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TOPICS

Current topics in endoscopic treatment of pancreatobiliary diseases

Interventional EUS for the treatment of pancreatic cancer

Reiko Ashida · Kenneth J. Chang

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Abstract Since the curved linear array echoendoscope (linear EUS) was developed in the 1990s, EUS has evolved from EUS imaging, to EUS-guided FNA, and now to EUS-guided fine needle injection (FNI), giving EUS even wider application. This advancement has brought "interventional EUS" into the pancreato-biliary field. Interventional EUS for pancreatic cancer includes delivery of contrast agents, drainage/anastomosis, celiac neurolysis (including ganglion neorolysis), radiofrequency ablation, photodynamic therapy, brachytherapy, and delivery of a growing number of anti-tumor agents. This review will focus on interventional EUS in the treatment of pancreatic cancer.

Keywords Endoscopic ultrasound · Interventional EUS · Pancreas cancer · Therapy

Introduction

Worldwide, pancreatic cancer is the 13th most common type of cancer and the eighth most common cause of cancer-related death for both sexes combined [1]. Most patients have advanced/metastatic disease at the time of diagnosis, or will relapse even after surgery. Pancreatic cancer still has a very poor prognosis with an overall 5-year survival rate of 20.3% for patients with localized disease and 8% for those with metastatic disease. Gemcitabine-based therapy is an acceptable standard for unresectable locally advanced/metastatic pancreatic cancer, but average median survival is only 6 months. The addition to gemcitabine of other chemotherapies or targeted therapies has failed to improve outcomes. Therefore, there is an urgent need for new and more effective diagnostic and therapeutic strategies for patients with pancreatic cancer.

Endoscopic ultrasound (EUS) is the most sensitive imaging procedure for the detection of small solid pancreatic masses and is also accurate in determining vascular invasion. Even compared to new CT techniques, EUS provides excellent results in tumor detection and staging of pancreatic cancer. Since the curved linear array echoendoscope (linear EUS) was developed in the 1990s, EUS has undergone evolution from EUS imaging to EUS-guided fine needle aspiration (FNA) to obtain tissue for cytologic diagnosis. Most recently, EUS–FNA has changed from aspiration into EUS-guided fine needle injection (FNI) which gives EUS even wider application. This advancement has brought "interventional EUS" into the field as an important modality for the diagnosis and treatment of pancreato-biliary diseases.

Interventional EUS includes delivery of contrast agents, drainage/anastomosis, celiac neurolysis (including ganglion neorolysis), radiofrequency ablation, photodynamic therapy, brachytherapy, and delivery of a growing number of anti-tumor agents. This review will focus on interventional EUS in the treatment of pancreatic cancer.

Contrast injection and drainage/anastomosis

Endoscopic retrograde cholangiopancreatography (ERCP) is sometimes difficult to perform, especially in patients with advanced pancreatic cancer which involves either the ampulla or common bile duct. EUS-guided injection of

R. Ashida · K. J. Chang (✉)
Irvine Medical Center, H.H.Chao Comprehensive Digestive Disease Center, University of California, 101 The City Drive, Orange, CA 92868, USA
e-mail: kchang@uci.edu

R. Ashida
e-mail: rashida@goo.jp

contrast through the duodenal wall into the common bile duct can provide a cholangiogram in patients where ERCP has failed. EUS-guided contrast injection followed by guidewire placement, through either the duodenum or the stomach, may salvage difficult ERCP cannnulations by EUS-guided "rendezvous" techniques [2]. EUS-guided choledochoduodenostomy is a newly reported method to create an anastomosis between the bile duct and the GI tract in patients for which ERCP has previously failed. This was first reported by Giovannini in 2001 [3]. There have been about 10 publications reporting a total of 25 patients who have undergone EUS-guided choledochoduodenostomy [4, 5]. Although the technical and treatment successes show promise, preliminary complications such as pneumoperitoneum or bile peritonitis raise some concern. Two prototypes have recently been developed in order to create tissue adherence with subsequent fistula formation. A hinged metallo-plastic biliary stent device causes compression by use of magnets placed endoscopically [6]. However, access into the bile duct through the ampulla is still required. Recently, an EUS-guided needle device using variable tension super-elastic compression coils has been reported in a dog model [7]. Once the needle traverses the duodenum and bile duct, the coil is released across both walls, with subsequent adhesion and fistula formation. Future work must include overcoming the problem of bile peritonitis by providing leak-tight tissue approximation between the bile duct and duodenum and by developing a one-step biliary drainage system.

Celiac plexus neurolysis (CPN) and ganglion neurolysis (CGN)

Pain management for the patients with advanced pancreatic cancer is very important to improve their quality of life. Celiac Plexus Neurolysis (CPN) traditionally has been performed by percutaneous, posterior approach under CT or ultrasound-guidance. However, since Wiersema et al. [8] reported EUS-guided CPN in 1996, CPN can be performed via a trans-gastric, anterior approach. After visualizing the celiac trunk by the linear array echoendoscope and utilizing a 22-gauge needle, injection of bupivacaine (0.25%) followed ethyl alcohol (98%) can then be performed on either side of the vessel or onto the area just at the angle above the celiac artery take-off from the aorta. We now use a mixture of bupivacaine (0.75%) and ethyl alcohol at our institution.

EUS-CPN has shown effectiveness for pain control. Wiersema et al. showed 79–88% improvement in pain with intra-abdominal malignancy patients (25/30 with pancreatic cancer). Gunaratnam et al. [9] showed 78% pain reduction in advanced pancreatic cancer patients. Only minor complications were seen, consisting of transient pain, diarrhea, and hypotension. In 2006, Gleeson et al. [10] reported that celiac ganglia can be visualized and accessed by EUS allowing for direct injection into the individual celiac ganglion to perform celiac ganglia neurolysis (CGN). Recently, they reported the initial evaluation of efficacy and safety of EUS-CPN for both pancreatic cancer patients and chronic pancreatitis patients [11]. They performed EUS–CGN in 17 patients with pancreatic cancer which resulted in 94% of patients reporting improvement of pain scores. Among these patients, narcotic use increased in two patients, remained equivalent in 13 patients, and decreased in 3 patients. Interestingly, they reported initial pain exacerbation lasting a mean duration of 2.2 days in 13 patients (34%) who had EUS–CGN. However, those patients who had initial pain exacerbation eventually experienced greater pain relief at follow up. No severe complication was observed except transient hypotension and diarrhea. Overall, EUS–CPN/CGN are safe and effective procedures for controlling pain in patients with pancreatic cancer. EUS–CPN/CGN may be the most cost-effective modality because it can be performed at the time of diagnosis. Further studies are needed to evaluate cost, injection method, quality of life and potential advantage for survival.

Radiofrequency ablation (RFA) and photodynamic therapy (PDT)

Radiofrequency ablation (RFA) is now an established tool for treating unresectable liver tumors. RFA produces coagulative necrosis of a tumor through local tissue heating. Liver tumors are treated percutaneously, laparoscopically, or during laparotomy using ultrasound, MRI or CT guided methods. However, EUS may be the safest and easiest method to deliver RFA therapy depending on the site of the lesion. Goldberg et al. [12] published in 1999 the feasibility and effectiveness of radiofrequency ablation in the pancreas under EUS-guidance with a 19 G needle in 13 pigs, confirmed by necroscopy. The area of necrosis measured 1 cm. One pig had mild hyperlipasemia, a focal zone of pancreatitis (<1 cm), and later a pancreatic fluid collection. Biochemical parameters were normal in the remaining pigs. Other complications included three gastric and one intestinal burn caused by improper electrode placement. In 2008, Carrara [13] demonstrated the feasibility and efficacy of EUS-guided RFA using a newly developed flexible bipolar ablation probe combining RF and cryotechnology in 14 pigs. The size of the ablation area was related to the duration of ablation. The complications were less than those for conventional RFA needle, showing histochemical pancreatitis in two pigs, one burn effect on the gastric wall and four gut adhesions which were found during necropsy.

Photodynamic therapy (PDT) is a treatment causing localized tissue necrosis using light after administration of a photosensitizing agent in the presence of oxygen. The first report of experimental PDT for a pancreatic cancer model was in the 1980s. Treatment with PDT resulted in extensive necrosis of the tumor without any obvious effect on the remaining pancreas [14]. Bown et al. [15] used PDT percutaneously under CT guidance in the palliation of 16 patients with advanced pancreatic cancer. All patients had substantial tumor necrosis without evidence of pancreatitis. Chan et al. [16] subsequently reported another animal experiment using EUS-guided PDT to multiple normal organs in a porcine model. The animal was injected with porfimer sodium intravenously. Subsequently, a 19-gauge needle was inserted into the pancreas, the liver, the spleen, and the kidney under EUS guidance. A small diameter quartz optical fiber was passed through the EUS needle and used to illuminate the tissue with laser light. Localized tissue necrosis was achieved in all organs, without significant complication. There was no significant difference in inflammation induced by photodynamic therapy within the various organs.

Animal and clinical studies suggest that EUS-guided PDT may be used to ablate pancreatic cancer while sparing normal tissue, although larger clinical studies are needed to determine safety, appropriate choice of drug type and dose, light wavelength, and drug-light interval.

EUS-guided Brachytherapy (EUS-BrTx)

Despite continuous improvements in traditional external-beam radiotherapy (EBRT), this technique has been limited by radiation toxicity to the normal tissues surrounding the tumor. Brachytherapy is a relatively safe procedure in which radiation seeds are delivered directly to the gland, allowing greater intra-organ radiation doses than achievable by EBRT alone. Brachytherapy has been widely used for various malignancies such as prostate, lung and esophageal cancer. Permanent seed brachytherapy can be done as a single-day outpatient procedure with few post-treatment radiation precautions required either during the procedure or after the procedure.

EUS-guided Brachytherapy (EUS-Brtx) was first reported by Maier et al. [17] in 1999 for head and neck tumors. Now EUS-BrTx allows us to approach multiple locations such as malignant biliary strictures, esophageal cancer, rectal cancer, and now pancreatic cancer. In 2006, Sun et al. [18] published a report of 15 patients with unresectable pancreatic cancer (8 patients with stage III and 7 patients with stage IV disease) who underwent EUS-BrTx using iodine (I^{125}). The average time of EUS-BrTx was 28 min. The mean number of seeds implanted was 22 (range 11 to 30 per patient), with a mean radioactivity of 0.89 mCi per seed and a mean total implanted activity of 20 mCi. The tumor size was measured by CT and EUS within 4 weeks after the treatment. Their results showed improvement in pain and performance status in five patients. There was a partial response in four cases (26.7%), minor response in three cases (20%), stable disease in five (33.3%) and disease progression in three cases (20%). The overall median survival was 10.6 months (range 4.2–25 months) (stage III; 12.2 months, stage IV; 6.5 months). Grade III hematologic toxicity such as neutropenia, anemia, and thrombocytopenia was seen in three patients. Three patients developed pancreatitis and two of these developed pseudocysts. No life-threatening complications were observed.

Combination chemotherapy and brachytherapy for pancreatic cancer has also been reported. In 2008, Jin et al. [19] published the first report using combination therapy chemotherapy (gemcitabine and 5-FU) and EUS-BrTx using iodine (I^{125}). Twenty-two unresectable pancreatic cancer patients were enrolled (stage II, 2 cases; stage III, 10 cases; stage IV, 8 cases). The mean number of seeds implanted was 14 (range 5–30 per patient), with a mean radioactivity of 0.706 mCi per seed. After treatment, there was significant improvement in visual analog scale (VAS) pain score from 5.07 ± 2.63 to 1.73 ± 1.91 ($p = 0.002$) in 18 patients (81.8%). Tumors were measured by CT 1 month after treatment. There was a partial response in three cases (13.6%), stable disease in ten (45.5%) and disease progression in nine cases (40.9%). The overall median survival was 9.0 months (range 6.7–11.3 months). Fever was observed in 12 patients (54.5%) within 24 h after the procedure and disappeared within 1 week following antibiotic treatment. No pancreatitis was reported.

These two reports show promising preliminary data that pancreatic cancer can be treated safely with EUS-BrTx. Again, additional larger studies are needed to establish this as an acceptable option for inoperable pancreatic cancer.

In addition to brachytherapy, EUS may be increasingly used in the management of gastro-intestinal cancers through the endoscopic placement of fiducial markers for image-guided radiation therapy (IGR) [20]. Any future development in fiducial markers will need to include thin caliber markers able to fit into a 22 gauge needle, a multi-marker deployment device, and differently shaped markers such as wires or coils.

Delivery of anti-tumor agents

Allogenic mixed lymphocyte culture (cytoimplant) in pancreatic cancer

We have examined the feasibility and safety of direct injection of cytoimplants in pancreatic adenocarcinoma

under EUS guidance [21]. In a phase I clinical trial, eight patients with unresectable pancreatic adenocarcinoma underwent EUS-guided fine needle injection (FNI) of cytoimplants. Four patients were in stage II, three in stage III, and one in stage IV. Escalating cytoimplant doses of 3, 6, or 9 billion cells were implanted using EUS-guided FNI. The median survival was 13.2 months with two partial responders and one minor response. Major complications such as bone marrow toxicity, hemorrhagic, infectious, renal, or cardiopulmonary toxicity were absent. Low-grade fever was encountered in seven of the eight patients and was symptomatically treated with acetaminophen. Our study showed that local immunotherapy is feasible and safe. Currently, there are no active clinical protocols evaluating cytoimplants for EUS-guided FNI.

ONYX-015 in pancreatic cancer

The technique of EUS-guided FNI was recently applied to deliver antitumor viral therapy [22]. ONYX-015 (dl1520) is an E1B-55-kDa gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells. Twenty-one patients with locally advanced adenocarcinoma of the pancreas or with metastatic disease, but minimal or absent liver metastases, underwent eight sessions of ONYX-015 delivered by EUS injection into the primary pancreatic tumor over 8 weeks. The final four treatments were given in combination with gemcitabine (IV, 1000 mg/m^2). After combination therapy, 2 patients had partial regressions of the injected tumor, 2 had minor responses, 6 had stable disease, and 11 had progressive disease. No clinical pancreatitis occurred despite mild, transient elevations in lipase in a minority of patients. Two patients had sepsis before the institution of prophylactic oral antibiotics. Two patients had duodenal perforations from the rigid endoscope tip. No perforations occurred after the protocol was changed to transgastric injections only. Currently, there are no active clinical protocols evaluating ONYX-015 for EUS-guided FNI.

TNFerade in pancreatic cancer

TNFerade^{TM} is the newest EUS-guided anti-tumor therapy, which involves a novel gene transfer approach [23–25]. The attractiveness of this new approach is the potential to maximize local anti-tumor activity and minimize systemic toxicity. TNFerade^{TM} was constructed as a second-generation (E1-, partial E3, and E4-deleted) adenovector, expressing the cDNA encoding human tumor necrosis factor (TNF). To further optimize local effectiveness and minimize systemic toxicity, a radiation-inducible immediate response *Egr-1* (early growth response) promoter was placed upstream of the transcriptional start site of the human TNF cDNA. This vector was engineered to ensure that maximal gene expression and subsequent TNF secretion are constrained in space and time by radiation therapy. Thus the synergistic 'triple threat' is formulated: 5-FU chemotherapy is directly toxic to cancer cells and is also a radiosensitizer; external beam radiation destroys cancer cells and upregulates TNF production; and TNFerade^{TM} causes cancer cell death and is itself a radiosensitizer.

TNFerade^{TM} in combination with radiation therapy has been studied in pre-clinical and early clinical (phase I) trials with encouraging results [26, 27]. The study design consisted of a 5-week treatment of weekly intratumoral injections of TNFerade (4×10^9, 4×10^{10}, 4×10^{11} particle units (pu) in 2 mL). EUS-guided FNI (Fig. 1) was compared with percutaneous approaches (CT or US). TNFerade was combined with continuous intravenous 5-FU (200 mg/(m^2 day) $\times$ 5 days/week) and radiation (50.4 Gy). TNFerade was delivered with a single needle pass at a single site in the tumor for percutaneous approaches (PTA), while up to four injections were given by EUS. The long-term results from a cohort of 50 patients showed that toxicities potentially related to TNFerade^{TM} were mild and well tolerated. Compared with two lower dose cohorts ($n = 30$) The higher dose group ($n = 11$) was associated with greater locoregional control of treated tumors, longer progression-free survival, a greater proportion of patients with stable or decreasing levels of CA 19-9, a greater percentage (45%) of patients resected, and improved median survival (6.6, 8.8, 11.2, and 10.9 months, in the 4×10^9, 4×10^{10}, 4×10^{11} or 1×10^{12} particle units cohorts, respectively). At the 4×10^{11} dose, four out of five patients whose tumors became surgically resectable achieved pathologically negative margins, and three

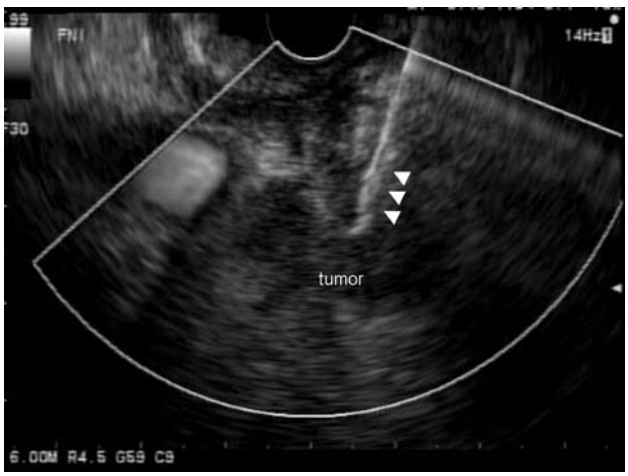

Fig. 1 EUS-guided FNI of TNFerade in pancreatic adenocarcinoma (*arrows*, needle within the tumor in the head of the pancreas with Doppler image)

survived >24 months. A randomized control trial is currently in progress.

Immature dendritic cells (DC) against pancreatic cancer

DC are potent antigen-presenting cells for induction of primary T cell dependent immune responses. DC, when injected intratumorally, acquire and process tumor antigens in situ, migrate to regional lymphoid organs, and initiate a strong tumor-specific immune response. In a recent study, seven patients with metastatic disease and/or locally advanced pancreatic cancer underwent EUS-guided FNI of DC into pancreatic cancer [28]. All patients had previously been unsuccessfully treated with gemcitabine. No procedure or drug-related complications were encountered in any patient. The median survival period was 9.9 months.

Oncolytic herpes simplex virus carrying the GM-CSF gene (Onco VEX^{GMCSF}) against pancreatic cancer

Recent technological developments have made these oncolytic viruses more tumor-specific [29]. These viruses have been reported to increase the immunosusceptibility of the tumor cells, and have been designed to express other genes to increase the susceptibility of tumor cells to agents such as chemotherapy. The therapeutic efficacy of this agent against pancreatic cancer is currently unknown and the results are pending.

Conclusions

EUS-guided FNI has truly paved the way for therapeutic/interventional EUS. The interventional endoscopist will now play a more active role in the treatment of pancreatic cancer by delivering anti-tumor agents in addition to palliating pain, relieving obstruction, and treating recurrences.

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