

Endoscopic ultrasound-fine needle injection for oncological therapy

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Abstract

The minimal invasiveness and precision of endoscopic

ultrasound (EUS) has lead to both its widespread use as a diagnostic and staging modality for gastrointestinal and pancreaticobiliary malignancies, and to its expanding role as a therapeutic modality. EUS-guided celiac plexus neurolysis is now a well-accepted modality for palliation of pain in patients with pancreatic cancer. EUS-guided ablation, brachytherapy, fiducial marker placement, and antitumor agent injection have been described as methods of performing minimally invasive oncological therapy. EUS-fine needle injection may be performed as adjunctive, alternative, or palliative treatment. This review summarizes the studies to date that have described these methods. A literature search using the PubMed/MEDLINE databases was performed. While most published studies to date are limited with disappointing outcomes, the concept of a role of EUS in oncological therapy seems promising.

Key words: Endoscopic ultrasound-fine needle injection; Endoscopic ultrasound-guided ablation; Photodynamic therapy; Radiofrequency ablation; Cryothermal ablation; Endoscopic ultrasound-guided brachytherapy; Fiducial markers; Endoscopic ultrasound-guided antitumor agent injection

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Core tip: In the present review, the novel use of endoscopic ultrasound-fine needle injection (EUS-FNI) in oncological therapy is described. EUS-FNI is a promising method to optimize treatment to a targeted area while minimizing procedure invasiveness and systemic toxicity. EUS-guided ablation, brachytherapy, fiducial marker placement, and antitumor agent injection have been described to date. While these procedures appear to be safe and reasonably well tolerated, their effectiveness and exact role in oncological treatment have yet to be established.

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INTRODUCTION

Since the introduction of endoscopic ultrasound (EUS) for the diagnosis and staging of gastrointestinal and pancreaticobiliary malignancies^[1], EUS has increasingly been described as a therapeutic modality. The same minimal invasiveness and precision that favor EUS as a diagnostic modality have generated interest in its therapeutic potential. EUS-guided celiac plexus neurolysis is now a well-accepted modality for palliation of pain in patients with pancreatic cancer, and EUS is now often used to facilitate bile duct identification and access during difficult endoscopic retrograde cholangiopancreatography (ERCP)^[2]. More recently, the role of EUS fine needle injection (EUS-FNI) has expanded to include ablation of malignant or pre-malignant tissue, placement of brachytherapy and fiducial markers, and direct delivery of antitumor agents into a targeted lesion under ultrasonographic visualization, theoretically minimizing systemic exposure and increasing local concentration. Injectable agents that have been described for this purpose include lymphocytic cultures, immature dendritic cells, and viral vectors, although most of these studies are limited by their small size, lack of control, and include patients with pancreatic cancer only^[2].

EUS-GUIDED ABLATION

Ethanol ablation

Ethanol causes cell-membrane lysis and protein degeneration and has been proposed as a method of ablating the cyst-wall epithelium of premalignant lesions or malignant lesions in poor surgical candidates^[3]. After initial cyst needle puncture, cyst fluid is partially aspirated and the cyst is lavaged for several minutes by alternating cyst aspiration and ethanol injection^[4]. Ethanol ablation of pancreatic cystic lesions was first described by Gan *et al*^[3] in 2005 in a study that included 13 patients with benign mucinous cystic neoplasms and 4 patients with intraductal papillary neoplasms. Complete cyst resolution was noted for 35% patients and cyst size decreased in 9% patients with no reported complications. Cyst resolution was maintained in most patients at long term follow-up^[5]. A more recent prospective study of 23 patients with pancreatic cystic neoplasms reported a higher treatment success rate of 52%, however only 2 patients had complete cyst resolution at long-term follow-up^[6]. Performing EUS-guided ethanol lavage followed by injection with paclitaxel increased pancreatic cystic tumor resolution

to 79% at 6-mo in an abstract of 14 patients^[7]. A prospective randomized double-blind single-center study of EUS-FNI of non-malignant mucinous pancreatic cysts with Paclitaxel and Gemcitabine following either ethanol or saline lavage is currently underway, with preliminary results showing 75% complete resolution at 1 year follow-up^[8]. To the best of our knowledge, EUS-FNI of Paclitaxel has yet to be performed in malignant lesions.

The use of EUS-FNI for ethanol lavage and ablation of malignant lesions has been described in a small study of adrenal metastatic lesions^[9] and in case reports of gastrointestinal stromal tumors, liver metastases, and insulinomas^[10-12]. A small study of 19 patients with unresectable pancreatic carcinoma who underwent repeated transgastroenteric injections with dehydrated absolute alcohol reported decreased cancer mass in all patients, with tumor mass decreased over 70% in 12/19 patients^[13].

Local ablation

Photodynamic therapy (PDT) utilizes a photosensitizer coupled with light omitted *via* small optic fibers to ablate a targeted area. The photosensitizer is infused systemically but preferentially accumulates in malignant tissue^[14,15]. By activating the optic fibers over an area of interest, the omitted light activates the photosensitizer, resulting in the formation of reactive oxygen species that cause tumor necrosis, vascular damage, and local inflammation^[16]. PDT has been used for inoperable esophageal, gastric, and biliary malignancies^[17]. The percutaneous application of PDT to pancreatic malignancy *via* a hollow metal needle has been shown to be safe and well tolerated, however no survival benefit was seen in one small retrospective study^[18]. Chan *et al*^[19] demonstrated the feasibility and safety of performing EUS guided PDT in porcine liver, pancreas, kidneys, and spleen, however the degree of necrosis was complete (100%) only in the pancreas. Yusuf *et al*^[20] similarly demonstrated successful porcine pancreatic tail necrosis with no observed complications. While, to our knowledge, EUS-guided PDT has yet to be performed in humans, this procedure may be a safe, effective, and less invasive method of locally ablating lesions that cannot be directly accessed endoscopically.

Radiofrequency ablation (RFA) is an ablation technique that uses high-frequency alternating current to create thermal energy and induce coagulative necrosis and may be applied percutaneously, intra-operatively, or endoscopically^[21]. RFA has proven successful in the treatment of both hepatocellular carcinoma and liver metastasis^[22]. The endoscopic application of RFA for malignant biliary obstruction has been shown to be feasible and safe^[23]. The open application of a cool-tip RFA for pancreatic cancer resulted in improved back pain and analgesia, but was associated with significantly high complication rates of up to 50% in patients with pancreatic head cancer, notably due to massive gastrointestinal bleeding^[24,25]. A recent small prospective

multi-center pilot study of EUS-RFA of pancreatic head neoplasms and neuroendocrine tumors was reported using a novel monopolar RF probe (1.2 mm Habib EUS-RFA catheter) placed through a 19 or 22 gauge FNA needle. The study reported successful procedure completion in 8/8 (100%) patients with complete cyst resolution noted in 2/6 patients with cystic neoplasms. No reported major post procedure complications were noted^[26].

Cryothermal ablation is performed using a cryotherm probe (ERBE Elektromedizin GmbH, Tübingen, Germany), which is an internally carbon-dioxide-cooled bipolar RFA probe. Cryothermal ablation performed under EUS guidance has been shown to reduce tumor size in a small cohort study of 22 patients with locally advanced pancreatic adenocarcinoma, with technical success achieved in 72% patients and no severe early complications noted^[27]. The potential application towards EUS ablation of other malignancies is unknown.

The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser is a technology that aims to achieve ablation of a target tissue by the direct application of low-power laser light energy. It has been reported to offer palliative or potentially curative treatment options for hepatocellular carcinoma, colorectal cancer liver metastasis, and malignant thyroid nodules^[28]. The EUS-guided application of the Nd:YAG laser ablation of the pancreas has been described in a pig model. Tissue necrosis was observed for all 8 cases with no severe complications^[29]. A single case report of EUS-guided Nd:YAG laser ablation through a 22-G needle for a patient with hepatocellular carcinoma of the caudate lobe has been reported^[28].

High-intensity focused ultrasound (HIFU) is a non-invasive technique for achieving extracorporeal ablation that induces thermal denaturation of a targeted tissue with minimal to no damage to surrounding tissue. HIFU has been shown to result in tumor ablation and symptom palliation in several studies of patients with liver malignancies^[29]. Targeting intra-abdominal tumors with an extracorporeal source may be limited by overlying bowel gas. To overcome this limitation, a new EUS-guided HIFU transducer was developed by Hwang *et al.*^[30]. This transducer has been shown to ablate liver and pancreatic tissue in a swine model^[31].

BRACHYTHERAPY AND FIDUCIAL MARKERS

Interstitial brachytherapy is used for malignancies of the prostate, breast, pancreatic, gynecologic, and brain cancer^[32,33]. Radioactive seeds are placed directly into malignant tissue, generating local gamma rays and damaging surrounding tissue. While these seeds are usually placed operatively, EUS-guided brachytherapy has been described in pancreatic^[34], esophageal^[35], and head and neck tumors^[36]. In Sun *et al.*^[34], 15 patients with unresectable pancreatic cancer underwent

placement of 22 seeds of iodine-125 under EUS guidance. Clinical benefit measured by improvement of pain was seen in 30% of patients with partial tumor response noted for 27% patients. Complications included pancreatitis and grade 3 hematological toxicity^[34]. A similar study by Jin *et al.*^[37] used EUS-guided brachytherapy with gemcitabine and 5-fluorouracil (5-FU) therapy in 22 patients for up to 24 wk. While no significant increase in survival was seen, tumor growth was effectively controlled in the majority of patients with improvement in pain scores^[37].

EUS-guided placement of fiducial markers provides another example of a minimally invasive technique that enables more precise targeting of neoplastic tissue. Typically placed either surgically or percutaneously, fiducial markers are radiographic markers that are placed around a tumor to serve as reference points for radiotherapy. Accurate fiducial placement is important to ensure the correct dose delivery to a target and minimize radiation applied to surrounding normal tissue. A prospective study of 13 patients with mediastinal and abdominal primary or secondary malignancies (with tumors located at the diaphragm dome, porta hepatis, gastroesophageal junction, mediastinum, retrocardiac, paraspinal area adjacent to the thoracic esophagus, and pancreas) demonstrated the feasibility of EUS-guided placement of fiducial markers. Real-time sonographic and fluoroscopic visualization was used to implant the fiducials into the target tissue with a success rate of 85% and post-procedure infection occurring in a single patient^[38]. Successful EUS-guided fiducial placement has been described in pancreatic cancer^[39-41], esophageal cancer^[42], prostate cancer^[43], and rectal cancer^[44] with varied migration rates depending on the type and length of marker used^[45].

EUS-GUIDED ANTITUMOR AGENT INJECTION

A multitude of injectable agents administered by EUS have been used in clinical trials for the treatment of malignancy. These agents include lymphocytic cultures, immature dendritic cells, and viral vectors. Current literature is limited by small sample size, lack of control, and primarily includes patients with pancreatic cancer only. Overall, studies have demonstrated the safety and feasibility of these injectables but have had disappointing clinical outcomes. However, the concept is promising. Local delivery of antitumor agents may optimize therapeutic drug concentration while minimizing systemic toxicity. Additionally, local treatment may allow for tumor downstaging prior to resection or for mass reduction in poor surgical candidates with obstructive symptoms. Larger studies are needed to establish a definitive role and safety profile, and to identify the optimal injectable agents and tumor types for application of this treatment. A new multiple injectable needle has been described that may improve drug distribution and potentially improve

outcomes^[46].

Allogenic mixed lymphocytic culture

Inducing cytokine production directly within a tumor has been proposed as a method to increase host antitumor defense and promote tumor regression. Chang *et al.*^[47] published the first human anti-tumor injection study in a phase I trial of unresectable pancreatic cancer in 2000. The study utilized intratumoral injections of activated allogenic mixed lymphocyte culture (cytoimplant) designed to increase cytokine release. The cytoimplant was formed by coculturing peripheral mononuclear cells from a healthy allogenic donor and the patient. Escalating doses of 3, 6, and 9 billion cytoimplant cells were injected into the tumor bulk under EUS guidance in eight subjects. Two partial responses and one minor response were noted. Side effects were mild and included low-grade fever and nausea^[47]. A subsequent randomized multi-center study of conventional chemotherapy vs EUS-guided cytoimplant injection was terminated early after survival and tumor response was noted to be inferior in the EUS-FNI arm^[48], however this treatment may still have a role as supplemental therapy.

Immature dendritic cells

Dendritic cells are potent antigen-presenting cells that can generate T-cell immune responses and induce antigen-specific acquired immunity^[49]. Prior studies have shown that dendritic cells exposed to tumor cells, when introduced to human subjects, generate a strong tumor specific T-cell response upon migration to regional lymph nodes^[50]. Hirooka *et al.*^[4] conducted a trial where five patients with inoperable locally advanced pancreatic cancer were treated with intravenous gemcitabine and biweekly EUS guided immature dendritic cell injections, followed by intravenous infusion of lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody (CD3-LAKs). One patient showed partial tumor response leading to tumor resection while two patients had stable disease^[51]. In a study by Irisawa *et al.*^[52], 7 patients had EUS-guided dendritic cells injection, 5 of whom underwent radiation prior to dendritic cell installation to theoretically induce apoptosis and necrosis and increase tumor-associated antigens for dendritic cell cross-presentation. The injections were well tolerated without notable complications and decreased CA 19-9 levels seen in two patients^[52]. A phase I clinical trial of patients with resectable pancreatic cancer compared 15 control patients who received standard care to 9 patients who received preoperative EUS-FNI injection of immature dendritic cells and Picibanil (OK-432), a lyophilized mixture of group A *Streptococcus pyogenes* with anti-neoplastic activity. While there were no significant differences in overall survival times between the two treatment groups, the procedure was well tolerated with mild side effects. A trend towards higher incidence of pancreatic fistulas was seen in the FNI group, however

this was not statistically significant (22% vs 7%)^[53]. A case report of two patients who received EUS-FNA of dendritic cells for advanced gastric cancer has been published^[54].

Tumor necrosis factor alpha

Tumor necrosis factor alpha (TNF- α) is an inflammatory cytokine with innate anticancer activity^[55]. TNFerade (GenVec, Inc.) is a second generation replication-deficient adenovector carrying the transgene encoding human TNF- α , which is regulated by a chemoradiation-inducible promoter. By injecting TNFerade into tumor cells, TNF- α may be delivered into tumor cells *via* gene transfer^[56]. In a phase I/II trial conducted by Hecht *et al.*^[57], 50 patients with locally advanced pancreatic cancer received five weekly injections of TNFerade at escalating doses, 27 of whom received TNFerade *via* EUS-guidance, along with a combination of 5-FU and radiation. Overall, the procedure was well tolerated, however complete or partial response was noted in only a small percentage of patients^[57]. A larger randomized study of 304 patients showed that TNFerade combined with standard treatment was safe but not effective in prolonging survival in patients with locally advanced pancreatic cancer. Receiving EUS-guided vs percutaneous application was actually risk factor for inferior progression free survival on multivariate analysis (HR = 2.08; 95%CI: 1.06 to 4.06)^[55]. A phase I study of neoadjuvant TNFerade biologic in combination with cisplatin, intravenous 5-FU, and concurrent radiation therapy in patients with locally advanced resectable esophageal cancer has been reported, with fatigue, fever, and nausea the most frequently reported adverse events^[58].

ONYX-015

ONYX-015 is a gene-deleted replication-selective adenovirus that targets malignant cells and replicates inside them, ultimately leading to their death^[59]. In a phase I/II trial conducted by Hecht *et al.*^[60], EUS-FNI of ONYX-015 was performed in combination with gemcitabine in 21 patients with advanced pancreatic cancer. Eight treatment sessions were conducted over a period of 8 wk with up to 10 injections received per session. Only 2 patients had partial tumor regression, while 8 patients had stable disease and 11 patients either had progressive disease or had to end the study prematurely. Duodenal perforations occurred in two patients, which were attributed to a stiff endoscope tip; no additional perforations were noted after the protocol was modified to mandate a transgastric approach^[60].

CONCLUSION

The role of EUS-FNI for treatment for gastrointestinal malignancies seems promising in theory, but studies are limited and outcomes have been disappointing to date. Larger multi-center randomized trials will be needed

before widespread application may be pursued.

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