients with a normal EUS of the pancreas. Nevertheless, follow-up information in these two cases at 4 and 5 months was available, and it seems unlikely that a diagnosis of pancreatic cancer was missed. Regardless of these limitations, the favorable outcome for this relatively large group of patients suggests that a normal EUS indicates a low risk of occult pancreatic malignancy.

The identification of patients with symptoms and signs of early stage, potentially treatable pancreatic cancer remains a challenge. Serologic markers, CA 19-9 in particular, have not been shown to be sensitive and are specific only at high levels.[14] CT imaging of the pancreas continues to improve but remains limited with respect to small (<2 cm) lesions.[22] Given the results of the present study and the well-established accuracy of EUS for pancreatic imaging, EUS should be the diagnostic test of choice for patients with clinically suspected pancreatic cancer.

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