

## Role of endoscopic ultrasound in diagnosis and therapy of pancreatic adenocarcinoma

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### Abstract

Since its advent more than 20 years ago, endoscopic ultrasound (EUS) has undergone evolution from an experimental to a diagnostic instrument and is now established as a therapeutic tool for endoscopists. Endoscopic ultrasound cannot accurately distinguish benign from malignant changes in the primary lesion or lymph node on imaging alone. With the introduction of the curved linear array echoendoscope in the 1990s, the indications for EUS have expanded. The curved linear array echoendoscope enables the visualization of a needle as it exits from the biopsy channel in the same plane of ultrasound imaging in real time. This allows the endoscopist to perform a whole range of interventional applications ranging from fine needle aspiration (FNA) of lesions surrounding the gastrointestinal tract to celiac plexus block and drainage of pancreatic pseudocyst. This article reviews the current role of EUS and EUS-FNA in diagnosis, staging and interventional application of solid pancreatic cancer.

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### INTRODUCTION

Since its advent more than 20 years ago, endoscopic ultrasound (EUS) has undergone evolution from an experimental to a diagnostic instrument and is now established as a therapeutic tool for endoscopists.

Endoscopic ultrasound cannot accurately distinguish benign from malignant changes in the primary lesion or lymph node on imaging alone. With the introduction of the curved linear array echoendoscope in the 1990s, the indications for EUS have expanded. The curved linear array echoendoscope enables the visualization of a needle as it exits from the biopsy channel in the same plane of ultrasound imaging in real time. This allows the endoscopist to perform a whole range of interventional applications ranging from fine needle aspiration (FNA) of lesions surrounding the gastrointestinal tract to celiac plexus block and drainage of pancreatic pseudocyst. This article reviews the current role of EUS and EUS-FNA in diagnosis, staging and interventional application of solid pancreatic cancer.

### EUS-GUIDE FNA/BIOPSY

With the advent of EUS-FNA, it becomes a viable and useful alternative procedure for acquiring a tissue diagnosis to confirm the presence of pancreatic cancer. The feasibility varies from 90% to 98% and the efficiency in terms of collecting analyzable biopsy specimens varies from 80% to 95%. For the diagnosis of pancreatic adenocarcinomas, the sensitivity of EUS-FNA varies from 75% to > 90%, the specificity being 82%-100%, with a mean accuracy of 85%<sup>[1-9]</sup>. What is the technique of choice to obtain cytologic and/or histologic material from a mass suspected to be pancreatic cancer? To respond to this important issue, we must discuss it in different clinical scenarios.

#### **Unresectable pancreatic tumor**

CT scan or magnetic resonance imaging (MRI) is a high-resolution, noninvasive, cross-sectional imaging modality. It is a very accurate technique in the diagnosis and predicting resectability when a pancreatic mass or cancer is suspected. It is generally the first test ordered in such cases<sup>[10,11]</sup>. If a pancreatic mass is clearly unresectable based on CT or MRI results, either percutaneous image-guided or EUS-guided FNA can be performed for a tissue diagnosis to confirm the presence of cancer and to offer chemotherapy or radiation.

#### **EUS-FNA with failed alternative biopsy techniques:**

There is strong support for the use of EUS-FNA in pancreatic masses when other biopsy techniques have failed. In fact, in virtually all series of EUS-FNA, failure

of another biopsy technique is a common indication for EUS-FNA and yet, in these series, they were still capable of obtaining a definite cytologic diagnosis in 80% to 95% of cases<sup>[12,13]</sup>.

**EUS-FNA for lesions not visible or accessible to other imaging modalities:** At times, small pancreatic masses may not be detectable, even on a multidetector CT scan<sup>[14]</sup>. The study by Hoewhat *et al*<sup>[15]</sup> contained 6 patients in whom CT or US could not discern small pancreatic lesions. Then EUS-FNA is clearly the preferred sampling technique if a pathologic specimen is indicated. A recently published retrospective study of 1000 cases of pancreatic FNA also found that EUS-FNA was more accurate than percutaneous techniques for masses < 3 cm<sup>[16]</sup>.

EUS-guided FNA is the only preoperative procedure which can demonstrate invasion of lymph nodes located in the celiac, lumboaortic, retroduodenopancreatic or superior mesenteric regions<sup>[7]</sup>. Aspiration of ascitic fluid with a cytological study done by EUS can validate a carcinomatosis that could not be revealed using conventional imaging<sup>[17]</sup>. Recently, Tenberge *et al*<sup>[18]</sup> demonstrated that small metastases of the left liver lobe could be found and were easily accessible to biopsy by means of EUS. The finding of such lesions modifies considerably the management of supposed resectable cancer.

**EUS-FNA when alternative techniques are possible:** When a pathology specimen is truly the only reason for EUS-FNA, published trials directly comparing EUS-FNA to alternative sampling techniques such as CT or TUS-guided FNA/biopsy or endoscopic retrograde cholangiopancreatography (ERCP) are extremely rare<sup>[15,19,20]</sup>. In a retrospective review of CT-FNA *vs* EUS-FNA for pancreatic masses, Qian and Hecht reported a sensitivity of 71% for CT-FNA and only 42% for EUS-FNA for pancreatic malignancies. Recently, Horwhat *et al* present the unique randomized, prospective cross-trial of EUS-FNA *vs* CT- or US-FNA for diagnosing cancer in pancreatic mass lesions. There was no significant difference in the sensitivity or accuracy of CT/US-FNA and EUS-FNA, although a trend was not observed for increased sensitivity of EUS-FNA.

Multiple factors favoring EUS-FNA over transcutaneous FNA of pancreatic cancer are as follows: (1) Decision analysis models have been used for the impact of EUS-FNA in patients with pancreatic cancer because of the similarities in sensitivities and specificities of the various biopsy techniques. EUS-FNA as the primary diagnostic modality was the most cost-effective approach<sup>[21]</sup>. Fritscher-Ravens *et al*<sup>[22]</sup> showed that EUS-FNA in pancreatic cancer changed the surgical approach in 21% of patients and the therapeutic approach in 44%. (2) A factor favoring EUS-FNS over transcutaneous FNA of pancreatic cancer is the possible risk of needle tract seeding. In a large series of percutaneous or CT-FNA of abdominal lesions and masses, seeding in pancreatic cancer occurred most commonly in the skin, or with EUS-FNA the skin is not traversed<sup>[23]</sup>. (3) Other advantages

of EUS-FNA may be a short needle track. Indeed, the aspiration needle travels from the gut lumen to the lesion, a pathway that usually does not cross peritoneal or pleural surfaces and the complete needle tract is included in the resected specimen. The exception to this is in EUS-FNA of liver lesions and of pancreatic body/tail masses where the lesser sac of the peritoneum is breached. A case of gastric wall seeding after EUS-FNA of a pancreatic tail adenocarcinoma was reported recently was reported<sup>[24]</sup>. Micames *et al*<sup>[25]</sup> with their retrospective, non-randomized series comparing CT-FNA with EUS-FNA of pancreatic masses showed that there were significantly more peritoneal failures after neoadjuvant chemoradiation in patients having had CT biopsy (16.3%) *vs* EUS-FNA (2.2%).

Because of its advantages in imaging pancreatic neoplasms, high diagnostic yields, and the concern over needle-tract seeding with transcutaneous aspiration, the 6th edition of the handbook on cancer staging by the American Joint Committee on Cancer recommended EUS-FNA as the preferred sampling technique in pancreatic masses if it is available<sup>[26]</sup>.

### **Equivocal resectability of pancreatic tumor**

If CT or MRI results show a pancreatic mass with equivocal resectability, EUS is generally the next staging procedure. If this reveals that the mass is clearly unresectable, one can proceed with EUS-guided FNA for tissue diagnosis. If the EUS results show that the mass is potentially resectable, then EUS-FNA should be reconsidered.

### **Resectable pancreatic tumor**

In case of a resectable tumor, a histological diagnosis is not necessary and of little use because it does not change the ultimate need for operation. However, because some institution has a protocol or policy of giving preoperative neoadjuvant chemotherapy or radiation in resectable pancreatic adenocarcinoma, tissue diagnosis would be a prerequisite for that<sup>[27]</sup>. Others argue that pre-operative diagnosis can exclude the occasional patients with unusual histology found in 5% to 10% of pancreatic tumors (lymphoma, endocrine tumors and metastases) who would not benefit from operation<sup>[28,29]</sup>. Sometimes a patient may demand a conclusive cancer diagnosis before consenting surgery.

### **Differential diagnosis of solid mass within the pancreas**

The presence of a solid mass within the pancreas does not necessarily imply the diagnosis of pancreatic cancer. It concerns the difficult problem of pseudotumor, chronic pancreatitis and autoimmune pancreatitis.

EUS-FNA may be problematic in case of chronic pancreatitis because differentiating well-differentiated carcinoma from inflammatory atypia can be challenging<sup>[30]</sup>. Recent reports indicate that EUS-FNA coupled with molecular analysis could improve the sensitivity (81%), the specificity (100%), and the accuracy (85%) of the diagnosis of pancreatic carcinomas in comparison with each technique alone<sup>[31]</sup>.

## INTERVENTIONAL APPLICATION OF EUS-FNA OF SOLID PANCREATIC CANCER

### **EUS-guided celiac block and neurolysis**

The pancreatic nerves are autonomic and are sensitive to chemical and mechanical stimuli. They transmit visceral afferent information to celiac plexus and then centrally *via* the splanchnic nerves. The plexus is composed of two ganglia, usually located anterior and lateral to the aorta at the level of the celiac trunk.

Debilitating pain is a common symptom in patients with pancreatic cancer. Pain tends to be a difficult symptom to treat and can require high-dosage narcotics for relief with a number of associated side effects.

Celiac plexus neurolysis (CPN) refers to permanent ablation of the celiac plexus. This is done with ethanol or alcohol. Celiac plexus neurolysis by a surgical or radiographic approach has been available for many years for palliative treatment of unresectable pancreatic cancer. The procedure is carried out via a posterior approach with potentially serious complications. More recently, the development of endoscopic ultrasound using curved-array linear echoendoscope allows direct access to the celiac ganglia. Theoretically, EUS-guided celiac plexus neurolysis should be safer than the posterior technique without the need to traverse the diaphragm, spinal nerves, or spinal arteries. In addition, a short needle can be used and the injection can be carried out with real-time imaging. A meta-analysis of 24 publications and 1145 patients treated with percutaneous celiac plexus neurolysis for cancer pain found good to excellent relief in 70%-90% of the patients for up to 3 mo<sup>[32]</sup>. In 1996, Wiersema and Wiersema<sup>[33]</sup> reported the safety and efficacy of endosonographic celiac plexus neurolysis with absolute alcohol in patients with pancreatic cancer. In their series, 79%-88% of patients had persistent improvement in their pain score and 82%-91% required the same or less pain medication. Gunaratnam *et al*<sup>[34]</sup>, in a prospective study of 58 patients with unresectable and painful pancreatic cancer found that 78% of the patients improved their pain score after EUS-guided celiac plexus neurolysis. Mild complications include transient diarrhea (4%-15%), transient hypotension (1%) and transient increase in pain (9%). The major complications (2.5%) include retroperitoneal bleeding and abscess formation.

Celiac plexus neurolysis with alcohol should be considered as a first-line therapy for patients with pain due to pancreatic cancer. It is important to emphasize a realistic goal, which is not to eliminate pain but to optimize oral pharmacologic therapy and to allow a dose reduction to minimize the side effects. In summary, despite the paucity of data, EUS CPN appears to be as effective and safe as other methods of CPN for providing pain relief from pancreatic cancer. The EUS approach may be the most cost effective if CPN is performed at the time of biopsy and staging.

### **Radiofrequency**

Image-guided ablative therapies with thermal energy sources such as radiofrequency (RF), microwaves, and

laser energy have received much attention as minimally invasive strategies for the management of focal malignant disease. Percutaneous RF-induced tissue coagulation has been used in early clinical trials for the management of hepatocellular carcinoma, hepatic, cerebral metastasis and benign bony lesions (osteoid osteoma). The development of endosonographically placed therapeutic devices may provide a unique alternative for the management of premalignant pancreatic lesions and potentially may offer palliative therapy for surgically unresectable malignant pancreatic tumors. The study of Goldberg *et al*<sup>[36]</sup> demonstrated the technical feasibility of EUS-guided RF ablation in the porcine pancreas. Resultant coagulation necrosis is well visualized with EUS or CT with excellent radiologic-pathologic correlation. This technique appears to be well tolerated.

### **Photodynamic therapy**

Photodynamic therapy (PDT) has emerged as a useful method for the ablation of malignant and benign tumors of epithelial-lined and solid organs<sup>[37]</sup>. Studies of PDT in the pancreas demonstrate that photosensitizers are avidly taken up by pancreatic tissue<sup>[38]</sup>. Light exposure with resulting localized tissue necrosis has been achieved by percutaneous placement of PDT catheters into malignant pancreatic tissue.

In the study of Chan *et al*<sup>[39]</sup>, EUS was used to guide placement of quartz optical fiber with light diffuser in the pancreas, liver, spleen and kidney of 3 farm swine. This study demonstrates that EUS-guided low-dose PDT ablation of pancreas is feasible and safe and it might be most applicable to small lesions in the pancreas and the liver.

### **EUS-guided transhepatic cholangiography**

ERCP with stent placement is the procedure of choice for biliary decompression in patients with obstructive jaundice due to pancreatic cancer. However, decompression may be unsuccessful because of an anatomic variation, peripapillary diverticulum, deep tumor infiltration or insufficient drainage despite successful stent placement. Alternative approaches for accessing and draining obstructed ducts include percutaneous transhepatic (PT) cholangiography and surgery. PT drainage has a complication rate of up to 32% including fistula, cholangitis, biliary peritonitis, hematoma and liver abscesses<sup>[40]</sup>. Surgery offers long-term decompression but is associated with high morbidity and postoperative mortality rates<sup>[41]</sup>. Interventional EUS-guided cholangiography (IEUC) is a relatively new technique, permitting therapeutic biliary procedures when ERCP is not successful. EUS-guided opacification and drainage of obstructed pancreatic and biliary ducts has been described in case report<sup>[42-46]</sup>. This usually involves a direct transgastric or transduodenal approach, with stent placement through an endoscopically created fistula. Advantages of IEUC over percutaneous transhepatic (PTC) drainage include puncture of the biliary tree with real-time US when using color-doppler information. This usually involves a direct transgastric or transduodenal approach with stent placement through an endoscopically



created fistula. Although the only reported complication is bile leak, potential complications include bleeding, bowel perforation, infection and pneumoperitoneum. The extrahepatic approach has a greater chance of complication than the intrahepatic approach. Long-term follow-up and further studies comparing IEUD with PTC are required before the use of these techniques becomes widespread.

### Delivery of anti-tumor agents

In 2000, Chang *et al*<sup>[47]</sup> was the first to publish a phase I clinical trial which showed that local immunotherapy, an allogenic mixed lymphocyte culture (cytoimplant), injected in 8 patients with unresectable pancreatic adenocarcinoma under EUS guidance is feasible and safe.

Hecht *et al*<sup>[48]</sup> delivered an anti-tumor viral therapy under EUS guidance, into the primary pancreatic tumor in 21 patients with locally advanced or metastatic disease. It was given in combination with gemcitabine IV. They obtained partial regression or stabilization of the disease in 10 of 21 patients.

In the United European Gastroenterology Week (UEGW) 2005, Farrell *et al*<sup>[49]</sup> presented their institution experience with EUS-guided delivery of TNFerade (replication deficient adenovector containing human TNF $\alpha$  gene, regulated by a radiation-inducible promoter Egr-1) for patients with unresectable, locally advanced adenocarcinoma of the pancreas in combination of 5 FU IV and radiation. Multiple injections within the pancreatic mass were done. Three fifth of patients subsequently underwent uncomplicated pancreatic surgical resection.

The most recent EUS-guided anti-tumor therapy involves a novel gene therapy. In this study, Chang *et al* delivered TNFerade percutaneously at a single site in the tumor while up to 4 injections were given by EUS-guided fine needle injections (FNI) in combination with 5 FU IV in 37 patients with unresectable pancreatic adenocarcinoma. Tumor responses and disease control were similar in the 2 groups except for site pain (35% PTA *vs* 0% EUS). The study was updated and has been presented at DDW 2006 with 50 patients<sup>[50]</sup>. Four fifth of patients were reassessed as surgically achieved pathologically negative margins and 3 patients survived greater than 24 mo.

This demonstrated that EUS-guided FNI of TNFerade with concurrent chemoradiation is feasible and generally well tolerated. TNFerade may optimize surgical and long-term outcomes. EUS may offer a safer and more accurate route of injection compared with a percutaneous approach.

### CONCLUSION

In conclusion, even if new-generation high-resolution CT scans can equally assess pancreatic cancer resectability, EUS is still useful for small tumors and doubtful findings after CT scan. EUS can also image and access pancreatic lesion and lymph nodes not visible or accessible by other imaging modalities. Endoscopic ultrasound-guided intervention has opened new and exciting clinical applications in the management of pancreatic cancer

including fine needle aspiration of lesion or lymph node and celiac plexus neurolysis. Recently, endoscopists can deliver anti-tumor agents under EUS in multiple sites inside pancreatic cancer which promises innovative clinical application of EUS.

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