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Differentiation of Benign From Malignant Pancreatic Masses by Endoscopic Ultrasound

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Background: It is often difficult to determine whether a mass in the pancreas is benign or malignant. The goal was to evaluate whether endoscopic ultrasound (EUS) can reliably establish whether a mass is benign or malignant.

Methods: One hundred five patients with possible pancreatic tumors were referred for EUS. Those who were found to have a lesion suspicious for carcinoma and did not have a known malignancy also underwent EUS-guided FNA.

Results: A mass suspicious for cancer was identified in 73 patients, whereas inflammatory changes or a normal pancreas was noted in 32 patients. Four of the latter 32 patients were subsequently found to have cancer. EUS-guided FNA was performed on 47 of the 73 patients with a suspicious mass and was read as cancer in 27 patients, atypia in 10 patients, and benign in 10 patients. All 10 patients with atypia were subsequently confirmed to have cancer, and 6 of the 10 patients with a benign FNA were proved to have a tumor at surgery. EUS could differentiate the lesion as malignant with a sensitivity of 95%, specificity 88%, positive predictive value 95%, and negative predictive value 88%.

Conclusions: Radial array EUS is helpful in supporting or refuting a diagnosis of cancer in a patient with a pancreatic mass. Although EUS-guided FNA can confirm the diagnosis, a negative FNA should not preclude exploration when clinically indicated.

Key Words: Pancreatic cancer—Endoscopic ultrasonography—Pancreatitis—Cytology.

A mass in the pancreas is sometimes unexpectedly discovered on either computed tomographic (CT) scan or ultrasound as a result of the work-up of a patient with abdominal complaints. Similarly, a patient who presents with frank jaundice and dilated extrahepatic bile ducts may also be discovered to have a mass in the head of the pancreas. The main differential diagnoses are pancreatic cancer or focal pancreatitis. Clinically, it is well known that the symptoms of one disease mimic the other. Anorexia, weight loss, pain, a history of alcohol abuse or gallstones, or any combination of these factors is common in both conditions. The tumor markers CEA or CA 19-9 can be normal or slightly elevated in either benign or malignant diseases of the pancreas. In addition, pancreatic biopsies and brushings often are unable to render a definitive diagnosis of malignancy because of the fibrotic nature of pancreatic cancers. Thus, it would be very helpful to have a diagnostic test that provides the clinician with information indicating whether a mass in the pancreas is likely to be benign or malignant.

Endoscopic ultrasound (EUS) is an effective tool in the evaluation of pathologic conditions of the pancreas (1). Findings on EUS of either calculi or an irregular contour of the main pancreatic duct have a positive pre-

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dictive value of 90% to 100% in the diagnosis of pancreatitis. Similarly, EUS has been shown to be more accurate than CT in the diagnosis of small pancreatic cancers (2–4). Nevertheless, a diagnostic tool that does not provide histologic or cytologic proof is unable to confirm a diagnosis of malignancy. The option of performing EUS-guided fine needle aspiration (FNA) biopsy, which has recently become available, gives the endoscopist the ability to obtain a tissue diagnosis (5–9). However, the clinical value of this tool in pancreatic cancer is not well defined. The purpose of this study was to determine whether EUS could successfully differentiate a benign pancreatic lesion from a malignant one, and assess the value of EUS-directed biopsy in supporting or refuting a diagnosis of cancer.

MATERIALS AND METHODS

Between July 1, 1994 and June 1, 1996, 105 patients with a possible pancreatic or periampullary cancer were referred for EUS (Olympus GF-UM20, Olympus America, Melville, NY). Most patients were referred because of radiologic evidence of a pancreatic mass. In some cases, the patient had a known diagnosis of pancreatic cancer, and the purpose of EUS was to determine the extent of the tumor. In other cases, the patient had evidence of chronic pancreatitis, but EUS was performed to determine whether a focal mass might be cancer.

Those patients who were found to have a lesion suspicious for cancer, and did not have a previous cytologic or histologic diagnosis of cancer, also underwent EUS-directed fine needle aspiration (FNA). A 23-gauge needle catheter aspiration assembly (4 cm long—Wilson Cook, Winston-Salem, NC, or 10 cm long—GIP/Mediglobe through Pentax Corp., Orangeburg, NY) was used with the linear array EUS system (Pentax FG32-UA echoendoscope) with color Doppler to identify vascular structures. This procedure, which has been described previously (10), involves the passage of the catheter through the biopsy channel and into the lesion with visualization in real time. Once the needle is in the lesion, the stylet is removed and suction is applied with a 10-ml syringe. After a number of passes into the mass, the needle is withdrawn into the catheter, and the catheter is removed. Slides of the aspirated material are initially stained with Diff-Quik and examined for adequacy of the specimen by the cytopathologist in the endoscopy suite.

Standard statistical techniques were used to determine sensitivity, specificity, and positive and negative predictive values.

RESULTS

Indications for EUS are listed in Table 1. An abnormality on a previous diagnostic test, usually a CT finding of either a mass in the pancreas or dilated extrahepatic ducts, was the most common reason for referral for EUS. A finding suspicious for cancer on endoscopic retrograde cholangiopancreatography (ERCP) was also a common complaint leading to EUS.

EUS identified a mass suspicious for cancer in 73 patients. Sixty-two of these lesions were in the head, nine in the body, and two in the tail of the pancreas. These pancreatic masses ranged in size from 1.8 to 8 cm (mean 3.6 cm). Thirty-two patients were noted to have either inflammatory changes (n = 16) or a normal pancreas (n = 16).

Four of the 32 patients in whom EUS failed to demonstrate a mass were subsequently diagnosed with cancer on follow-up. In three of these cases, the patient had evidence of chronic pancreatitis on EUS, making it difficult to identify the cancer. EUS of the fourth patient was initially interpreted as normal, but cancer was subsequently diagnosed in the tail of the pancreas.

All 26 patients who were found to have a mass suspicious for cancer on EUS but did not undergo EUS-directed biopsy had a pathologic diagnosis of cancer on a biopsy performed either before EUS or subsequent to the procedure. The sensitivity of EUS at differentiating a lesion of the pancreas as benign or malignant was 95%, and the specificity was 88%. The positive predictive value of EUS was 95%, and the negative predictive value was 88%.

Forty-seven (64%) of the 73 patients who were noted to have a mass on EUS also underwent EUS-guided FNA (Table 2). Cancer was conclusively diagnosed in 27 (57%) of these patients, whereas atypia was found in 10 (21%) of them. All patients with cancer or atypia were confirmed to have cancer. A diagnosis of cancer or atypia on EUS-guided FNA had a sensitivity of 86% and a specificity of 100%. The positive predictive value was 100%.

In 10 of the 47 (21%) patients suspected to have cancer by EUS, no malignant cells were contained in the

Table 1. *Indications for EUS referral (n = 105)*

	No. (%)
CT	68 (65)
CT and ERCP	13 (12)
ERCP	12 (11)
Restaging	7 (7)
Ultrasound	3 (3)
MRI	1 (1)
Abnormal CA 19-9	1 (1)

Table 2. *Results of EUS-guided FNA of a mass in the pancreas (n = 47)*

FNA result	Final diagnosis	
Cancer (n = 27)	Adenocarcinoma	24
	Lymphoma	1
	Squamous cell cancer	1
	Undifferentiated cancer	1
Atypia (n = 10)	Adenocarcinoma	9
	Neuroendocrine tumor	1
Benign (n = 10)	Adenocarcinoma	5
	Neuroendocrine tumor	1
	Serous cystadenoma	1
	Pancreatitis	3

FNA. Pathologic findings from surgery on these 10 patients showed adenocarcinoma in 5 patients, a neuroendocrine tumor in 1 patient, a serous cystadenoma in 1 patient, and focal pancreatitis in 3 patients. The negative predictive value was 40%. These pancreatic masses ranged in size from 3 cm to 8 cm (mean 3.8 cm). One was in the body of the pancreas, whereas the other 9 were in the head/uncinate region. One of the 4 patients with chronic pancreatitis on EUS was subsequently found to have cancer, and another was the patient ultimately found to have a cystadenoma.

Most patients tolerated the EUS-guided procedure without complication. One developed an infection in a serous cystadenoma and subsequently required percutaneous drainage. When this resolved, the tumor was surgically excised.

DISCUSSION

Early reports of EUS in the evaluation of pancreatic disease showed it to be excellent at differentiating benign from malignant lesions (4,11). EUS has also been shown to be effective in the diagnosis of chronic pancreatitis (12,13). In a study comparing EUS with other diagnostic tests for chronic pancreatitis, EUS had a sensitivity of 88% and specificity of 100% (14). However, there is considerable overlap between features of pancreatic cancer that can be detected by EUS and those of chronic pancreatitis (Figs. 1 and 2).

A number of criteria can be used to help differentiate a benign pancreatic lesion from a malignant one: (1) the endosonographic characteristics of the tumor; (2) coexistent features in the pancreas separate from the tumor; and (3) alterations in the tissue adjacent to the pancreas and at distant sites (15). Most malignant tumors present as a hypoechoic mass with irregular margins. Benign lesions tend to have smooth margins. Features in the remainder of the pancreas, such as calcifications, cysts, prominent interlobular septae, irregularity of the duct wall, and increased echogenicity of the parenchyma, are strongly suggestive of chronic pancreatitis (11,15). Extension of a pancreatic mass into the portal vein or superior mesenteric vein, or significant enlargement of peripancreatic or celiac nodes, is suspicious for cancer.

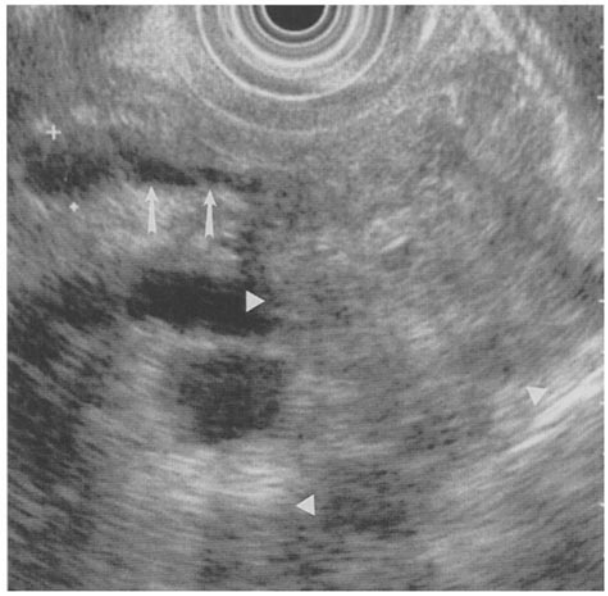

FIG 1. EUS image of pancreatic cancer. This is an example of a hypoechoic tumor *(arrowheads)* obstructing the common bile duct *(arrows)*.

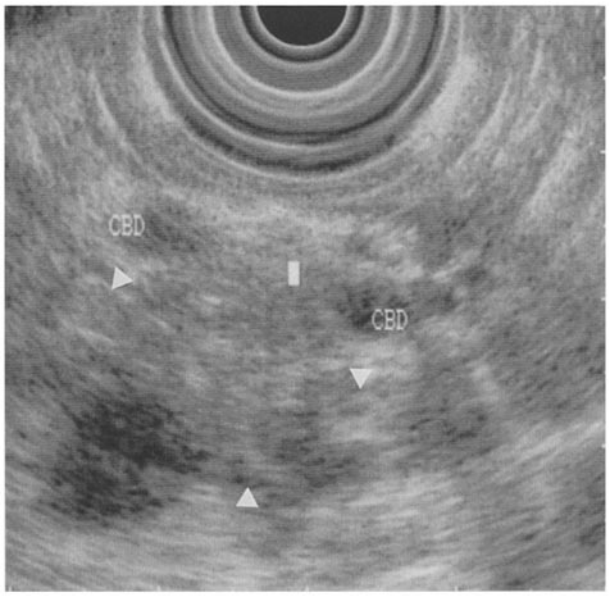

FIG 2. EUS image of pancreatic pseudotumor. This hypoechoic mass *(arrowheads)* in the head of the pancreas abutting the common bile duct (CBD) is an example of focal pancreatitis mimicking pancreatic cancer. This lesion is distinguished as a benign pseudotumor by the FNA aspirate negative for cancer and by changes of chronic pancreatitis in the remainder of the pancreas.

Unfortunately, there are no EUS findings that can render a definitive diagnosis of cancer or pancreatitis.

EUS has not been widely used in the United States for many reasons, including the high cost of equipment, the long procedure time, and the relatively low reimbursement (16). Another major problem is that significant experience is necessary before accurate results can be obtained from the endoscopist. This is particularly relevant to the pancreas. It has been estimated that technical competence with EUS of the esophagus and stomach can be achieved after 25 and 30 examinations, respectively. In contrast, it is estimated that a minimum of 94 examinations of the pancreas is needed for an endoscopist to become safe and efficient at manipulating the scope. Similarly, an accurate interpretation of EUS of the esophagus and stomach can be accomplished only after 43 and 44 examinations, respectively. Interpretive competence in evaluating the pancreas requires at least 121 examinations (16). Although this procedure appears to have a great deal of value in evaluating the pancreas, it can be accurately performed only in the relatively small number of facilities in the United States where sufficient skills can be maintained because of the volume of pancreatic disease referrals.

Four of the 32 patients believed to have pancreatitis on EUS were subsequently found to have cancer. Three of these had carcinoma in the setting of chronic pancreatitis. It is difficult to differentiate a focal area of pancreatitis, so-called pseudotumor, from a small pancreatic cancer by EUS. A lesion that is predominantly hypoechoic, with a smooth, regular border, most likely will turn out to be focal chronic pancreatitis. However, other researchers have noted that it is often difficult to differentiate these pseudotumors from pancreatic cancer on EUS (17–19). Artifacts created by calcifications that give acoustic shadows obscure the ability to view the tumor. The specificity of EUS in differentiating between cancer and focal pseudotumorous pancreatitis has been reported to be 78.6% (20). Often, however, the patient has biliary obstruction, and surgery is warranted. If a diagnosis of cancer is made, a Whipple procedure can be planned. If benign disease could be confirmed, a choledochoenterostomy might be the operation of choice.

When a patient is referred for EUS evaluation of the pancreas, the goal is to determine whether or not there is an abnormality, and if the problem is likely to be benign or malignant. The recently gained ability to perform EUS-directed biopsy enables the endoscopist to perform an FNA of the mass at the same sitting, and thereby to obtain a diagnosis later the same day. We found this technique to have a sensitivity for malignancy of 86% and a specificity of 100% in 47 pancreatic masses. These results are virtually identical to those from Chang et al. (21), in which EUS-guided FNA of 20 pancreatic lesions had a sensitivity of 91% and specificity of 100%.

Ten patients suspected of having a pancreatic tumor on EUS had an FNA negative for cancer. Eventually, six of these patients were found to have either an adenocarcinoma or a periampullary neuroendocrine tumor, confirming the initial radial-array EUS diagnosis. The large inflammatory or fibrotic reaction around pancreas tumors makes it virtually impossible to obtain a definitive diagnosis of cancer in all cases in which an FNA is performed. As a result, the negative predictive value in this small number of cases was low (40%). It should be emphasized, however, that only 4 of the 73 (5%) patients considered likely to have cancer by EUS criteria alone ultimately had a benign diagnosis. Thus, most patients found to have a mass on EUS will turn out to have cancer. The ability to perform an FNA of the pancreas at the same sitting as the initial EUS is valuable. Those patients who have biopsy proof of cancer and are found to have unresectable disease by EUS alone can go on to palliative biliary decompression by ERCP (5,9). In addition, they can be treated with chemoradiotherapy to control the disease or possibly shrink the tumor to facilitate subsequent resection (22–24).

This series reports our first experience with a complication related to EUS-guided FNA of the pancreas. In this case, the patient had a serous cystadenoma, which became secondarily infected following biopsy. In general, most centers have seen few complications from this procedure (21), probably because the needle placement is visualized at all times with ultrasound guidance. In addition, color Doppler, by visualizing blood vessels adjacent to the pancreas, tends to prevent puncture of the vessel.

Overall, we found that EUS can effectively differentiate a lesion of the pancreas as benign or malignant with a sensitivity of 95% and a specificity of 88%. These high numbers substantiate the ability of EUS to evaluate a patient with a mass in the pancreas that may be either cancer or focal pancreatitis. The positive predictive value of 95% indicates that most patients found to have a mass on EUS probably have cancer. An EUS-directed FNA can then be performed to verify the diagnosis and guide treatment. The negative predictive value of 88% indicates that patients in whom a mass is not found on EUS most likely have either pancreatitis or a normal pancreas. Clinical judgment still plays an important role, however, especially in cases in which a mass is not present on EUS. On the one hand, if the suspicion of cancer is high, it would be reasonable to proceed with surgical exploration, despite the negative EUS. On the other hand, if the

likelihood of cancer is low and the patient most likely has pancreatitis, it would be appropriate to follow the patient closely on the chance that a small pseudotumor may actually be a carcinoma. These patients may therefore benefit from either an ERCP or a repeat EUS about 6 weeks after the initial EUS.

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