Endoscopic Ultrasound and Fine Needle Aspiration for the Evaluation of Pancreatic Masses

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Hypothesis: Endoscopic ultrasound (EUS) and endoscopic ultrasound–guided fine needle aspiration (EUS-FNA) are accurate for the preoperative staging of pancreatic ductal carcinoma.

Design: Retrospective medical record review.

Patients: A prospective registry of 98 patients having EUS-FNA for peripancreatic masses from April 1994 to April 1998 was analyzed.

Main Outcome Measure: The accuracy of EUS-FNA for preoperative diagnosis and staging of peripancreatic neoplasms.

Results: Ninety-eight patients, aged 41 to 91 years (mean age, 67 years) with peripancreatic masses were evaluated by EUS-FNA. All patients had initial computed tomography scanning with a mass seen in 49 patients, “fullness” to the pancreas in 28 patients, and no mass seen in 21 patients. Evaluation with EUS-FNA revealed 22 benign lesions, 18 T2 masses, 37 T3 masses, 1 T4 mass, and 20 masses representing nonpancreatic tumors. Results of EUS-FNA of adjacent lymph nodes were positive in 27 patients. Twenty-seven patients had surgical resection or palliation permitting operative and pathologic staging. On comparison of EUS-FNA staging with surgical staging, 12 patients were the same stage, 14 patients were upstaged, and 1 patient was downstaged. The remaining patients who did not have surgery have been followed up for a mean of 15 months. Overall accuracy of EUS-FNA for differentiating benign from malignant masses was 96%.

Conclusions: Endoscopic ultrasound–guided fine needle aspiration is a useful technique for the evaluation of pancreatic masses. It is highly accurate for differentiating between benign and malignant lesions and for predicting T stage, but is limited for predicting nodal status.

PATIENTS AND METHODS

Ninety-eight patients with suspected peripancreatic malignant neoplasms were evaluated by EUS and EUS-FNA at Scott & White Clinic and Memorial Hospital, Temple, Tex, from April 1993 to April 1998. Patients were identified from a prospective registry of patients undergoing EUS-FNA evaluation, and their medical records reviewed in a retrospective fashion. All procedures were done under the direction of a single endoscopist (R.A.E.) in the endoscopy suite. All patients with the exception of one had an initial CT evaluation. All patients had masses or pancreatic or bile duct dilatation demonstrated on CT scan or otherwise had continued clinical suspicion for a pancreatic malignancy.

Endoscopic ultrasound was performed as previously described.13 After conscious sedation with medazolam and meperidine hydrochloride, upper endoscopy was performed prior to EUS to rule out any unsuspected mucosal abnormality. A diagnostic EUS examination was then performed using a radial scanning echoendoscope (Olympus GF-UM20; Olympus America, Inc, Lake Success, NY). This device produces 360° live images of surrounding structures at 7.5 or 12 mHz with a range of up to 12 cm. If a pancreatic mass, lymph node, or liver lesion requiring FNA was visualized, the radial scanning instrument was removed, and a curved linear array scanning echoendoscope (Pentax/Hitachi FG-32UA or FG-36UX, Pentax Precision Instrument Corporation, Orangeburg, NY) was inserted. This instrument allows for real-time visualization of the fine needle exiting the biopsy channel and entering the lesion of interest. It scans at 5 or 7.5 mHz and has color flow and Doppler capabilities, which allow for distinguishing vessels from other echoluent structures. The lesion was then located by linear array EUS, and a path for FNA, whereby no major vascular structures were traversed in aspirating the lesion, was found using color flow and/or Doppler ultrasonography. Fine needle aspiration was performed using either the Mediglobe (GIP-Medi-Globe, Grassau, Germany) or the Wilson-Cook EchoTip (Wilson-Cook, Medical, Inc, Winston-Salem, NC) 22-gauge aspiration needles. A reusable aluminum handle controls the insertion of the aspiration needle with a plunger that can extend the needle up to 12 cm from the tip of the echoendoscope. A cytopathologist was present for all EUS-FNA procedures. Aspiration specimens were stained with Diff-Quik (Stat Lab Medial Products, Lewisville, Tex), as well as rapid Papanicolaou stain. Aspiration sampling was continued until the cytopathologist examining the slides reported that adequate tissue had been obtained for diagnosis of the lesion. The mean number of FNA passes was 3.5 (range, 1-10 passes). After the EUS-FNA, the patient recovered for 30 to 60 minutes and was discharged from the endoscopy suite.

Results of the EUS evaluations were compared with operative and pathologic findings in the patients who underwent surgery and with the clinical course in those patients who did not undergo surgery.

Results of EUS-FNA were pancreatic adenocarcinoma in 56 patients (57%), a benign mass or fluid collection in 23 patients (23%), and nonpancreatic ductal tumors in 20 patients (20%). The nonpancreatic tumors included cholangiocarcinoma, lymphoma, islet cell tumors, gastric adenocarcinoma, gallbladder carcinoma, paraganglioma, metastatic breast cancer, leiomyosarcoma of the inferior vena cava, duodenal carcinoma, and cancer of unknown origin. For patients with ductal adenocarcinoma, 45 occurred in the head (80%), 6 in the neck (10%), and 6 in the body and tail (10%). Using TMN criteria, 18 masses were graded as T2, 37 masses as T3, and 1 mass as T4. One recurrent lesion was diagnosed at the margin of the gastric anastomosis 3 years after resection. The size of the carcinomas averaged 3.9 cm, with a range of 1.7 to 8 cm.

Assessment with EUS and EUS-FNA of adjacent lymph nodes determined that 18 patients (32% of patients with pancreatic adenocarcinoma) had positive lymph nodes. Node positivity was determined by EUS alone in 11 patients and node negativity was determined by EUS alone in 34 patients. Node positivity was confirmed by EUS-FNA in 7 patients, negative node status was diagnosed by EUS-FNA in 4 patients, and hepatic metastases were diagnosed by EUS-FNA in 2 patients.

Twenty-seven patients with pancreatic adenocarcinoma underwent operative intervention for resection or palliation. Findings of EUS were correlated with operative findings. Twelve patients (44%) were the same stage, 14 patients (52%) were upstaged, and 1 patient (4%) was downstaged. The upstaged patients had nodal metastasis (8 patients), increase in T stage (1 patient), distant metastasis (2 patients), and T and N stage (1 patient); 2 patients whose masses were diagnosed as benign were found to have carcinoma at celiotomy. One patient was downstaged from T3 to T1b at surgery owing to the surgeon’s ability to peel the tumor away from the portal vein.

Nonoperative patients have been followed up for a mean of 15 months (range, 4-36 months). Two patients determined to have benign masses by EUS-FNA were subsequently diagnosed as having carcinoma. This translates to a false-negative rate for adenocarcinoma of 7%. Three of the 4 patients with false-negative cytologic diagnosis had chronic pancreatitis. The overall accuracy of EUS-FNA for differentiating benign from malignant masses was 96%.

COMMENT

Pancreatic adenocarcinoma carries a poor prognosis with fewer than 20% of affected individuals surviving more than 1 year and only 3% remaining alive at 5 years after diagnosis.6,14 Currently, complete resection offers the only hope for long-term survival. In the past, radical pancreaticoduodenectomy has had an unacceptably high operative mortality rate. Several recent series, however, have shown operative mortality of less than 5% for the Whipple procedure.5,17,18 Survival following resection has improved in recent years with 5-year survival rates rang-
ing from 14% to 33%. This increase in survival probably reflects improved patient selection as much as improvements in treatment.

The preoperative diagnosis and staging of peripancreatic neoplasms has been difficult. Transabdominal ultrasound and CT are commonly used but can fail to image cancers of less than 3 cm in up to 40% of cases. In addition, a mass lesion of the pancreas can occur from inflammatory disease and mimic carcinoma. False-positive diagnoses by ultrasound and CT may occur as a result of common bile duct dilatation that occurs from causes other than malignant obstruction. Endoscopic retrograde cholangiopancreatography is another imaging option, but relies on indirect signs of ductal obstruction and is therefore less accurate.

Endoscopic ultrasound represents a new imaging modality for lesions in the upper gastrointestinal tract. It utilizes high-frequency ultrasound (5-12 MHz), which provides excellent resolution and detailed visualization of the pancreas and surrounding structures. Computed tomography detected a mass in 79% of our patients, but no mass was seen in 21% by CT. The masses seen on CT scan averaged 3.7 cm in diameter, whereas the masses measured 2.9 cm in the 21 patients with “negative” CT. Endoscopic ultrasound has previously been compared with transabdominal ultrasound and CT. Palazzo et al.17 compared EUS with ultrasound and CT in 64 patients with suspected pancreatic adenocarcinoma. Endoscopic ultrasound was more accurate (91%) than CT (66%) and ultrasound (64%) for the diagnosis of pancreatic cancer. Endoscopic ultrasound was also more accurate for detecting lymph node metastases than CT and ultrasound (74% vs 42% and 37%, respectively). Nakazumi et al.12 analyzed 232 patients for pancreatic carcinoma by EUS, CT, and ultrasound. They reported accuracy of 96% for EUS compared with 88% for CT and ultrasound.

Helical CT offers advantages over conventional CT in that it has faster scanning times, dynamic injection of contrast, and reconstruction of images for multiplanar depictions of anatomy.18 This has led to higher-quality images. Helical CT has been compared with EUS and found to produce similar results with the exception of small tumors. For tumors less than 3 cm, EUS carries a greater sensitivity than helical CT.3,4

Endosonography alone can be used to predict lymph node metastasis. The endosonographic features of lymph node metastasis include size greater than 10 mm, rounded contour, sharply demarcated borders, and hypoechoic structure. Catalano et al.19 found that EUS had a sensitivity of 89% and a specificity of 92% when lymph nodes were imaged endosonographically. They also found that, regardless of specific sonographic features, the likelihood of N1 disease was 86% in patients who had lymph nodes imaged. In patients who did not have lymph nodes identified, the chance of N0 disease was 79%.

Endoscopic ultrasound-guided fine needle aspiration is another application of echoendoscopy and was first reported in 1992.1 It permits cytologic biopsy of the pancreas and areas of metastatic disease. It is performed using the curved linear array echoendoscope so that the biopsy needle passes within the view of the ultrasound imaging. The presence of a cytopathologist during aspiration avoids the problem of inadequate cellularity of the FNA specimen. In our experience, a mean of 3.5 passes of the biopsy needle was required to achieve a diagnosis. The morbidity associated with EUS-FNA is less than 2% for solid lesions, with bleeding, infection, and pancreatitis as the main concerns. The risk of malignant seeding along the needle biopsy tract has been expressed as a concern, but this complication has not been reported with use of EUS-FNA. In patients with resectable disease, the course of the needle tract will be resected at the time of pancreatic resection.

The accuracy of EUS-FNA has been reported by other investigators. A collaborative multicenter study of 164 consecutive cases showed a sensitivity of 83% and a specificity of 90%.20 Sensitivities and specificities in other reports range from 85% to 90% and 85% to 100%, respectively. Sensitivity in our series was 96% and specificity was 100%. Four patients in our series had false-negative biopsy results. Three of these 4 patients had coexistent pancreatitis. Other authors have reported similar difficulty in patients with chronic pancreatitis. In this setting, surgical exploration may be warranted, even with a negative FNA result.

Although EUS-FNA was highly accurate for differentiating between benign and malignant masses, it was less accurate for preoperative staging of malignancy. Staging by EUS-FNA of patients in our series who had surgery for pancreatic carcinoma showed that 44% were the same T M N stage after surgery. Fourteen patients were upstaged because of undetected nodal metastasis (8 patients), an increase in T stage (1 patient), distant metastasis (2 patients), and an increase in T and N stage (1 patient); and 2 patients originally diagnosed as having benign masses had carcinoma at exploration. In addition, 1 patient was downstaged from T3 to T1b at surgery owing to the surgeon’s ability to peel the tumor away from the portal vein at surgery.

Use of EUS-FNA has several potential applications in clinical practice. It is useful in differentiating between benign and malignant masses, it delineates the relationship of the pancreatic cancer with the portal vein, and, finally, it allows detection of lymphatic metastasis in a significant number of patients. These latter patients could be entered into neoadjuvant therapy protocols for advanced disease. With improved preoperative diagnosis and staging, patients can be better selected for potentially curative resection vs palliative care.

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REFERENCES


DISCUSSION

Fabrizio Michelassi, MD, Chicago, Ill: I am here to read the discussion prepared by Dr Daniel Deziel, who could not be here because of a family medical emergency. Dr Deziel was kind enough to contact me and fax his discussion which follows. Mr Suits and his colleagues have presented their experience with EUS for the evaluation of peripancreatic masses with an appropriate emphasis on ductal carcinoma of the pancreas. In general, our therapeutic strategy for pancreatic cancer will be improved by earlier diagnosis to increase resectability and by more accurate staging to minimize unnecessary interventions in patients who are not likely to benefit. High-resolution ultrasound performed by endoscopic, laparoscopic, or intraoperative approaches, has inherent advantages over any conventional external imaging techniques.

From the standpoint of early diagnosis, we would be interested in knowing how useful EUS was for identifying tumors that were not detected otherwise. There were 49 patients without a definite mass on CT scan. Can you tell us first how often EUS discovered a pancreatic lesion in this group? Second, tell us whether cancers only discovered by EUS were potentially more curable based on stage and resectability?

As a cautionary note regarding diagnosis, 4 of the 22 patients felt to have benign lesions by ultrasound and FNA actually turned out to have pancreatic cancer. The distinction between benign and malignant was particularly difficult in patients with chronic pancreatitis when the sonographic diagnosis should not obviate the need for an operation.

As far as staging is concerned, there are a number of current modalities at our disposal including CT and MRI [magnetic resonance imaging], laparoscopy, and endoscopic or laparoscopic ultrasonography. The utility of any particular staging strategy is determined by a comparative evaluation of its accuracy and cost and by an assessment of how it influences therapy by increasing resectability rates, or by decreasing the rate of nontherapeutic operation. Results of this report show a poor correlation (44%) between operative staging and the findings on EUS, over one half of patients had higher stage tumors than ultrasound suggested. The main discrepancy was in regard to lymph node status where, in general, the sensitivity of ultrasound is more limited since one of the primary criteria it depends on is the lymph node size and small nodes can still be malignant. How often, however, did this change in stage affect your treatment or decision to resect?

Finally, how does laparoscopy with laparoscopic ultrasound fit into your current approach for staging pancreatic cancer? In many centers this has become an important tool for staging a variety of intra-abdominal malignancies. Experience with pancreatic cancer has demonstrated about a 90% accuracy in predicting resectability and has allowed about 25% of patients deemed resectable by other imaging techniques to avoid laparotomy. Laparoscopic staging with laparoscopic ultrasound is capable of detecting occult liver and peritoneal metastases that other modalities, including EUS cannot. It has a positive predicted value for vascular invasion that exceeds 90%. How useful did you find EUS for assessing the peripancreatic vessels?

Gerald Aranha, MD, Maywood, Ill: It took me many years to convince the residents and some of my colleagues. A preoperative biopsy is unnecessary in patients who had resectable mass in the head of the pancreas with obstructive jaundice. Now comes a test which some of our colleagues may use, not to operate on patients with pancreatic cancer and avoid giving them the only chance they have at cure. My questions to you are the following: (1) Do you think it is important to get a biopsy in those patients who present with pancreatic mass, obstructive jaundice and for all purposes on CT have a resectable lesion? (2) Did you do peritoneal cytology on your patients whom you operated on for cancer? Dr Warshaw has shown that in patients with peritoneal cytology washings, 75% of those who had preoperative biopsy had a positive peritoneal cytology. (3) How do you think that this test will ultimately be used? Would it be for those who will receive neoadjuvant therapy and for those whose tumors appear unresectable?

Richard Thirby, MD, Seattle, Wash: For the most part, I agree with the concept of EUS with biopsy. This technology is very expensive, but provides true potential gains for our patients. One is to confirm the diagnosis of cancer more safely in patients who do not have resectable disease. The issue raised by the previous discussant regarding concern for seeding with percutaneous biopsies is not a problem with the technology since it is transduodenal biopsy.

The distressing finding in the paper to me, however, was the downstaging at operation. One patient was felt to have portal vein invasion on EUS, but this was found not to be the case in the operating room. It is very distressing if patients are potentially denied curative operation based on this test. Can the authors tell us how many patients went to the operating room with the EUS suggesting venous invasion?

Dilip Parekh, MD, Los Angeles, Calif: This paper reflects a series of papers now published largely in the medical literature emphasizing the role of EUS for staging pancreatic cancer. There is one problem with most of the papers that I have seen so far including this one—the quality of CT scanning that is utilized in these studies is not state of the art. Did the au-
We will then avoid the cost and the morbidity to the patient of staging these patients which we are in the process of completing. We found that the diagnostic accuracy for staging vascular involvement with a state of the art, double-spiral CT is about 85% to 90%. In this study, only 40% of the patients were accurately staged with CT. So, clearly the problem here was not the value of EUS as much as the fact that the quality of CT scanning that was utilized in this study was poor. Endoscopic ultrasound is very much operator dependent. Our experience at USC [University of Southern California] has found that in about one third of the patients, the endoscopist is unable to make the determination of vascular involvement. There are 2 critical factors for resectability of pancreatic cancer: vascular involvement and metastatic disease. Very little data are present on this in this paper and correlated with accuracy of EUS. There are 2 specific questions that I would like the authors to address. What type of CT scanning technique was used in this study? How accurate was ultrasound assessment for identifying vascular involvement? Did the authors use intraoperative laparoscopy to rule out small metastatic deposits?

Richard Prinz, MD, Chicago: I also wonder about the need for preoperative biopsy in patients with resectable pancreatic lesions. My question concerns the fact that more than half of the patients in this study did not undergo operation. I would like to know the reasons why these patients were not explored, and whether patients with resectable lesions were denied pancreaticoduodenectomy?

Steven Stain, MD, Los Angeles: Did you actually compare your sensitivity of CT scan in predicting portal vein involvement?

Dr Frazee: Dr Michelassi, you asked, does ultrasound lead to an earlier diagnosis? This is one of the advantages of EUS in that it is very sensitive for detecting small tumors. That is one factor that has been shown to be an independent predictor of survival, and is one of the potential advantages of EUS over the other modalities.

The other questions pertain to cost-effectiveness. The importance of EUS in this area is by eliminating a variety of other diagnostic procedures. By going straight to the EUS examination with FNA, a number of adjuvant tests that have been done in the past, including ERCP [endoscopic retrograde cholangiopancreatography] and angiography, can be eliminated as part of the diagnostic workup and leads to a more cost-effective evaluation. The other area where it leads to cost-effectiveness is identifying patients who would not benefit from surgical therapy. We will then avoid the cost and the morbidity to the patient of unnecessary abdominal exploration.

You asked about laparoscopic ultrasound. We are just initiating that process in the evaluation of our patients with pancreatic tumors, so we do not have enough data to comment on that at this point.

Several of the discussants asked about EUS and its use for vascular invasion. Actually, this is one of the benefits of EUS. It is very accurate for detecting the relationship of the pancreatic mass to the portal and superior mesenteric veins. We had 1 patient in whom EUS overpredicted the portal vein invasion. This was out of a total of 10 patients shown to have vascular invasion. Three patients in our series had portal venous resection as part of their operation. It helps to identify preoperatively those patients who you are considering for portal venous resection. We used a criteria of 1.5 cm of interface between the mass and the portal vein as a prediction of portal venous invasion.

Dr Aranha, you brought up the issue of preoperative biopsy in the patient with a pancreatic mass. In the past, my philosophy regarding operative biopsy of a pancreatic mass in the patient who clinically presents with carcinoma has been similar to your own. I based the decision to perform resection upon clinical criteria and suspicion for a carcinoma. Because EUS-FNA can be done with such minimal morbidity, and gives a tissue diagnosis, I have now changed my philosophy in regards to preoperative biopsy. It is also very useful in those patients who are not candidates for surgical therapy. It is a very safe way to obtain a cytologic diagnosis and then put those patients in the category of palliative care or enter them into neoadjuvant therapy protocols in the hopes of performing later resection.

You mentioned the concern of peritoneal cytology and, as Dr Thirlby mentioned, the path of the needle is transduodenal and so it does not traverse the peritoneal cavity. In theory, this should not create problems with peritoneal seeding, but again, this is something that needs further study.

You also asked, does this open the door to neoadjuvant therapy, and indeed it does. If we can identify the patients who have metastatic lymph node involvement who do not have distant disease preoperatively, it opens the door for entering those patients into neoadjuvant therapy protocols and then offer them later resective therapy.

One of the discussants brought up the use of double-phase helical CT and the majority of the CT scans in this series were standard CT. The purpose of our paper was not to compare those, but other authors have done that and have shown similar results in delineating the relationship of the tumor in relationship to the vascular structures. Helical CT, however, was not as sensitive in detecting small tumors measuring less than 3 cm. So, for the tumor size, 3 cm and under, EUS is more accurate.

Dr Prinz, you asked why half the patients were not explored. A significant number of the patients had benign disease and therefore did not receive exploration. The others had disease that was not amenable to resective therapy. They were entered into palliative care at that stage.