Mini-Review

Interventional Therapy for Pancreatic Cancer

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Key Words

Endoscopic ultrasound · Endoscopy · Pancreatic cancer · Therapy

Abstract

Background: Palliative therapy and primarily chemoradiotherapy are the mainstream treatments in patients with locally advanced or metastatic pancreatic cancer (PC). Conventional endoscopy and endoscopic ultrasound (EUS)-guided interventional therapy has emerged as an important procedure for PC management. In this review, the progress in conventional endoscopy and EUS for PC management is discussed. **Summary:** For local palliative therapy against PC, EUS-guided fine needle injection (FNI) could deliver different kinds of agents, such as radioactive seeds and fiducials. Although their feasibility and safety have been proven, the long-term efficiency of EUS-FNI is still not established. For pain, EUS-celiac plexus neurolysis (CPN) is effective. However, CPN can only relieve the pain to a limited degree, with short duration. Endoscopy-guided stent placement is the preferred strategy for biliary and duodenal obstruction. Plastic and metal stents are equally effective for the relief of obstructive jaundice. The functional times of metal stents are longer than those of a plastic stent. **Key Message:** For biliary obstruction, a metal stent is the first choice. The long-term efficiency of EUS-FNI still needs further study. **Practical Implications:** Endoscopy and EUS-guided interventions have gradually become the mainstream method for local treatment of PC due to mini-invasiveness and real-time observation. PC is the second most common gastrointestinal malignancy and the sixth leading cause of cancer mortality in the United States, leading to about 4.0% of all cancer deaths [Siegel et al: CA Cancer J Clin 2014;64:9–29]. The only curative approach for patients with PC is surgical resection, but unfortunately 80–90% of patients have a surgically inoperable disease, with 53% having local metastases at the time of diagnosis [Weinberg et al: Oncology (Williston Park) 2015;29:809–820, 886]. Therefore, palliative therapy and primarily chemoradiotherapy are the mainstream of treatment in patients with locally advanced or metastatic PC. Although overall survival has improved from 6 to 8.5–11 months

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(some of them even survived for a year or more), the overall survival rate has not improved, and the 5-year survival is less than 4% [Weinberg et al: *Oncology* (Williston Park) 2015;29: 809–820, 886; Greenlee et al: *CA Cancer J Clin* 2001;51:15–36; Zhang et al: *Gastroenterol Res Pract* 2016;2016:8962321]. Hence, it is crucial to develop more effective local treatment strategies for tumor tissue and symptom palliation. At present, endoscopy has gradually become the mainstream method for local treatment of gastrointestinal cancer due to mini-invasiveness and real-time observation. Conventional endoscopy can be used to manage the complication caused by PC, including endoscopic biliary stent placement for obstructive jaundice, and duodenal stent placement for duodenal obstruction. In addition, in those cases in whom obstructive jaundice failed to be relieved by endoscopic biliary stent placement, EUS-guided biliary drainage has emerged as an alternative procedure. Furthermore, antitumor agents can be delivered into tumor tissue or celiac plexus directly under interventional EUS guided to manage the tumor or the pain caused by the tumor. In this review, the progress in conventional endoscopy and EUS for PC management is discussed.

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Endoscopic Ultrasound-Guided Interventional Therapy

Endoscopic Ultrasound-Guided Brachytherapy

Endoscopic ultrasound (EUS)-guided radioactive seed implantation has emerged as a novel strategy for the treatment of pancreatic cancer (PC). EUS-guided brachytherapy has proven to be a mini-invasive, simple and safe procedure, using sufficient and durable radiation, and to minimize surrounding normal tissue damage. This technique is feasible and safe for the treatment of PC, and it could also relieve pain due to PC. In 2006, Sun et al. [1] reported that EUS-mediated implantation of ^{125}I seeds can be used for patients with locally advanced PC. Fifteen patients with PC were enrolled in this study, and most of the cases are in stage III or IV. During a median of 10.6 months of follow-up, 27% of patients had partial response and 20% had minimal response. In a prospective pilot study published by Jin et al. [2], the median survival of 22 patients was 9.0 months, but only 3 had partial remission. In addition, the pain score on the visual analog scale (VAS) decreased 1 week and 1 month after ^{125}I seed implantation. Du et al. [3] conducted a study enrolling 100 cases to determine the long-term effects of ^{125}I seed implantation. It showed an estimated median progression-free survival and overall survival of 4.5 and 7.0 months, respectively. Similarly, VAS scores dropped dramatically 1 week after implantation and remained significantly low until the third month. However, all of those studies had only one cohort, and the advantage of this technique needs to be confirmed by comparison studies.

EUS-Guided Fiducial Placement

Radiation therapy is one of the main treatment methods for unresectable or metastatic PC. However, due to the low-contrast character of soft issue, pancreatic tumors are poorly visible on cone-beam CT. Hence, for allowing precise and real-time tracking of the tumor under the guidance of fiducial markers placed in the tumor tissue, image-guided radiation has become a significant method in PC treatment. Traditionally, fiducials were inserted either surgically or percutaneously under image guidance. As a mini-invasive and visualization approach, EUS-guided fiducial placement has gradually turned into a mainstream treatment. In 2006, Pishvaian et al. [4] used EUS for fiducial placement, and several studies were published to evaluate its safety and feasibility under EUS guidance [5–9]. The technical success rate of this technique was 90–100% [5, 6, 9, 10]. In addition, the complication rate associated with this technique was low, and the tumor migration rate of fiducial markers was

7% [11]. In order to have appropriate tracking, it is recommended to place fiducials with 'ideal fiducial geometry' (IFG) [10]. The main disadvantage of EUS is that it is hard to achieve IFG. However, a recent retrospective study showed that IFG may be unnecessary for successful tracking and delivery of radiation. In this study, 77 patients were enrolled to compare the difference between EUS-guided fiducial placement and surgical placement. Although surgical placement had a higher IFG proportion, the success rate of fiducial tracking used for CyberKnife therapy was similar between the two groups [10]. Therefore, with the merit of mini-invasiveness and little complications, EUS-guided fiducial placement is feasible and safe for PC treatment.

EUS-Guided Fine Needle Injection

Antitumor agents can be directly delivered into tumor tissue for the treatment of locally advanced PC by EUS-fine needle injection (FNI). Chang et al. [12] were the first to publish a phase I clinical trial study of the usage of antitumor injection for advanced PC. Allogeneic mixed lymphocyte culture was delivered to 8 patients by EUS-FNI. Three of them had partial or minor response, with a median survival of 13.2 months and without procedure-related complications. In a phase I/II trial conducted by Hecht et al. [13], 21 patients with PC received 8 weeks of injections of ONYX-015. After a combination with gemcitabine, 2 patients had partial regression, 2 had minor responses, 6 had stable disease, and 11 had progressive disease or had to quit the study because of treatment toxicity. Complications presented in 4 patients, including sepsis and duodenal perforations. After that, they conducted another phase I/II study on injection TNFerade combined with 5-fluorouracil and radiotherapy for treatment of locally advanced PC [14]. Fifty patients were given EUS-FNI, 1 of them had complete response, 3 partial responses, and 12 stable disease. However, although the feasibility and safety had been confirmed by the above study, until now the long-term efficiency of EUS-FNI is still undefined.

EUS-Guided Radiofrequency Ablation

The efficacy and safety of percutaneous ultrasound-guided radiofrequency ablation (RFA) for PC have been confirmed. Currently, EUS-RFA has emerged as an alternative procedure. Several studies have reported an animal experiment for normal porcine pancreas [15, 16]. Recently, Song et al. [17] demonstrated the technical feasibility and safety of EUS-RFA for unresectable PC. This study enrolled 6 patients; 4 patients had stage 3 disease and 2 patients had stage 4 disease. After the procedure, 2 patients experienced mild abdominal pain, but there were no other adverse events such as pancreatitis or bleeding. As expected, 2 patients had mild abdominal pain, and no major complication was noted.

EUS-Guided Ethanol Ablation

EUS-guided ethanol ablation is a novel treatment strategy for pancreatic cystic neoplasms (PCNs) and pancreatic neuroendocrine tumors. The use of EUS-guided ethanol ablation for pancreatic cystic lesions was first described by Gan et al. [18] in a pilot study including 25 patients. After evacuation of the cyst with needle aspiration, the cyst cavity was lavaged with ethanol for 3–5 min. None of the patients reported any symptoms in the short or long term, and 8 of them had complete resolution of their cyst after 1 year of follow-up. This study suggested that ethanol lavage of pancreatic cystic lesions is safe and feasible. A randomized controlled trial (RCT) study conducted by DeWitt et al. [19] showed that EUS-guided ethanol lavage resulted in a greater mean percentage of decrease in the cyst surface area compared with saline solution alone (43 vs. 11%), and 12 of 36 PCNs showed complete resolution. Long-term follow-up data also suggested that ethanol ablation had a durable, image-defined resolution [20]. Oh et al. [21] reported an experiment to evaluate the usage of EUS-guided injection

and lavage of ethanol, followed by injection of paclitaxel for PCNs. One year later, 62% of the PCNs showed complete resolution without complication, which demonstrated that ethanol lavage combined with paclitaxel injection may be more effective. EUS-guided ethanol ablation is also used for the management of pancreatic solid tumors. Recently, Park et al. [22] investigated the safety, feasibility, and treatment response after EUS-guided ethanol injection for small pancreatic neuroendocrine tumors. EUS-guided ethanol injection was successfully performed in 11 patients with 14 tumors. Ten patients underwent clinical follow-up after treatment. After 3 months of follow-up, a single treatment session resulted in complete responses for 7 of 13 (53.8%).

EUS-Guided Celiac Plexus Neurolysis

Pain is the most common complication in patients with PC and difficult to treat in clinical practice. Traditionally, this symptom was alleviated by opioid analgesics. However, these medications usually lead to serious side effects, including sedation, chronic constipation, delirium, nausea, vomiting, and a negative impact on quality of life [23]. In order to overcome these disadvantages, Wiersema and Wiersema [24] described the treatment method of EUS-guided celiac plexus neurolysis (EUS-CPN) for PC pain in 1996. A meta-analysis including 119 patients showed that the effective rate of EUS-CPN to alleviate abdominal pain was 72.54% in patients with PC [25]. Another meta-analysis conducted by Arcidiacono et al. [26] identified a difference in efficacy between CPN and opioid consumption. Compared with opioid consumption, EUS-CPN was demonstrated to reduce pain after the fourth and eighth week, which consequently significantly reduced opioid consumption. In fact, EUS-CPN may increase the survival of patients with PC. In a case-control study conducted by Fujii-Lau et al. [27], EUS-CPN was associated with longer survival compared with non-EUS approaches. However, instead of completely eliminating the pain, EUS-CPN can only relieve pain to a certain degree, and the majority of patients still needs opioid drugs. In addition, this technique also has some adverse events, and the adverse event rate related to EUS-CPN was about 30% [11]. The most common adverse events are diarrhea, abdominal pain and hypotension. Other serious adverse events are bleeding, abscess, abdominal ischemia, permanent paralysis as well as death. Therefore, to increase the efficacy and safety of EUS-CPN, different kinds of techniques were conducted. In 2011, an RCT study reported that there was no difference in the onset or duration of pain relief when either 1 or 2 injections were used [28]. However, EUS-guided direct celiac ganglia neurolysis may be superior to conventional EUS-CPN in cancer pain relief [29]. The study by Doi et al. [30] showed that the positive and complete response rates were significantly higher in the EUS-guided direct celiac ganglia neurolysis group than in the EUS-CPN group. However, all of these studies have small sample sizes. Therefore, a large-sample study should be carried out to define these controversies and evaluate the efficacy and safety of those techniques.

CPN can only relieve pain to a limited degree, with a short duration, and the analgesic effect is inversely correlated with the extent of invasion of celiac ganglia [31]. Therefore, a series of novel approaches were conducted to improve this technique. In 2012, Wang et al. [32] implanted ^{125}I around the celiac ganglia with EUS guidance and found that EUS-guided direct celiac ganglion irradiation with ^{125}I seeds can reduce the VAS score and analgesic drug consumption in patients with unresectable PC. Recently, a case report was published by Jin et al. [33] describing a patient with uncontrolled pain caused by advanced PC who received EUS-RFA. An RF probe was inserted into the center of the celiac ganglion and fixed RF power (heating) with 10 W for 120 s and 15 W for 120 s. After 2 days, the VAS score decreased from 8 to 2. Two weeks after the procedure, the VAS score stabilized at 4, and opioid analgesics were still not needed. Additional larger studies are warranted to establish this as an acceptable option for pain relief of inoperable PC.

EUS-Guided Biliary Drainage

Most of the patients with PC, especially tumors in the pancreatic head area, present bile duct obstruction. On those occasions, endoscopic retrograde cholangiopancreatography (ERCP) is the preferred procedure for biliary drainage. However, about 3–10% of the cases cannot be managed by ERCP due to complete tumor obstruction of the distal common bile duct and papilla invasion [34, 35]. Recently, EUS-guided biliary drainage has emerged as an alternative procedure for relieving biliary obstruction in cases in which ERCP has failed. EUS-guided biliary drainage broadly includes EUS-guided rendezvous technique, EUS-guided choledochoduodenostomy, EUS-guided hepaticogastrostomy, EUS-guided antegrade stenting, and EUS-guided gallbladder drainage [36–40]. A system review conducted by our group has recently shown that the technical success rate and functional success rate of EUS-guided biliary drainage for malignant obstruction were 94.55 and 92.49%, respectively [41]. However, data regarding the efficacy and safety of this technique for unresectable PC are lacking. Most studies are case reports or case series [35, 37, 42–44]. Therefore, the next step is to conduct large-sample studies to evaluate the efficacy and safety of EUS-guided biliary drainage for unresectable PC.

Endoscopic Biliary Stenting for Obstructive Jaundice

80% of patients with PC will suffer from obstructive jaundice and may require biliary drainage either preoperatively or merely for palliation [45]. Currently, endoscopic biliary stenting still is the preferred strategy, because it is minimally invasive [46–48]. Since 1980, plastic stents have been widely used for endoscopic relief of malignant biliary obstruction [49]. Because of the large diameter, metal stents may be better than plastic stents in the long term and less susceptible to occlusion. At present, there are numerous studies comparing the use of plastic versus metal stents in the population with PC. They are equally effective for the relief of malignant obstructive jaundice, with both showing a technical success rate of >90% [50]. However, metal stents have a higher safety rate than plastic stents. The study by Adams et al. [51] found that the complication rate of plastic stents was almost 7 times higher than that of metal stents, and the rate of hospitalization for stent-related complications was 3-fold higher in the plastic stent group than in the metal stent group. Moreover, the study by Tol et al. [52] showed that for resectable PC, both preoperative biliary drainage-related and stent-related complication rates were smaller in the metal stent group than in the plastic stent group (24 vs. 46, and 6 vs. 31%, respectively). The above data suggest that metal stents yield a better outcome compared with plastic stents. However, metal stents are also more expensive, which should be considered in clinical application. Recently, Walter et al. [53] conducted an RCT to evaluate which type of stent, either a plastic or self-expandable metal stents (SEMS), is superior for the palliation of malignant extrahepatic bile duct obstruction with regard to clinical effects and associated costs, both in patients with a short and long survival time. They found that the functional stent times of SEMS are longer compared with those of plastic stents (288 vs. 172 days), and although the SEMS placement leads to higher costs, the total costs are not different between both stent types. Therefore, metal stents are the preferred option for all patients with malignant extrahepatic bile duct obstruction.

Besides the traditional stent placement for the palliation of obstructive jaundice, radioactive stent placement is a novel strategy. To date, few studies have evaluated the efficacy and safety of radioactive stents. In 2007, Yan et al. [54] published an animal experiment for the usage of radioactive stents in PC. The procedures were successfully performed on all pigs without perforation of the common bile duct wall. Next, a pilot study was published by Liu et al. [55], in which a total of 16 radioactive stents were successfully placed in 11 patients,

without life-threatening complications. After 2 months of follow-up, 8 patients (72.7%) showed stable disease, whereas 3 patients (27.3%) showed progressive disease. Liu et al. were the first to demonstrate that radioactive stent placement for palliative treatment is effective and safe. Recently, a study compared the difference between the irradiation stent and the conventional stent for biliary obstruction [56]. The stents were successfully placed in 23 patients, and obstructive jaundice was relieved in all patients except 3 in the control group. The median and mean overall survival rates were higher in patients with an irradiation stent than in those with a conventional biliary stent, and the irradiation stent group has a longer stent patent time. However, all the above studies only included small simple sizes. Therefore, the efficacy and safety of radioactive stent placement needs further investigation.

Endoscopic Duodenal Stent Placement

About 10–25% of patients with PC developed malignant duodenal outlet obstruction [57, 58]. However, this rate increased to 38% because of the advances in diagnosing duodenal outlet obstruction with imaging and endoscopy as well as treatment with chemoradiation [59]. As first described by Topazian et al. [60], the duodenal SEMS placement has become the first choice for the palliation of duodenal obstruction due to minimal invasiveness. Compared with surgical gastroenterostomy, endoscopic SEMS placement has a higher clinical success rate, a shorter procedure time until starting oral intake, less morbidity, a lower incidence of delayed gastric emptying, and a shorter time of hospitalization [61]. In order to achieve the best clinical outcome of SEMS placement, the principal element is choosing the appropriate type of stent according to the tumor type, the stricture site and morphology. Woo et al. [62] showed that although the technical and clinical success rates were similar, uncovered SEMS present a lower complication rate than the covered group for the treatment of malignant duodenal obstruction caused by pancreaticobiliary (34.8 vs. 62.5%).

In conclusion, with the development of the endoscopic technology, endoscopy-guided interventional therapy has played an important role in PC treatment from tumor killing to pain relief and drainage with minimal invasiveness. However, there are still some deficiencies, and more studies should be conducted to improve the efficacy of endoscopy-guided interventional therapy.

Disclosure Statement

The authors have nothing to declare.

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