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MINI REVIEW

Endoscopic ultrasound in pancreatic cancer treatment: Facts and hopes

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Summary Pancreatic ductal adenocarcinoma is one of the most common causes of cancer-related deaths. Since most patients present with advanced disease, its prognosis is dismal. New and more effective therapeutic strategies are needed. Endoscopic ultrasound is currently an indispensable tool for the diagnosis and staging of pancreatic ductal adenocarcinoma. In recent years, endoscopic ultrasound has evolved to become also a therapeutic procedure. On one hand, the role of endoscopic ultrasound in the management of pancreatic cancer-related symptoms (pain, obstructive jaundice, and gastric outlet obstruction) is now well established. On the other hand, its use as a mean to the delivery of anti-tumor therapies (injecting anti-tumor agents, assisting in radiotherapy, and guiding ablative therapies) is still mostly experimental, despite growing evidence supporting its feasibility, safety and efficacy.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth cause of cancer-related deaths in the United States (US) [1]. Its incidence is on the rise, while mortality rates have remained relatively unchanged [2]. It is forecasted that it will become the second leading cause of cancer-related death within a couple of decades [3]. Overall 5-year survival rate is 6% in the US [4]. The low survival rate stems mostly from the late stage at which most patients are diagnosed [5]. Only 15—20% of patients are amenable for initial surgical resection [4], with the majority of patients receiving either palliative chemotherapy or best supportive care [6]. Thus, new and more effective therapeutic strategies for patients with PDAC are urgently needed.

Since the introduction of endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) in the 1990s, it has become a mainstay in assisting in the diagnosis and staging of PDAC. Over the last few decades, however, EUS has evolved from a diagnostic tool to a minimally invasive therapeutic alternative to radiologic and surgical procedures for pancreatic diseases, including PDAC. Current evidence supports its use in the management of symptoms related

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to PDAC. In addition, growing data suggests its efficacy for the administration of anti-tumor therapies. In this comprehensive review we sought to evaluate the current and emerging roles of therapeutic EUS in management of patients with PDAC. The English literature was searched up to December 2018 and was conducted using PubMed, Scopus, Medline, ISI Web of knowledge and Google using the terms ''endoscopic ultrasound'', ''pancreatic adenocarcinoma'', ''pain'', ''obstructive jaundice'', ''gastric outlet obstruction'' and ''tumour targeted therapies''. Recursive searches, cross-referencing, and hand-searches of article reference lists were performed.

Treatment of cancer-related symptoms

Pain

Pain is an important symptom in PDAC, with some 75% of patients experiencing significant pain in advanced stages of the disease, with a dramatic impact in their quality of life [7]. Management of pain is a key integral part of the comprehensive therapy strategy in the patients with PDAC. Celiac plexus neurolysis (CPN) and celiac plexus block (CPB) are considered first line adjuvant therapies for the management of pain in pancreatic disorders [6,8].

CPN denotes permanent chemical ablation of celiac plexus (CP) through the injection of alcohol- or phenol-based solution into the CP, whereas CPB refers to the disruption of afferent pain signals transmission from the pancreas typically involving the injection of the CP with a local anesthetic mixed with a corticosteroid [9]. CP interventions are performed via a gastric approach using EUS-guidance and have high success rates and relatively low complication rates. EUS-guided approach is preferred over percutaneous or surgical approaches since it is associated with fewer side effects [9].

Currently, there are three modalities of CP ablation interventions guided by EUS in the setting of PDAC: CPN, celiac ganglia neurolysis (CGN), and broad plexus neurolysis (BPN) [10]. In addition, implantation of iodine-125 seeds into the celiac ganglia guided by EUS has been shown to be feasible, safe and efficacious in an animal model [11].

In 1996, Wiersema [12] reported for the first time the safety and efficacy of EUS-guided CPN in patients with pain due to intra-abdominal malignancies. Later, Gunaratnam et al reported a series of 58 patients with advanced PDAC submitted to EUS-guided CPN; pain scores improved significantly two-weeks after the procedures [13]. A retrospective study including 47 patients reported that EUS-CPN was successful in 68% of cases [14]. More recently, Wyse et al reported the results of a randomized, double-blinded, controlled trial, in which 96 patients with recently diagnosed inoperable PDAC were assigned to early EUS-CPN or conventional pain management. Pain relief was greater at 1- and significantly greater at 3-months in the EUS-CPN group compared to the conventional pain management group [15]. Although opioid consumption was similar in both groups at 1-month, it tended to be lower at 3 months in the CPN group compared to the conventional management group [15]. The above studies show the efficacy of EUS-CPN in obtaining temporary pain relief, however, long lasting analgesia following CPN is not always achieved. Refractory pain has been reported in over 50% of patients [16]. One study comprising 24 PDAC patients evaluated the success rate with repeated CPN. The study showed that repeated CPN did not provide the same degree of pain relief as the initial procedure [17].

Due to the limitations of the long-term efficacy of CPN, there has been an interest in the diffuse injection directly into the celiac ganglia. Rate of ganglia detection varies between 70 to 80% depending on the instrument and the operator [18]. An initial retrospective study reported a 94% efficacy at 2- and 4-weeks for EUS-CGN in 17 patients with unresectable PDAC [19]. Another study compared the efficacy of EUS-CGN ($n = 40$) versus EUS-CPN ($n = 24$) in the setting of PDAC [20]. Pain relief was higher in the EUS-CGN group (65%) compared to the EUS-CPN-group (25%) [20]. More recently, a randomized study confirmed the superiority of EUS-CGN. This study, in which 34 patients were randomized to either EUS-CGN vs. EUS-CPN, showed that the former was associated with an efficacy that was significantly higher in the former than in the latter (73.5% vs. 43.5%, $P < 0.05$) [21].

Lastly, a Japanese group recently reported the effectiveness of EUS-BPN that extends over the superior mesenteric artery (SMA) using a 25-gauge needle [22]. For that purpose, they have compared 34 patients submitted to EUS-BPN vs. 33 patients treated with EUS-CPN, and showed that EUS-BPN patients exhibited significantly greater reductions at days 7 and 30 visual analogue pain scale scores than EUS-CPN patients [22]. A recently published randomized double-blinded trial compared the efficacy of CGN versus that of CPN in patients with unresectable PDAC and abdominal pain [23]. Compared to CPN, CGN reduced median survival time without improving pain, quality-of-life, or adverse events [23].

In conclusion, EUS-guided celiac plexus intervention, in combination with conventional analgesia management, may be useful for pain management in patients of patients with PDAC. An earlier and more frequent use of such approach will definitely lead to a better quality-of-life of patients with PDAC experiencing pain. The more recently described approaches, through a broader blockage, may result in better response in selected cases; however, until further studies definitely prove their efficacy, they should be reserved for those cases in which conventional blockage fails.

Obstructive jaundice

Most patients with PDAC, particularly those arising from the head of the pancreas, present with bile duct obstruction. Endoscopic retrograde cholangiopacreatography (ERCP) is the preferred procedure for biliary drainage. However, ERCP failure occurs in 3—10 % of PDAC patients. In such cases, rescue options include percutaneous transhepatic drainage (PTBD), surgical interventions, and more recently EUS-guided biliary drainage (EUS-BD).

Following the first description the use of EUS-guided puncture of the bile duct for diagnostic purpose in 1996 [24], Giovannini et al reported a case of a patient with obstructive jaundice in whom a successful EUS-BD was perfomed after failed conventional ERCP [25]. Since then there are

over 1000 cases published in the literature, overall reporting technical and clinical success rates of 91% and 88% respectively [26].

Biliary access can be achieved via an intrahepatic or an extrahepatic route [26]. Technical and clinical success seems to be similar for both accesses, although the extrahepatic route seems to be safer [26]. After ductal access, biliary drainage can be achieved by three different approaches (Fig. 1):

- direct transluminal, either transgastrically (hepatico-gastrostomy) or transduodenally (choledocho-duodenostomy), which involves dilation of the tract followed by stenting for transmural BD;
- rendezvous technique, in which intrahepatic or extrahepatic bile duct is punctured from the gastrointestinal tract, a guidewire is then advanced into the lumen of the duodenum via the papilla, allowing retrograde biliary intervention [26];
- antegrade, in which a stent is placed across the papilla, usually after passing a guide-wire via a transduodenal approach [27,28].

An initial prospective randomized study compared the success and efficacy of EUS-BD vs. PTBD [29]. Twenty-five patients were randomized (13 in the EUS-BD group and 12 in the PTBD group). All procedures were technically and clinically successful in both groups, and no differences were noted between the groups in terms of complication rates, cost or quality of life [29]. Conversely, two subsequent retrospective studies, comprising over 120 patients, suggested that EUS-BD is superior to PTBD in terms of safety, efficacy, and overall associated costs [30,31]. More recently, a multicentre, open-label, randomized trial compared EUS-BD vs PTBD in 66 patients with unresectable malignant distal biliary obstructions and failed primary ERCP [32]. Although technical, functional and clinical (quality of life) efficacy did not differ between the two groups, EUS-BD was associated with significantly fewer procedure-related adverse events, and significantly lower frequency of unscheduled re-interventions [32]. A retrospective expertise-based study from two centres reported that EUS-guided hepaticogastrostomy had similar success and adverse-event rates compared to PTBD, but associated with lower rates of re-intervention and length of hospitalization [33]. Lastly, the superiority of EUS-BD over PTBD has been recently confirmed in a meta-analysis comprising 9 studies with 483 patients [34]. Although there were no differences in terms of technical success between the 2 groups, EUS-BD was associated with better clinical success, fewer adverse events, and lower rate of re-intervention [34]. Recently, the efficacy of a fully-covered lumen-apposing metal stent (LAMS, Hot AXIOS; Boston Scientific, Massachusetts, United States) for EUS-guided choledochoduodenostomy in PDAC was shown in two case reports [35,36]. In one case, it was performed through an uncovered metal duodenal stent [36]. Although the results are promising, particularly in the latter setting, further studies are warranted.

In conclusion, in cases of ERCP failure, EUS-BD may be preferred over PTBD. However, it should be performed only by an experienced endoscopist with expertise in both ERCP and EUS, and at a high-volume center where surgery and radiology can provide support in case of adverse events.

Gastric outlet obstruction

Gastric outlet obstruction is a common late manifestation of PDAC. It can cause significant morbidity including severe weight loss, malnutrition, dehydration, and electrolyte abnormalities [37]. In PDAC patients, gastric outlet obstruction usually develops due to progression of the primary tumor causing extrinsic compression of the duodenum, but it can also be caused by lymphadenopathy, carcinomatosis, or liver metastases [37].

The main goal of palliative therapy in this setting is to establish a way by which patients can maintain their oral food intake, and consequently improve their quality of life [38]. Management of gastric outlet obstruction can be performed endoscopically, with placement of a gastroduodenal stent [38]. When endoscopic gastroduodenal stent placement is unsuccessful, bypass surgery is an option [37]. However, in poor surgical candidates, an EUS- guided approach may be considered [9]. In this procedure, a gastrojejunal fistula is created by obtaining an access to the jejunum via EUS-guided needle, followed by placement of a LAMS [39,40]. The use of a double-balloon enteric tube to distend the jejunum at the EUS-guided needle puncture has also been reported [41]. Another approach to create a gastro-jejunal anastomosis consists on the use of magnetic compression devices [9]. Following the early report in the animal setting [42], two human studies have been reported. In the first study, 15 patients with malignant obstruction were submitted to endoscopic gastroenteric anastomosis using magnets and a yoyo stent [43]. Success rate was nearly 90%, and no immediate major complications were observed [43]. Subsequently, a prospective multicenter cohort study investigated the safety and efficacy of endoscopic creation of a gastroenteric anastomosis formed by magnetic compression and self-expandable metal stent placement [44]. Briefly, under fluoroscopic guidance, a jejunal magnet (14-mm diameter) was mounted on a catheter and advanced to the horizontal part of the duodenum, while a gastric magnet [16-mm diameter) was inserted in the stomach attached to the endoscope until mating with the previously placed jejunal magnet occurred. After 8 to 10 days, a gastroscopy was performed to identify the gastroenteric fistula and to remove the magnets. Subsequently, a self-expanding metal stent with a was delivered through the gastroenteric fistula. Although the procedure was successful in 66.7% of patients, the study was terminated after inclusion of 18 patients due to a serious adverse event (stent perforation) leading to the death of the patient. In addition, stent migration occurred in three patients [44].

Although the endoscopic magnetic gastroenteric anastomosis is a promising concept, it cannot yet be recommended for routine clinical use. Further developments in technique and prospective studies are warranted before it becomes a feasible alternative to surgery in high risk surgical candidates.

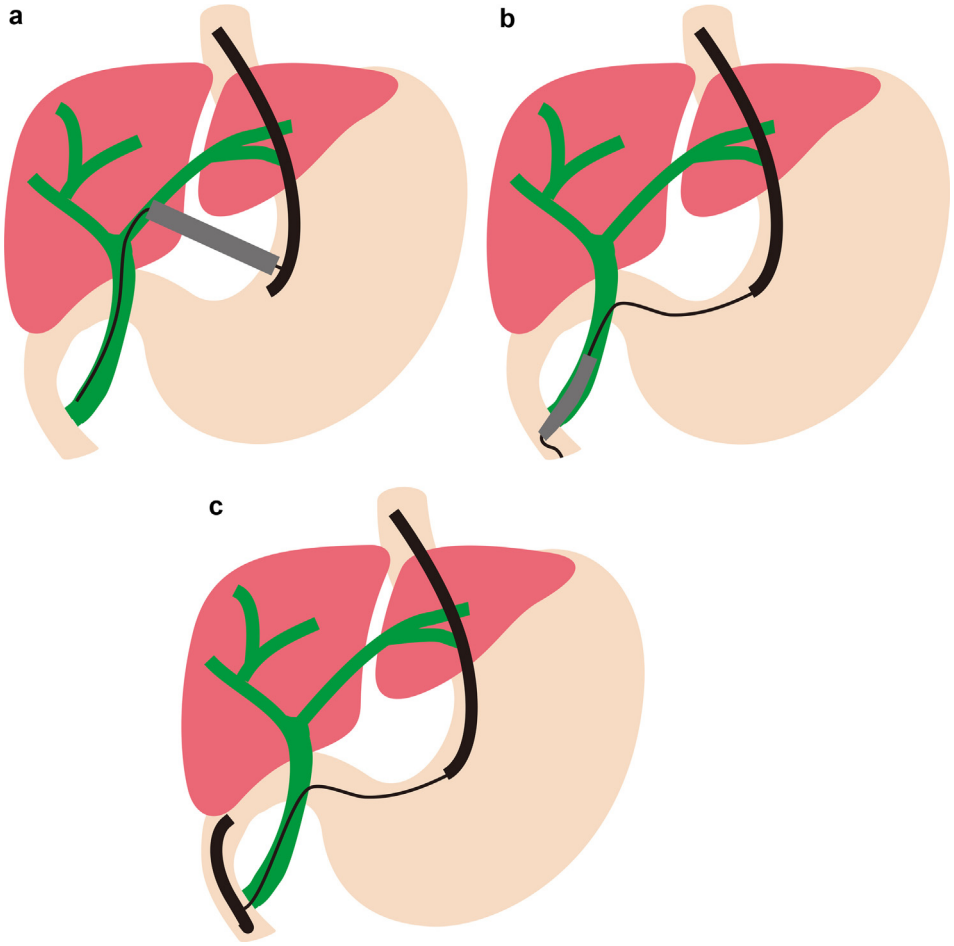

Figure 1 Different modalities of EUS-guided biliary drainage. When biliary drainage cannot be achieved by ERCP, an EUS-guided approach should be considered as a first line rescue option, given its advantages in relation to surgical derivation and percutaneous transhepatic procedures. EUS-guide biliary access can be obtained via an intrahepatic (trough the stomach) or an extrahepatic (trough the duodenum) route. After ductal access, biliary drainage can be achieved by three different approaches: a: direct transluminal, either transgastrically (hepatico-gastrostomy) or transduodenally (choledocho-duodenostomy), which involves puncturing the biliary tree using a FNA needle, passing a guidewire, followed by dilation of the tract and stent insertion for a transmural drainage; b: antegrade, in which, after puncturing the common bile duct and successfully passing a guidewire to the duodenum, following track dilation, a stent is inserted inside the duct through the papilla; c: rendezvous technique, in which after intrahepatic or extrahepatic bile duct puncturing, a guidewire is advanced into the lumen of the duodenum through the papilla; subsequently the wire is captured and inserted retrogradely into the operating channel of a duodenoscope, allowing a retrograde biliary intervention (ERCP).

Tumor-targeted therapies

PDAC follows an aggressive clinical course, which is mirrored by complex underlying biologic features [45]. Hallmark pathogenic features of PDAC include oncogenic KRAS signaling, genomic instability, metabolic rewiring to support proliferation and survival, and a desmoplastic stroma with an immune-suppressive microenvironment [45]. The latter feature promotes tumor growth, is associated with the development of resistance to chemotherapy and radiotherapy, and constitutes a barrier to the delivery of therapeutic agents [46,47]. Since EUS offers real time dynamic images and a unique access to the pancreas, it has the hypothetical advantage of directly targeting the tumor through the desmoplastic stroma whilst minimizing systemic effects and complications [9]. This advantage has been recently exploited as a mean to the delivery of anti-tumor agents, in assisting radiotherapy, and guiding ablative therapies (Table 1).

EUS-fine needle injection of anti-tumor agents

Progressive knowledge on the molecular pathogenesis of PDAC has directed increased attention toward studies on EUS-guided injection of chemical or biological agents for its treatment.

One of such examples is the injection guided by EUS of an allogeneic mixed lymphocyte culture (cytoimplant). Its administration induces potent cytokine secretion leading to the activation of the effector immune mechanisms, ultimately causing tumor regression [48]. A phase I trial

Table 1 Endoscopic ultrasound-guided tumor-targeted therapies for pancreatic adenocarcinoma.

Reference	Year	Therapy	Type of trial	Number of patients	Median survival (months)	Response
EUS-fine needle injection of anti-tumor agents						
Chang et al.	2000	Cytoimplant	I	8	13.2	3 partial response
Irisawa et al.	2007	Dendritic cells	I	7	10	1 complete response 3 partial response
Hirooka et al.	2009	Dendritic cells (+ gemcitabine)	I	5	16	1 partial response
Hecht et al.	2012	TNFerade	I/II	50	13.2	1 complete response 3 partial response
Herman et al.	2013	TNFerade	III	304	10	8 partial response
Hecht et al.	2003	ONYX-015	I/II	21	7.5	2 partial response
Hanna et al.	2012	BC-819	I/II	9	Not reported	3 partial response
EUS-assisted radiotherapy						
Sun et al.	2006	Brachytherapy	I	15	Not reported	4 partial response
Jin et al.	2008	Brachytherapy (+ chemoradiation)	I	22	Not reported	3 partial response
Saunders et al.	2010	SBRt	I	51	Not reported	Not reported
Park et al.	2010	SBRt	I	57	Not reported	Not reported
Khashab et al.	2017	SBRt	I	39	Not reported	Not reported
EUS-guided ablative techniques						
Song et al.	2016	RFA	I	6	Not reported	Not reported
Arcidiacono et al.	2012	RFA	I	22	6	6 partial response
Crino et al.	2018	RFA	I	8	Not reported	8 partial response

EUS: endoscopic ultrasound; SBRt: stereotactic body radiotherapy; RFA: radiofrequency ablation.

enrolled eight patients with advanced PDAC. Cytoimplant was obtained following the co-incubation of host and allogeneic healthy donor peripheral blood mononuclear cells, and then injected in escalating doses (3, 6, and 9 billion cells) into the pancreatic tumor by a single EUS-fine needle injection (EUS-FNI) [48]. No procedure-related complications were observed. The median survival was 13.2 months, with two partial and one minor responses [48]. Currently, there are no active clinical protocols evaluating cytoimplant for PDAC.

Dendritic cells (DCs) are the potent antigen-presenting cells, capable of priming naïve T cells and stimulating memory T cells to generate antigen-specific responses [49]. DCs have the capacity to active T cells, interact with natural killer cells in tumor microenvironment, and directly kill tumor cells.

DC-based immunotherapy has been used in clinical trials for various cancers, including in PDAC. One pilot trial enrolled seven patients with advanced PDAC who had previously failed gemcitabine [50]. Patients received injection of 10-billions of DC at two or three sites. No procedure-related complications were reported. Median survival was 10 months, with one complete and three partial responses [50]. In another pilot trial, five patients with advanced PDAC received a combination therapy with gemcitabine and OK432-pulsed DCs [51]. Median survival was 16 moths, with two patients exhibiting sustained stable disease symptoms for over 6-months, with a further patient having a partial response [51].

Another immune strategy consists in the administration of tumor-necrosis factor (TNF)-erade (TNFerade™), a replication-deficient adenovirus carrying the human *TNF* gene. It is regulated by a radiation-inducible promoter [Egr-1) [52], which ensures maximal gene expression and subsequent TNF secretion to be constrained in space and time by radiation therapy, thus reducing the potential for systemic toxicity. In phase I/II trial, 50 patients with advanced PDAC were injected either percutaneously or under EUS-guidance with TNFerade™ along with systemic therapy with 5-fluorouracil and radiotherapy [53].

Median survival was 297 days; one and three showed complete and partial response respectively, while ten patients experienced stable disease symptoms. Interestingly, seven patients were eventually submitted to surgical resection, with six having clear margins, and three surviving for over two-years [53]. However, a later multicenter randomized phase III trial, which has included 304 patients with advanced PDAC, failed to show a survival benefit of combining TNFerade™ with chemo and radiotherapy over chemoradiotherapy alone [54].

Another approach that is currently receiving attention in PDAC pertains to the use of oncolytic viruses (adenoviruses, herpesviruses, and reoviruses). Putative mechanisms of action include: viral replication cyclically within the cell causing its rupture, production of a cytotoxic protein, and/or inducing anti-tumor immunity [55]. One such example is ONYX-015, an engineered adenovirus lacking the *E1B* gene that preferentially replicates in malignant cells, leading to cell death [56]. Phase I/II trial included 21 patients with unresectable PDAC who received eight injections of ONYX-015 plus intravenous gemcitabine at the time of last injection [57]. Four serious adverse events were reported (sepsis in two, and duodenal perforation in another two). Median survival was 7.5 months, with two partial and two minor responses, and with further six patients showing stable disease symptoms [57]. Another example is the administration of HF10, a spontaneously mutated oncolytic virus derived from a herpes simplex virus-1, in combination with erlotinib and gemcitabine [58]. Phase I study showed this strategy was safe for treatment of locally advanced PDAC [58], suggesting that further large studies should explore the efficacy of combination therapy of HF10 with chemotherapy.

DNA plasmids have also been studied in the setting of PDAC, namely BC-819; it is DNA plasmid that targets the expression of diphtheria-toxin gene under the control of H19 regulatory sequences. BC-819 has the potential to treat PDAC that overexpresses the *H19* gene [59]. EUS-guided or computed tomography (CT)-guided injection of BC-819 has been tested in a phase I/IIa trial, which included nine patients with advanced PDAC treated with concurrent chemoradiation [60]. No serious adverse events were reported. Three patients had partial response and two were successfully down staged and subsequently submitted to surgery [60].

Lastly, there is the possibility of delivering chemotherapy directly into the pancreas with EUS-guidance. In an animal model, paclitaxel bound to a thermosensitive gel carrier (OncoGel) was delivered to eight pigs. All animals tolerated well the procedure, and after two weeks high and sustained localized concentrations were detectable within 30 to 50 mm from the injection site [61].

Although EUS-fine needle injection of anti-tumor agents has not yet shown to significantly improve the survival in patients with PDAC, it seems that it can induce tumor cell death. Additional studies, however, are needed to further explore this therapeutic application in the future.

EUS-assisted radiotherapy

Radiotherapy is a therapeutic option for patients with locally advanced PDAC [6]. This group of patients is conventionally offered fractional external beam radiation therapy combined with chemotherapy. Other therapeutic options are emerging such as brachytherapy and stereotactic body radiotherapy (SBRt) after fiducial placement [9].

Brachytherapy is a procedure that involves placing of a radioactive seed directly into the tumor. Iodine-125 is the most commonly used seed. EUS-guided brachytherapy was first reported in a pilot study in which 15 patients with locally advanced PDAC received brachytherapy without chemotherapy or external radiotherapy [62]. Local complications (pancreatitis and pseudocyst formation) occurred in three patients, while grade III hematologic toxicity occurred in other three patients. After a median follow-up time of 10.6 months, 27% and 20% of patients experienced partial and minimal respectively, whereas 33% of patients had stable disease. In addition, reduction in pain severity was documented in 30% of patients, though this effect was short-termed [62]. In another study, 22 patients received EUS-guided brachytherapy combined with gemcitabine plus 5-fluoruracil chemotherapy [63]. Although tumor growth was effectively controlled in 59.1% of patients and reduction in pain severity was noted in all patients, no significant survival benefit was observed [63].

SBRt allows a precise administration of radiotherapy, therefore minimising irradiation of adjacent normal tissue. Early studies have shown that SBRt is comparable with external beam therapy in terms of both local tumor control and overall survival [64—66]. Placement of fiducial markers prior to SBRt allows precise tumor targeting. Although traditionally placed by surgical or percutaneous approach, EUS seems ideal for placement of fiducial markers in PDAC. EUS-guided fiducial marker placement was first reported in 2006; in this study fiducial markers were successfully place in six out of seven PDAC patients [67]. Later, two other studies, together including 106 patients, reported 88 and 90% successful rate, therefore confirming the feasibility and safety of EUS-guided fiducial marker placement [68,69]. More recently, Khashab et al. compared 2 types of commercially available fiducials (traditional vs. visicoil) [70]. Visibility score was significantly higher for traditional compared to visicoil fiducial, but no differences in terms of migration rates, technical success or complication rate were observed between the two [70].

EUS-guided ablative techniques

Radiofrequency ablation (RFA) is a well-established technique to ablate dysplastic and neoplastic tissue via local thermal coagulative necrosis [71]. It has been demonstrated to be feasible via open, laparoscopic or percutaneous approaches for locally advanced PDAC [72,73]. EUS-guided RFA offers the best combination of excellent visualization, real-time imaging guidance, precise localization, with minimal invasiveness. Previous studies have shown that EUS-RFA is feasible and safe for the porcine pancreas [74,75]. Recently, a small pilot study including six patients with unresectable PDAC showed that EUS-RFA was performed successfully in all six patients [76]. Side effects were reported in two patients who experienced mild abdominal pain [76]. One study was the feasibility and safety of the use of cryotherm probe, a flexible bipolar device that combines radiofrequency with cryogenic cooling. Amongst 22 patients

with unresectable stage III PDAC, the cryotherm probe was successfully performed in 16 (success rate 72.8%) [77]. No severe adverse events related to the procedure were observed. Median post-ablation survival was six months, and a reduction in tumor size was noted on follow-up CT in six out of sixteen patients [77]. A recent study reported the safety and efficacy EUS-RFA in 8 patients, showing that in all an ablated area inside the tumor was obtained. Although three patients reported minor post-procedural pain, no major adverse event was observed after a mean follow-up of 6 months [78].

Photodynamic therapy (PTD) is an approach where a needle placed in the target tissue is used to deliver a specific wavelength of light. Following activation by a photosensitizing agent, it produces localized tissue necrosis, through the generation of reactive oxygen species [79]. Although encouraging results of PDT have been reported in the setting of cholangiocarcinoma, its use in PDAC is still lagging behind. One study in an animal model showed that EUS-guided PDT is a safe and able to induce areas of focal tissue ablation within the pancreas [80]. More recently, a phase I/II study comprising fifteen patients with advanced stage PDAC demonstrated that PDT is a feasible and safe technique, allowing the induction of tumor necrosis [81].

Conclusion

EUS is an indispensable tool in the management of PDAC; it is useful not only for tissue diagnosis and staging, but also for therapeutic purposes. Some EUS-guided therapies, such as CP interventions for pain control and obstructive jaundice management after failed ERCP have become widely accepted, whereas other techniques, namely anti-tumor injection and ablative therapies, are still mostly experimental, and have yet to evolve before becoming routine practice. Data on the long-term efficacy of these new approaches, and large prospective randomized studies are needed to confirm its real clinical benefits. Given the lack of effective systemic treatments at present, continuous research in therapeutic EUS is warranted.

Disclosure of interest

The authors declare that they have no competing interest.

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Author's contributions

PMR — study concept and design, literature review, and draft of the manuscript; RL — literature review, and draft of the manuscript; GM — supervision.

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