Endoscopic ultrasound-guided tumor ablation

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A B S T R A C T

Endoscopic ultrasound (EUS)-guided interventions for treatment of peripancreal tumors allows for a minimally invasive alternative to other more invasive methods of tumor therapies such as surgery or percutaneous ablation. For many tumors, especially pancreatic and peripancreatic tumors, EUS allows the most direct access for providing therapy. However, our experience with EUS-guided tumor ablation therapy remains limited. Several promising methods for EUS-guided ablation are in development or undergoing clinical evaluation. There have been case reports and several limited studies evaluating various injection therapies such as alcohol or biologic agents. In addition, laser, photodynamic therapy, radiofrequency ablation, and high-intensity focused ultrasound are currently being investigated as possible modalities for EUS-guided ablation. These methods for performing EUS-guided ablation are reviewed.

Keywords: ablation, endoscopic ultrasound, tumor therapy

Introduction

Endoscopic ultrasound (EUS) has expanded into a therapeutic as well as diagnostic tool since it was first introduced more 30 years ago. Linear EUS has made it possible for endoscopists to sample specific lesions with fine needle aspiration. Furthermore, modalities for EUS-guided therapy are expanding. These modalities are especially valuable for elderly and high-risk patients in whom pancreatic surgery may be considered too high risk.

EUS-guided fine-needle injection

Pancreatic cysts are increasingly being discovered incidentally as the use of cross-sectional imaging becomes more common. In one autopsy study, the prevalence was estimated to be 25%. For pancreatic cysts with malignant potential, surgical resection remains the mainstay of therapy, although with substantial morbidity. EUS with fine needle aspiration was first introduced as a diagnostic modality in 1992 when the advent of linear-array EUS allowed for direct sampling of a pancreatic cyst under ultrasound guidance. The subsequent development of EUS-guided fine needle injection (EUS-FNI) is currently being investigated as a possible nonsurgical method for managing pancreatic cysts.

EUS-guided ethanol ablation has previously been shown to be effective in renal, hepatic, and thyroid cysts by leading to cell membrane lysis. The first published series of using ethanol lavage of pancreatic cystic lesions was published in 2005. In this study, Gan et al demonstrated complete resolution of pancreatic lesions after a single lavage session in eight out of 25 patients. Subsequently, a randomized controlled trial showed significant size reduction in patients who underwent ethanol lavage compared to saline lavage, with complete resolution of the cyst in 33.3% of patients. DiMaio et al demonstrated greater size reduction and rate of cyst resolution with two treatments of ethanol lavage compared to one. EUS-guided ethanol lavage with paclitaxel injection has also been reported as a safe and effective alternative to ethanol injection alone. Ethanol has also been used for ablation of metastatic lymph nodes and other pancreatic lesions such as insulinomas, although these modalities have not yet been studied in clinical trials.

EUS-FNI has been used to inject donor and host mononuclear cells into pancreatic adenocarcinomas on the theory that it will stimulate an immune response and cytokine release to slow tumor progression. Although the procedure appeared to be safe in a Phase I trial in eight patients, it has not been replicated or proven to be clinically beneficial. TNFerade is an adeno viral vector containing the human TNF-alpha gene, which is thought to slow tumor progression. Although initially proven to be safe and effective when injected into pancreatic adenocarcinoma by EUS or percutaneously, a subsequent Phase III clinical trial failed to show a statistically significant benefit in tumor suppression and was stopped early. Safety and efficacy have also been shown in a single trial of esophageal cancer.

We also reported a case study of EUS-FNI delivery of interferon beta-1B into a peripancreatic tumor followed by systemic T cell in-
sion, an adoptive T cell therapy, in a patient with Merkel cell carcinoma, a highly aggressive neuroendocrine skin malignancy. The drug had previously been administered systemically, but had failed to reach the lesion in sufficient concentration. Through EUS-FNI, the drug was able to be delivered directly into the tumor site, resulting in a significant reduction in the tumor size.

**EUS-guided radiofrequency ablation**

EUS-guided radiofrequency ablation (RFA) uses high-frequency alternating current to cause a thermal-induced coagulative necrosis. Although used commonly in liver, kidney, and prostate cancers, its utilization in pancreatic cancers has been limited by its retroperitoneal location. Advances in RFA electrodes have created a potential for its use as a palliative and curative tool. EUS-guided RFA was first studied in an animal model by Goldberg et al in 1999, when they used it to complete coagulation necrosis in a porcine pancreas. In 2009, Varadarajulu et al reported on EUS-guided RFA of the liver in a porcine model with successful coagulation necrosis of the targeted areas. Radiofrequency has also been combined with simultaneous cryogenic cooling and been shown to be effective and with fewer complications than radiofrequency alone in a porcine pancreas, liver, and spleen. Kim et al recently reported the safe and effective use of an 18-gauge RFA electrode to directly puncture a porcine pancreas under EUS guidance. They demonstrated successful tissue ablation in a spherical distribution in 10 pigs with no procedure-related complications. Of note, only the body and tail of the pancreas was targeted.

**EUS-guided laser therapy**

Photodynamic therapy (PDT) has been shown to be effective at inducing coagulation with the photosensitizing agent porphyrin sodium. EUS-guided PDT was first described by Chan et al in 2004 as an effective form of tissue ablation in porcine liver, pancreas, kidney, and spleen. After inserting a 19-gauge needle into the target organ, they passed a quartz optical fiber through the needle to deliver the PDT directly into the organ. Yusuf et al demonstrated effectiveness using PDT with verteporfin, as it has been associated with less photosensitivity than porphyrin sodium. They performed EUS-PDT using a porcine pancreas model, varying the amount of time the pancreas was exposed to the laser therapy, and found increased amounts of tissue ablation as the duration of laser therapy was increased.

The neodymium:yttrium aluminum garnet (Nd:YAG) laser is a more recent development in EUS-guided laser therapy. Di Matteo et al initially reported on EUS-guided Nd:YAG delivering between 500 J and 1000 J of energy in a porcine pancreas with no complications and successful tissue ablation on pathology. Later, the same group reported the successful application of Nd:YAG therapy to a hepatocellular carcinoma. More recently, Di Matteo et al studied the optimal setting of laser by comparing a range of laser output powers from 1.5 W to 20 W, again in a porcine pancreas model, measuring tissue ablation volume and carbonization volume, a measure thought to approximate risk of thermal injury to surrounding tissues. They found that as the laser output power is increased from 1.5 W to 20 W, the carbonization volume increases constantly, whereas the tissue ablation volume plateaued between 10 W and 20 W. This model could be an effective tool for determining safe but effective therapeutic doses of Nd:YAG laser in future studies.

**EUS-guided brachytherapy**

Brachytherapy is a type of radiation therapy where the radiation source is inserted directly into or adjacent to cancer tissue. Although brachytherapy has been studied extensively in the treatment of many cancers, its use in pancreatic adenocarcinoma is still investigational. The largest clinical trial included 15 patients, and demonstrated improvement in pain for a limited period. However, there was no survival benefit and local complications (pancreatitis and pancreatic pseudocyst formation) occurred in three of the 15 patients. Larger studies have not yet been performed to confirm these findings or demonstrate survival benefit.

**EUS-guided high intensity focused ultrasound**

High-intensity focused ultrasound (HIFU; Fig. 1) is a rapidly developing technology that is becoming more widely used for noninvasive and minimally invasive ablation of benign and malignant tumors. This therapy was first reported by Prat et al, who demonstrated effective ablation in an animal model. A more recent prototype EUS-guided HIFU endoscope has been developed using an endobronchial ultrasound transducer for image guidance with overall dimensions that allow the device to be passed through the oropharynx into the stomach. HIFU works by delivering ultrasound energy to the tumor bed, leading to an elevation in tissue temperature and subsequently tissue denaturation. Recent studies suggest that the unique mechanical effects of HIFU may help to enhance targeted drug delivery and stimulate an antitumor immune response in many tumors including pancreatic tumors.

HIFU is potentially beneficial both for curative and palliative treatments for pancreatic cancer, and has been shown to safely reduce pain in patients with unresectable pancreatic cancer, with pain relief achieved in up to 87.5% of patients treated with extracorporeal HIFU. However, targeting peripancreatic tumors using an extracorporeal source is often not possible owing to the lack of an adequate acoustic window because of the presence of overlying bowel gas. The development of an EUS-guided HIFU transducer has many potential benefits including improved targeting, decreased energy requirements, and decreased potential for injury to intervening structures.

**Conclusion**

Since its development as a purely diagnostic technique 30 years ago, EUS has undergone an expansion into the therapeutic realm. EUS-guided ablative therapies are increasingly being used in clinical settings and studied in preclinical settings. Clearly, there is a need for a minimally invasive tool that is able to deliver therapy in...
close proximity to the lesion. These tools are especially beneficial for patients at high risk for surgery and for therapies with potentially high morbidity.

Conflicts of interest

All authors declare no conflicts of interest.

References