Endoscopic Ultrasound in Pancreatic adenocarcinoma
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INTRODUCTION

Endoscopic ultrasound involves placing small, high-frequency ultrasound transducers on the tips of fiberoptic or video-endoscopes (1). A variety of transducer designs are used, but the two main varieties are a 270 to 360 degree rotating or non-rotating radial transducer and non-moving, convex longitudinal array transducers. By placing the transducer within the gut lumen, EUS overcomes the two major technologic problems for pancreatic imaging by transcutaneous ultrasound: obscuring overlying gas filled bowel and the necessity to use low frequency and therefore low resolution ultrasound to penetrate to the depth of the pancreas. Using ultrasonic imaging through the stomach and duodenum, the whole of the pancreas can be brought to within a few centimeters of a 5 to 20 MHz ultrasound transducer providing resolutions in the sub-millimeter range. Like transcutaneous ultrasound, EUS is also a “live” procedure which offers the advantage of being an interactive examination of the pancreas and surrounding tissues where subtle abnormalities can be imaged by the endoscopist from different perspectives, at different frequencies and ultimately cytologically sampled if necessary. In addition, as clinicians, endosonographers usually have the advantage of bringing much more clinical information to the procedure than the radiologist typically has in performing an abdominal CT or MRI. Furthermore, EUS now allows combining the biopsy (EUS-guided fine needle aspiration) and therapeutic capabilities of EUS (eg. tumor injection therapy or celiac neurolysis) with the initial diagnostic procedure. Finally, when EUS is combined with its sister endoscopic procedure, therapeutic ERCP, it results in a powerfully efficient combination of diagnostic, staging and therapeutic techniques that are very difficult to match with any other set of procedures.

EUS IN THE DIAGNOSIS OF PANCREATIC NEOPLASMS

The utility of EUS in visualizing pancreatic neoplasms was apparent soon after its clinical introduction in the mid-1980s in Japan (2) and Germany (3). Since then, there have been many series demonstrating the diagnostic superiority of EUS to CT and MRI in pancreatic neoplasms (4-12). Even for lesions less than 3 cm, EUS diagnosis rates have been consistently in the range of 95-100%. Another powerful aspect of EUS is that its specificity for ruling out pancreatic neoplasia is nearly 100% as long as the patient does not have underlying chronic pancreatitis (13). Although, ERCP is not generally used as a diagnostic technique anymore for pancreatic neoplasms, EUS is also superior to ERCP in the diagnosis of small pancreatic neoplasms (14) although they have similar sensitivities in detecting pancreatic head lesions (15).

With the advent of multidetector, high speed spiral CT, the advantage of EUS over CT in the diagnosis of pancreatic cancer is now narrowing. Series comparing state-of-the-art helical CT with high quality endoscopic ultrasound are still few (13). Spiral CT have overall detection rates above 90%; however, EUS still seems to be superior at detecting small (<2 to 3 cm) pancreatic carcinomas (8). There are a number of problems confounding series comparing EUS and CT. Rarely do institutions have similar levels of expertise in both procedures. In addition, in almost all series, the endosonographers are not blinded to the results of prior imaging or clinical information whereas radiologists rarely have access to the EUS information since it is usually performed after CT (17). It has been shown that clinical assessment has similar accuracy to imaging procedures in patients with suspected pancreatic cancer (18). Patient groups may also not be the same when comparing studies of the two procedures. In endosonographic series, patients presenting with metastatic liver disease (about one third of patients) or large, unresectable tumors are generally not included because there is less indication for EUS in these patients. However, these patients are often included in series assessing the diagnostic accuracy of CT (19,20). This inclusion can increase the overall diagnostic sensitivity of CT in pancreatic cancer detection by 5-15% compared to series focused only on those patients undergoing both EUS and CT (21).

There is little comparative data for EUS versus MRI in pancreatic cancer (22). Since series comparing CT to MRI for pancreatic masses show CT to currently have a slight advantage over MRI, it would be reasonable to presume EUS is superior to MRI at least for small masses. MRI has the additional advantage of being able to show
ductal anatomy using Magnetic Resonance Cholangiopancreatography (MRCP).

When patients have underlying chronic pancreatitis, all diagnostic modalities (CT, MRI, EUS, ERCP, and PET) are poor at detecting a superimposed pancreatic malignancy. EUS rarely misses pancreatic neoplasm when the pancreas is normal; however, this does not hold when chronic pancreatitis is present (10,11,23-26). When faced with this kind of patient, one has to use multiple diagnostic modalities, fine needle aspiration (27), tumor markers (28), close clinical follow-up and occasionally empiric resection (29) to find underlying pancreatic cancers in chronic pancreatitis. Molecular diagnostic techniques on FNA specimens may hold some promise in this area (30,31).

Despite the superior diagnostic capabilities of EUS, the frequency of its use in patients with suspected pancreatic neoplasms in the United States is still disappointingly low (4-9). This is a multifactorial problem. Initially this was primarily secondary to a lack of expert endosonographers at many institutions. However, in the last few years, high quality EUS has become available at most major institutions caring for significant volumes of cancer patients. Education of primary care practitioners, oncologists, radiologists and surgeons as to the capabilities of EUS and its appropriate role in patients with suspected pancreatic cancer is a current priority.

**EUS GUIDED FINE NEEDLE ASPIRATION:**

**Technique:**

The first EUS-FNA of a pancreatic cancer was reported in 1994 (32) and there have been numerous series since then (4,11,24,26,33-44). EUS-FNA techniques has been described extensively elsewhere (26,38,41,45-47) and involve passing an 18 to 25 (usually 22) gauge stainless steel, echogenic aspiration needle through the biopsy port of an echoendoscope under real-time guidance into an endosonographically visualized pancreatic mass, lymph node, liver metastasis or fluid collection. The needle is moved back and forth through the lesion with varying degrees of suction applied to it and the sample is deposited on a cytology slide(s) for immediate staining and cytopathologic examination.

**Yield of EUS-guided fine needle aspiration:**

EUS-FNA can provide a cytologic diagnosis in 80-95% of pancreatic malignancies (4,11,24,26,33-46) even in patients with previously negative attempts at tissue diagnosis (46). As with fine needle aspiration techniques in other organs (49), the diagnostic yield of EUS-FNA is dependent on technique (56), especially the training of the endosonographer (50) and the active involvement of a cytopathologist (51). Having a cytopathologist available in the room or close enough to give immediate feedback on the adequacy and preliminary cytologic diagnosis of an aspirate is a common clinical practice in endosonography centers in the United States (24,26,33,34,37-40,51,52). Cytopathologic feedback during the EUS-FNA probably increases the yield of a definitive cytologic diagnosis by about a 10% (26,36,40,51). As long as the lesion is visible, similar definitive cytologic yields are possible with transcutaneous ultrasound or CT-guided FNA of pancreatic masses, especially if a cytopathologist participates in the procedure. However, since EUS still seems superior for small lesions, the net overall yield of a definitive cytologic diagnosis will be higher with EUS-FNA than with CT guided techniques. An additional advantage of EUS-FNA is that being a real-time procedure, when an abnormality is found in the pancreas, one can proceed directly on to FNA at that time rather than scheduling a separate procedure as with CT. This may just be a matter of patient inconvenience in an ambulatory setting, but add additional days of hospitalization for inpatients. False positive EUS-FNA cytologies of the pancreas do occur rarely mainly because of interpretation errors (53).

It takes an average of three to four passes to provide a definitive cytologic diagnosis of a pancreatic malignancy (26,36,48,50,54). However, malignant lymph nodes and liver metastases generally require only one or two EUS-FNA passes for a definitive diagnosis (26). There are no clinical or endosonographic features that predict when a patient’s lesion may take more FNA passes to make a diagnosis. The major determinant of FNA pass number is the differentiation of the tumor (26,55) with some masses taking up to ten or more passes or more to make a diagnosis to make a definitive diagnosis in well-differentiated tumors (56). If a cytopathologist is not immediately available, generally five to six passes into the lesion are recommended, realizing that this approach may still result in a non-diagnostic specimen 15-20% of the time (26,45). Larger needles and “Tru-cut” designs have been used obtain actual tissue biopsies (57-59); however, these larger needles have failed to significantly improve diagnostic accuracy (59,60) except perhaps in the case of unusual histology (46). Using cell surface markers also makes it possible to make a cytologic characterization of pancreatic lymphomas as long as enough cells are obtained (61,62). EUS-FNA of cystic tumors of the pancreas present special challenges, as cytology is often non-diagnostic and must be supplemented by chemical analysis of fluid for tumor markers such as CEA or CA19-9 and amylase (63-66).

Whether a cytologic diagnosis is necessary in all patients with a pancreatic mass seen by EUS, CT, MRI or ERCP is a topic of significant debate (4-9,68) with some physicians (69,70) feeling that attempts at obtaining a tissue diagnosis in potentially resectable pancreatic masses does not change management and therefore is of little use.
Other physicians (21,71), feel there are numerous rationales for attempting to make a preoperative tissue diagnosis in all of these patients.

Complications of EUS-guided fine needle aspiration:

The overall complication rate of EUS-FNA appears to be about 0.5-3% (4,11,24,33-48,52,54), similar to that reported with CT or ultrasound-guided FNA or biopsy (72-74). The major complications reported with EUS-FNA (47) are pancreatitis (75) and bleeding (45,76) with rare deaths having been reported from cholangitis associated with biopsy of a liver metastasis in a patient with poorly drained biliary obstruction from a pancreatic cancer (77) and uncontrolled bleeding from a pseudoaneurism (37). Bile peritonitis (78) and acute portal vein thrombosis (79) have also been reported with pancreatic EUS-FNA. As of yet, there has been only one published case of tumor seeding with EUS-FNA (80). This has also been reported with CT-guided biopsy or US-guided biopsy (81). In addition, a recent study reported peritoneal recurrence significantly higher in patients having had CT or US guided pancreatic biopsy than with EUS-FNA (82). Clinically significant bacteremia following EUS-FNA is rare (83); however, EUS-FNA of cystic lesions may have a higher risk complication due to the risk of infecting the cyst with luminal bacteria (84). Because of this intravenous antibiotics with oral antibiotics are routinely used for a few days for EUS-FNA of pancreatic cystic lesions (4-9,62,66). In addition, we use transluminal povidone iodine solution to minimize bacterial contamination during EUS-FNA of cystic pancreatic lesions (85).

EUS FOR PancreATIC CANCEr STAGING:

Overview:

The primary impact of endosonography on the management of pancreatic cancer is in detection and cytologic diagnosis. Early in its introduction there was considerable excitement for EUS as an accurate staging tool in these patients (4-9,86-89). However, more recent studies (17,90) have tempered the initial enthusiasm for EUS as a staging procedure. In addition, the progressive technologic advances in cross-sectional imaging have largely overshadowed many of the perceived advantages of EUS staging. Despite this, EUS does offer some potentially unique staging information in patients with pancreatic cancer primarily in the detection of occult metastatic disease and evaluation of splanchnic venous involvement by tumor near the portal vein-superior mesenteric vein-splenic vein confluence.

There are a number of staging systems for pancreatic cancer, but the most frequently used in the United States is the recently modified (91), sixth edition of the American Joint Committee on Cancer (AJCC) TNM-based staging system. To address the evolution of surgical approaches to pancreatic cancer (92-94), the most recent modification of this staging system has made involvement of the splanchnic venous system less relevant to advanced staging. How this modification will affect the accuracy and utility of EUS in overall staging is unclear.

T- staging: The accuracy of EUS for T staging of pancreatic cancer is generally reported to be about 80-85% at all stages (50,86-89,95-97) although other studies put this accuracy at only 70% (98). This is similar to CT and MRI; however, this degree of accuracy is dependent on the experience of the endosonographer (86) and the fact that clinical data is accessible to the endosonographer at the time of the procedure (17,90). Since the small (< 2cm) T1 lesions are difficult to even image by other cross-sectional techniques, EUS by default would be expected to have an advantage in T staging these lesions. Patients presenting with jaundice generally have bile duct compression by encasement or direct invasion. The region of the ampulla and pancreatic portion of the common bile duct is very easily seen by EUS, although distinguishing between encasement (T1 or T2) and invasion of the bile duct (T3) can be difficult. However, this distinction is largely irrelevant to management. Duodenal wall invasion also is a T3 criteria and this is usually easily visualized both endoscopically and endonsonographically at EUS.

Many major oncologic centers no longer consider splanchic venous involvement as an absolute contraindication to resection (93,94,99) since these patients appear to have the same post-operative survival rates as successful resections without venous involvement in some institutions. To reflect this trend, the new AJCC staging criteria changed splanchic venous involvement from a T4 stage to a T3 stage lesion (92). However, a number of surgeons consider significant splanchic involvement a relative or absolute contraindication to an attempt at curative resection because of poor survival outcomes (96,100,101). Thus, depending on the local institution, accurate information regarding splanchic involvement with tumor may still significantly affect there management although it may not affect their staging.

The interface between the portal and superior mesenteric vein and a pancreatic head tumor is usually well visualized by both radial and linear endosonography. The overall accuracy of various endosonographic criteria for invasion have been assessed in detail (102) and include an irregular venous wall (87%), loss of acoustic interface
inaccessible to endosonographic imaging. However, only 4-6 cm of the left lobe and periduodenal right lobe are

proximity of mass to the portal vein (73%), and absolute tumor size (39%). Using these criteria, EUS was
more accurate (78%) than angiography (60%) at assessing portal vein involvement (102). Another recent large study
reported an overall accuracy of 93% for vascular invasion (86) but also noted a considerably poorer accuracy for
endosonographers having staged less than one hundred tumors. The presence of collateral formation as evidenced by
the presence of peripancreatic head or periportal venous collaterals invariably indicates extensive portal vein
involvement with tumor. The presence of gastric varices can indicate portal or splenic vein obstruction by tumor.

As discussed in the previous chapter, dual phase spiral CT and gadolinium contrasted MRI show similar or better
accuracies at assessing major venous invasion (102,103).

Some anatomical regions relevant to T staging are difficult to assess by EUS. The distal superior
mesenteric vein and especially the superior mesenteric artery are often too far from the duodenal lumen to visualize
adequately by EUS. Since major arterial (superior mesenteric, hepatic or celiac) invasion is a T4 stage criteria, the
ability to consistently assess these vessels is a significant advantage of CT or MRI over EUS. EUS also has trouble
assessing colonic invasion because most of this organ is out of range of the echoendoscope or visualization is limited
because ultrasound cannot penetrate the air in the colonic lumen. Peritumor edema or pancreatitis can result in
overstaging by EUS (86); however, this problem is not unique to ultrasound. The above T staging criteria have not
been validated for non-adenocarcinomas. Thus, my own practice is to be very conservative in calling portal vein
invasion with neuroendocrine tumors.

In summary, T staging of pancreatic cancer by EUS is correct about 80-85% of the time (104), similar to
CT and MRI. It has unique staging advantages in small tumors and lesions of the pancreatic head but has the
disadvantage of being highly operator dependent and unable to see deep areas of mesenteric root and pancreatico-
colonic interface. EUS provides T stage information that is often complimentary to CT, MRI, and angiography but it
cannot usually replace these procedures.

**N Staging:** EUS can detect very small (<0.5 cm) lymph nodes in the regions around the celiac axis, porta hepatis
and pancreatic head, neck, body and tail. However, nodes at the root of the small bowel mesentery and subduodenal
periaortic regions are often poorly seen. Just visualizing a lymph node by EUS does not make it malignant. For
example, benign nodes around the porta-hepatis are a common finding, especially in the setting of previous
inflammatory processes such as cholecystitis or pancreatitis. Endosonographic criteria for malignant adenopathy
have been established (105,106) and include lymph node size greater than 1 cm, echolucency, homogeneity, round
shape, and sharp edges. However, even if all these criteria are present, they have an overall accuracy of only about
80 to 90%. Using computerized analysis of nodal appearance has not improved this accuracy (107).

Although uniformly superior to CT or MRI, there have been multiple series showing the N stage accuracy
of EUS in pancreatic cancer to be disappointingly low at 65-70% (86-89). This poor result is due to the lack of
specificity of endosonographic criteria for malignant adenopathy, undetectable micrometastatic nodal disease and the
inability to visualize some areas of metastatic nodes, especially the small bowel mesenteric root. The addition of
EUS-FNA has greatly enhanced the specificity of N staging by EUS for pancreatic and other cancers (88,106) even
in nodes as small as five millimeters.

Pancreatic surgeons debate the relevance of cytologically documented nodal disease (99). Some argue that
cytologically documented nodal metastases is a contraindication to resection because of the poor survivals in such
patients (108,109). However, others argue that although survivals are poorer with nodal metastases, it is still better
than with no resection at all (110,111). All agree that nodal disease remote to the primary tumor such as the
mediastinum (112) should mitigate against resection. Thus, the significance of EUS-FNA documentation of nodal
spread will depend on the institutional approach to such patients. If malignant adenopathy is considered a
contraindication to resection, EUS and EUS-FNA can result in significant cost savings when used for pancreatic
cancer assessment (40). In our own series of EUS-FNA for pancreatic cancer, approximately 8% of patients
undergoing diagnostic and staging EUS were found to have nodal spread by EUS-FNA (26). The relevance of EUS
and EUS-FNA nodal staging may be significantly increased by the advent of molecular diagnosis of occult
malignancy within nodes that are cytologically negative by EUS-FNA (113,114). In addition, as effective
neoadjuvant regimens are developed for locally advanced disease, EUS-FNA demonstration of nodal metastases may
have even more impact.

**M Staging:** EUS is limited in its ability to assess metastatic disease to only those regions that are accessible to
EUS-FNA. About 80% of the liver is visible to EUS with the far right lobe and high dome of the liver usually being
inaccessible to endosonographic imaging. However, only 4-6 cm of the left lobe and periduodenal right lobe are
amenable to EUS-FNA. Liver metastases as small as 5 mm can be seen by EUS and sampled by EUS-FNA (26,35,77,88,115-117). If cytologically positive, these findings would obviate any attempt at curative resection and thus dramatically change the approach to managing that patient. Likewise, small amounts of peritoneal fluid can be easily aspirated by EUS-FNA (116,117) and if found to contain malignant cells represent metastatic, inoperable disease. However, only about 10% of peritoneal aspirates will have a positive cytology (117). Because ultrasound does not penetrate into air, the lungs cannot be examined for metastatic disease. Small right pleural effusions are, however, easily seen and tapped by EUS-FNA. Again, in our series (26), we found occult metastatic disease in about 7% of our patients, primarily small liver metastases.

Summary:
EUS is probably now inferior to CT and MRI in overall T staging accuracy because of its inability to visualize the superior mesenteric artery. EUS may still have an advantage over these procedures in detecting occult malignant adenopathy. It can only be considered a supplementary procedure for M staging. If it will obviate operative intervention, cytologically documenting occult remote nodal disease or metastatic disease can dramatically and cost-effectively (38,118,119) affect the future management of the patient with pancreatic cancer. If EUS is used purely as a staging procedure, it has to be considered complimentary, not superior, to findings on CT and MRI. However, if EUS is being used primarily for its diagnostic, biopsy and/or therapeutic capabilities, then the staging information obtained is an added bonus of the procedure.

**THERAPEUTIC EUS IN PANCREATIC CANCER:**

EUS also has therapeutic applications in pancreatic cancer. Celiac neurolysis can be performed through the posterior gastric wall under direct endosonographic guidance using bupivacaine and absolute alcohol injected on either side of the celiac artery (120,121). This is a relatively simple approach to the procedure compared to the radiologic transabdominal or anesthesiologic transthoracic approaches to celiac neurolysis. EUS celiac neurolysis takes about 10 minutes and can be done under the same sedation after a diagnostic EUS or EUS-FNA. EUS-guided fine needle injection (EUS-FNI) is now also being used experimentally for tumor injection therapy using activated lymphocytes (122) and viral gene vectors (123,124). Finally, now that therapeutic channel echoendoscopes are available, transduodenal or transgastric biliary (125-128) and pancreatic (129) stent placement is possible by EUS in the patient when ERCP has failed.
SCREENING FOR PANCREATIC CANCER IN HIGH RISK PATIENTS

5-10% of all pancreatic cancer appears to be familial (130). There are rare kindreds where the risk of developing pancreatic cancer is very high (131). How to screen for presumed precursors (132) of neoplastic transformation, pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMNs) in these families is unclear. Both imaging, cytologic, and molecular techniques are being used (131,133) with EUS and EUS-FNA usually being the cornerstone of this kind of surveillance. Decision analysis studies have suggested that this type of survey can be cost-effective compared to other accepted forms of cancer screening (134).

THE ROLE OF ENDOSCOPIC ULTRASOUND IN PANCREATIC CANCER:

Where high quality EUS and EUS-FNA is readily available, EUS can play a central and early role in the evaluation of the patient with suspected pancreatic cancer (4,9,13,14,97,135-137). Its superiority as a diagnostic tool and very high high specificity make it a ideal definitive test for patients suspected to have any pancreatic abnormality by CT, transcatheter US or clinical evaluation. Since cytologic diagnosis and staging information can also be obtained at the same time, EUS with EUS-FNA usually provides most, if not all, of the data needed to go on to definitive stage-specific therapy. State-of-the-art staging CT or MRI can be used before or after EUS to compliment the EUS staging information provided, especially in equivocal operative cases and to rule out occult liver metastases. In the rare situation where CT, EUS and EUS-FNA have failed to provide a definitive diagnosis, other modalities such as CA 19-9 (138), ERCP, repeat EUS in a month or two, PET or laparoscopy can be used depending on the clinical situation. Our own approach to incorporating EUS and EUS-FNA into the management of pancreatic cancer is summarized in the above figure. Using EUS as an imaging procedure of last resort minimizes the clinical impact and cost effectiveness of this powerful procedure by placing it at the end of the evaluation instead of near the beginning.

REFERENCES: