

Endoscopic ultrasound-guided fine needle injection for cancer therapy: The evolving role of therapeutic endoscopic ultrasound

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Abstract: Endoscopic ultrasound (EUS) is central to the diagnosis and staging of many malignancies, but now has an evolving role in cancer therapy. EUS-guided fine needle injection (FNI) is already used for palliative interventions such as treatment of pain through nerve blockade and to guide biliary decompression when conventional ERCP is not possible. More recently, EUS-FNI has been used to deliver specific anti-tumor agents for pancreatic cyst ablation and local control of tumor growth in patients with unresectable solid malignancies. The agents used to date include ethanol, brachytherapy seeds, and chemotherapeutic agents such as paclitaxel. In addition, FNI of new immunomodulating cell cultures such as mixed lymphocyte and dendritic cell cultures has also been reported, as has FNI of several different viral vectors for antitumor therapy. Although experience with these agents remains preliminary, EUS-FNI is a minimally invasive approach to deliver local antitumor agents, and is likely to have an expanding role in cancer therapy.

Introduction

Endoscopic ultrasound (EUS) is rapidly evolving from a primarily diagnostic imaging modality into a vehicle for therapy of a variety of disorders, ranging from biliary obstruction to gastrointestinal bleeding to cancer. The development of linear array echoendoscopes has made possible the use of fine needle aspiration (FNA) under direct endosonographic visualization, and more recently, fine needle injection (FNI) has followed. EUS-FNI is currently used in cancer patients in several ways. EUS-guided cholangiopancreatography through injection of contrast into a biliary system inaccessible by traditional endoscopic retrograde cholangiopancreatography (ERCP) has been used with success to accomplish palliative biliary drainage and stent placement [Kahaleh *et al.* 2005; Burmester *et al.* 2003; Giovannini *et al.* 2003; Kahaleh *et al.* 2003; Wiersema *et al.* 1996]. FNI can also facilitate difficult ERCP by contrast injection and guide-wire placement for 'rendezvous' procedures [Kahaleh *et al.* 2005; Mallery *et al.* 2004], or injection of dyes such as methylene blue to facilitate identification of a target duct for ERCP and drainage [Carrara *et al.* 2007]. EUS-FNI has also been used in surgical and radiation planning by injecting dyes to tattoo pancreatic lesions [Ashida *et al.* 2006; Gress *et al.* 2002], and implanting

radiopaque markers in malignant mediastinal and celiac lymph nodes [Magno *et al.* 2007]. The treatment of cancer pain with EUS-FNI of bupivacaine and ethanol for celiac plexus blockade is now a well-accepted practice [Levy *et al.* 2008; Michaels and Draganov, 2007; Collins *et al.* 2006; Levy and Wiersema, 2003; Gunaratnam *et al.* 2001; Wiersema and Wiersema, 1996]. In addition, EUS-FNI has been used for precise submucosal injection of saline prior to endoscopic mucosal resection of intramucosal neoplasia and submucosal lesions [Sun *et al.* 2002].

Most recently, EUS-FNI has been used for precise delivery of antitumor agents into target lesions. Localized rather than systemic chemotherapy is gaining favor in cancer treatment in a variety of settings as it theoretically minimizes the unwanted toxicities of therapy while possibly increasing therapeutic concentrations in the tumor itself. Local therapy may be used in patients with advanced or metastatic disease for tumor downsizing prior to resection or for relief of symptomatic mass effect, such as in the case of duodenal or biliary obstruction from pancreatic cancer. One major limitation of this approach to cancer therapy thus far has been the invasive procedures required for delivery of such agents.

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The precision of EUS-FNI and the proximity of the device to intraluminal lesions and masses in the portal confluence may help overcome these limitations. To date, the literature on the use of EUS-FNI is largely limited to animal feasibility studies and case series in humans. However, EUS-guided injection of a variety of antitumor therapies for the treatment of head and neck, esophageal, pancreatic, hepatic, and even adrenal masses have now been reported in the literature and EUS-FNI may play an expanding role in a new era of cancer therapy.

Ethanol ablation

Detailed EUS examination with FNA of visualized fluid is central to the diagnosis and surveillance of pancreatic cysts. Endoscopic therapies for cyst ablation, however, remain limited. Brugge *et al.* were the first to report on the use of EUS-FNI for ethanol lavage and ablation of cystic pancreatic lesions [Gan *et al.* 2005]. Twenty-five patients with pancreatic cysts (13 mucinous cystic neoplasms, 4 intraductal papillary mucinous neoplasms, 3 serous cystadenomas, 3 pseudocysts, and 2 of uncertain etiology) in the head, body, and tail of the pancreas were treated with varying concentrations of ethanol. No complications were reported, and eight patients had resolution of the cyst. Five patients underwent surgical resection, the pathology of which showed epithelial ablation. Although this is a report on a small group of patients and long-term follow-up is not available, EUS-FNI treatment of pancreatic cysts may be an important and minimally invasive therapeutic advance given the enlarging number of incidental pancreatic cysts diagnosed. Careful examination of the cyst walls and surrounding tissue will be required to ensure that surrounding malignancy is not missed. This ethanol lavage of pancreatic cysts was subsequently combined in another series with injection of paclitaxel [Oh *et al.* 2008], as described in the section on chemotherapeutic agents below, with slightly better rates of cyst resolution. However, these are both small series with short follow-up and small numbers of each type of cyst, and it remains unknown whether the addition of chemotherapy will improve outcomes.

EUS is also crucial in the diagnosis and staging of gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors. It is used to confirm location, facilitate FNA for pathologic diagnosis, and provide information on tumor staging and risk

of metastases. More recently, EUS-FNI was also used in case reports to deliver ethanol for ablation of a GIST and an insulinoma in patients who were poor surgical candidates [Gunter *et al.* 2003; Jurgensen *et al.* 2006]. In the first case, a 59-year-old man with a 4 cm gastric GIST in the muscularis propria, with mitotic activity of 1% on FNA, was treated with injection of 1.5 ml of 95% ethanol in a single session. Repeat endoscopy at seven weeks revealed no endosonographic evidence of residual tumor but a 1.5 cm ulcer, which subsequently healed on acid suppression therapy. In the second case, a 78-year-old woman with a 13 mm insulinoma in the body of the pancreas and recurrent symptomatic hypoglycemia was treated with 8 ml of 95% ethanol in a single session. The authors report mild post-procedure pancreatitis, but subsequent resolution of glycemic control and absence of the lesion on follow-up EUS. Although this approach to the treatment of GISTs and neuroendocrine tumors is unlikely to replace endoscopic or surgical resection, it may have a role in selected cases in which a minimally invasive technique is required.

EUS-guided ethanol ablation of intra-abdominal metastatic lesions has also been reported including lesions in the adrenal glands [Artifon *et al.* 2007] and the liver [Barclay *et al.* 2002]. Hepatic lesions are being treated with local therapy such as RFA and chemoembolization with increasing frequency, and may be an important target for EUS-FNI, especially near the portal confluence where anatomic constraints may favor an endoscopic approach. In the case of the liver metastasis [Barclay *et al.* 2002], seven injections were administered over several years with acceptable local control of tumor growth.

Brachytherapy

Interstitial brachytherapy is used for local therapy of a variety of cancers, including pancreatic carcinoma. This technique involves the placement of radioactive seeds directly into the tumor, followed by local gamma ray emission and tissue destruction. The radiation seeds are generally placed operatively, but more recently, EUS-FNI of these seeds has been accomplished in pancreatic [Jin *et al.* 2008; Sun *et al.* 2006], esophageal [Lah *et al.* 2005] and head and neck [Maier *et al.* 1999] tumors.

Initial experience with EUS-guided brachytherapy of the pancreas was performed by

Sun *et al.* [2005] in porcine models, proving the feasibility of this technique. This group then translated the technique into humans in a small series of 15 patients with unresectable pancreatic adenocarcinomas (11 in the head of the pancreas and four in the body and tail) [Sun *et al.* 2006]. A mean number of 22 iodine-125 radiation seeds (range 11–30) were endoscopically placed into each tumor with a mean number of 14 passes (range 6–21). At a median of 10.6 months follow up, four patients had partial response, three had minimal response, and five had stable disease. Three patients suffered local complications of pancreatitis and pseudocyst and three experienced transient grade III hematologic toxicity. At the conclusion of this report, the authors conjecture that endoscopically implemented brachytherapy might have increased efficacy if used in combination with systemic chemotherapy.

Jin and colleagues [2008] subsequently reported 22 patients with pancreatic cancer who were treated with iodine-125 brachytherapy in conjunction with systemic chemotherapy with gemcitabine and 5-fluorouracil. A mean of 14 seeds (range 5–30) were placed per patient. Due to limitation of puncture angle, the number of EUS passes, patient tolerance and time of operation, the number of seeds implanted was less than predicted by the treatment planning system in some patients, possibly affecting the results. At one month follow up, partial remission was seen in three patients, stable disease in ten and partial development (defined as increase in tumor volume of over 25% or identification of a new lesion) in nine. Complications included fever in twelve patients, seed migration in one patient and mild elevation in serum amylase in one patient. Notable in both of these series is the absence of gastrointestinal hemorrhage and pancreatic fistula known to be complications of the percutaneous and surgical approaches. Both series also report improvement in pain, even in patients with progressive disease.

EUS-guided brachytherapy has also been reported in a series of 39 patients with primary and recurrent head and neck cancers [Maier *et al.* 1999], as well as in a single case report of esophageal cancer metastatic to celiac lymphnodes [Lah *et al.* 2005].

EUS-FNI of radioactive seeds requires an operator with great expertise as permanent insertion of a radioactive substance in the incorrect location

may have adverse consequences. In addition, brachytherapy involves the handling of therapeutic radioisotopes, a field usually foreign to gastroenterologists. Learning from our urology colleagues who have been using brachytherapy for prostate cancer for years, as well as radiation oncologists who will likely continue to assist in planning of seed placement and the loading of the EUS needle, will be crucial. Additional data on safety and combination with systemic therapies are needed.

Radiofrequency ablation and photodynamic therapy

Local ablative therapies such as radiofrequency ablation and photodynamic therapy may also be candidates for EUS-guided anti-tumor therapy, although they have not been reported in the literature in humans. Radiofrequency ablation is emerging as one of the safest and most predictable techniques for thermal tumor ablation. It is gaining favor for the treatment of pancreatic and hepatic lesions, and is traditionally administered with percutaneously or open surgical approaches. However, the risks of repeated rounds of radiation for percutaneous administration or of the operative approach may be significant, and a less invasive approach would be desirable. Preliminary studies in porcine models have now shown that EUS-guided insertion of the catheter into the pancreas is feasible [Goldberg *et al.* 1999]. If the feasibility and safety of the EUS-FNI approach can be proven in humans, this could be a major advance for this field.

Photodynamic therapy involves the systemic administration of a photosensitizing agent, followed by the imaging-guided placement of light-defusing photodynamic fibers into the target malignant tissue. These fibers are generally placed percutaneously, but have now been successfully placed endoscopically with EUS guidance in the pancreas in two porcine models, each with a different photosensitizing agent [Yusuf *et al.* 2008; Chan *et al.* 2004]. Neither of these EUS-guided therapies, however, has been reported in humans.

Injection of chemotherapeutic and biologic agents

One of the first phase I trials of immunotherapy in pancreatic cancer was published by Chang *et al.* [2000], who used EUS-FNI to

deliver an allogeneic mixed lymphocyte culture (cytoimplant) directly into unresectable pancreatic cancers in eight patients. This mixed lymphocyte therapy is based on the observation that cytokine production directly within a tumor may lead to regression by host immune mechanisms, and that mixed lymphocyte culture implantation produces such a cytokine response. In this small series, toxicities were minimal, and included fever, nausea and elevated bilirubins (although all patients who developed cholestasis had resolution upon changing of biliary stents). Two of the eight patients experienced partial response in tumor size, and one had a minimal response; however, a phase II/III trial comparing this technique to gemcitabine was terminated early due to inferior efficacy of cytoimplant immunotherapy [Bhutani, 2003]. Perhaps combinations of systemic chemotherapy with cytoimplant injection, rather than a single agent comparison, would improve outcomes.

Dendritic cells (DC), which are potent antigen-presenting cells for induction of T-cell immune responses, have also been used in a variety of ways for anti-tumor therapy. Irisawa and colleagues [2007] recently published a letter describing the injection of DC directly into advanced pancreatic tumors with EUS-FNI, in conjunction with systemic gemcitabine. These cells were predicted to activate in the presence of tumor antigens and stimulate a tumor-specific immune response upon migration to regional lymph nodes. Seven patients underwent a range of 2–21 injections of DC, five of whom underwent radiation prior to initiation of therapy to maximize antigen exposure through radiation-induced necrosis. Median survival was 9.9 months and two patients had mixed results while two had stable and three had progressive disease. No toxicities or adverse events were observed. Additional experience with immunotherapy agents will be required before they can be recommended broadly, but the limited toxicity and at least moderate efficacy are likely to inspire further investigation.

Antitumor therapy delivered by viral vectors is another rapidly expanding field. Two viral constructs have now been delivered into advanced pancreatic cancers with EUS-FNI in humans. Replication-selective viruses are viruses that preferentially replicate in and lyse malignant cells and subsequently spread between tumor cells. ONYX-015, the first of these viruses to enter

clinical trials, is an adenovirus chimera engineered to selectively replicate in p53 deficient cells. This agent was recently administered percutaneously in a phase I trial for patients with pancreatic cancer [Mulvihill *et al.* 2001] but the results were somewhat hindered by difficulties with the multiple percutaneous injections required. A phase I/II trial was therefore performed using EUS-FNI to deliver the virus into pancreatic tumors, in combination with systemic gemcitabine [Hecht *et al.* 2003]. Twenty-one patients were treated with eight injections over eight weeks. Two patients experienced partial regression, two had minor responses, six had stable disease, and eleven had progressive disease or terminated treatment due to side effects. Among the most serious complications were two patients with sepsis before prophylactic antibiotics were instituted and two patients with duodenal perforations, prompting the subsequent use of the transgastric approach only.

TNFerade (GenVec, Inc., Gaithersburg, MD) is another adenovirus vector that has been endoscopically injected into tumors [Farrell *et al.* 2006; Chang *et al.* 2006, 2004]. TNFerade is a second-generation replication-deficient adenovirus with a transgene encoding human TNF- α regulated by a chemoradiation-inducible promoter. EUS-FNI of TNFerade was initially used in the endoscopic treatment of pancreatic cancer in 27 patients (an additional 23 patients were treated percutaneously) [Farrell *et al.* 2006]. Each patient received five weekly dose-escalating injections, combined with chemoradiation. The same group went on to endoscopically treat 24 patients with esophageal cancer, again with systemic chemoradiation [Chang *et al.* 2006]. Detailed follow-up is lacking in both series as these data were presented in abstract form, but one case of a 72-year-old man with locally advanced pancreatic cancer was recently reported in a manuscript. He was treated with EUS-guided TNFerade administration in addition to neoadjuvant chemoradiation therapy and ultimately surgical resection [Chang *et al.* 2008].

Direct EUS-FNI of more conventional chemotherapeutic agents incorporated into long-acting biodegradable polymers has also been attempted in the pancreas in canine [Sun *et al.* 2007] and porcine [Matthes *et al.* 2007] models. In the latter study [Matthes *et al.* 2007], Matthes and colleagues injected OncoGel (MacroMed Inc., Sandy, UT), a new gel formulation of

paclitaxel for intralesional injection, into eight pigs, resulting in high and sustained local concentrations of paclitaxel. Although this injection was feasible, the authors noted some technical issues such as the high viscosity of the gel, which may perhaps require modification prior to more widespread use. In addition, it remains unclear as to how the presence of the gel will affect the image quality and sensitivity of subsequent exams. 5-Fluorouracil injection has also been used in canine models [Sun *et al.* 2007], and was also shown to be feasible in a series of six dogs. To date, no studies of these agents have been performed in humans.

Most recently, EUS-FNI of paclitaxel in conjunction with ethanol lavage was used in a series of 14 patients with pancreatic cysts [Oh *et al.* 2008]. Two of these lesions were presumed mucinous cystic neoplasms, three were serous cystadenomas, three peripancreatic lymphangiomas, and six were indeterminate. Cysts in communication with the pancreatic duct were excluded due to risk of pancreatitis. EUS-guided ethanol lavage and paclitaxel injection was successfully performed in all but one patient in whom the viscosity of the cyst fluid precluded sufficient aspiration. One patient had mild pancreatitis, while six developed hyperamylasemia without abdominal pain. At a median of nine months follow-up, eleven patients had complete resolution of the cyst and two patients had partial resolution. The median initial diameter of the lesions with complete response was 21 mm (range 17–52 mm). The authors concluded that EUS-FNI treatment of cystic lesions of the pancreas may be applicable to patients with lesions that are increasing in size over time without overt evidence of malignancy, unilocular or oligolocular cysts of unclear etiology for which a diagnostic EUS-FNA will be performed, and cystic lesions >2 cm that require regular follow up. Larger series of patients with longer follow up are needed to make definitive recommendations, but the enlarging population of patients with pancreatic cysts warrants further investigation of cyst ablation techniques.

Conclusions and future applications

Therapeutic EUS is a rapidly expanding field that is likely to play an important role in the management of malignancies. EUS is already central to the diagnosis of many cancers, and now with FNI it can also be used to tattoo lesions,

guide palliative relief of biliary obstruction and treat cancer-related pain. As technology evolves, additional indications are likely to follow. For example, EUS-FNI may have the potential to increase the sensitivity of EUS for vascular staging, as it is now being used for angiography as well [Magno *et al.* 2007].

The use of EUS-FNI for specific anti-tumor therapy and pancreatic cyst ablation may also be a significant advance in our treatment armamentarium. Although it is not likely to replace curative resection of localized lesions or systemic therapy for metastatic disease, there are many instances in which augmented or minimally invasive localized treatment would be ideal. For example, the treatment of symptomatic mass lesions obstructing a portion of the gastrointestinal lumen or biliary tree, or lesions causing significant pain, may be most effectively managed with local therapy. In addition, patients with small lesions who are not operative candidates may benefit. Perhaps most importantly, EUS-FNI of antitumor agents, especially when combined with systemic therapy, may increase the efficacy of neoadjuvant treatment prior to attempted curative resection.

Experience with EUS-FNI in cancer therapy remains largely limited to animal feasibility studies and human case series, and prospective trials will be required before widespread use of these techniques can be advocated. Many future challenges and technical issues for EUS-FNI remain. Safety continues to be a concern, and the risk of serious adverse events such as duodenal perforation is unknown. In addition, the number of reported complications is likely to increase with the number of treatments performed. Improved equipment may help to overcome some specific concerns such as difficulties with the transduodenal approach to pancreatic lesions and the limited ability to aspirate or inject viscous materials. Prospective trials of EUS-FNI techniques with and without systemic therapies are needed in specific patient populations. However, these trials may be difficult to recruit adequate numbers of patients for, as the growing number of treatments available and the variety of cancers and stages of disease that could be tested may dilute the power of each trial. Given the current lack of experience and data, these techniques should therefore remain limited to specialty centers with ongoing enrollment of patients in such protocols. However, as local injectable therapies improve,

EUS-FNI may be an important solution to the need for invasive procedures to deliver targeted therapy, and play an active role in the future of cancer treatment.

Conflict of interest statement

None declared.

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