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Systematic review of novel ablative methods in locally advanced pancreatic cancer

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Abstract

Unresectable locally advanced pancreatic cancer with or without metastatic disease is associated with a very poor prognosis. Current standard therapy is limited to chemotherapy or chemoradiotherapy. Few regimens have been shown to have a substantial survival advantage and novel treatment strategies are urgently needed. Thermal and laser based ablative techniques are widely used in many solid organ malignancies. Initial studies in the pancreas were associated with significant morbidity and mortality, which limited widespread adoption. Modifications to the various applications, in particular combining the techniques with high quality imaging such as computed tomography and intraoperative or endoscopic ultrasound has enabled real time treatment monitoring and significant improvements in safety. We conducted a systematic review of the litera-

ture up to October 2013. Initial studies suggest that ablative therapies may confer an additional survival benefit over best supportive care but randomised studies are required to validate these findings.

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Key words: Pancreatic cancer; Radiofrequency ablation; Photodynamic therapy; Cryoablation; Microwave ablation; High frequency focused ultrasound; Irreversible electroporation

Core tip: Unresectable locally advanced pancreatic cancer with or without metastatic disease is associated with a very poor prognosis. Current standard therapy is limited to chemotherapy or chemoradiotherapy. Few regimens have been shown to have a substantial survival advantage and novel treatment strategies are urgently needed. Initial studies of ablation in the pancreas were associated with significant morbidity and mortality, which limited widespread adoption. Modifications to the various applications, in particular combining the techniques with high quality imaging such as computed tomography and intraoperative or endoscopic ultrasound has enabled real time treatment monitoring and significant improvements in safety.

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BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is the tenth most common cancer in the UK but the fifth commonest

cause of cancer death. At diagnosis more than 80% of patients have locally advanced or metastatic disease and are unsuitable for curative surgical resection. Prognosis in pancreatic cancer is dismal; median survival for locally advanced disease is just 6-10 mo, however in patients with metastatic disease this falls to 3-6 mo. Overall 5 year survival is less than 4%^[1].

Standard options available for treating patients with inoperable PDAC are limited to chemotherapy, radiotherapy, or a combination of the two. Gemcitabine is the most commonly used chemotherapy agent in pancreatic cancer, however recent studies have shown that in combination with other chemotherapy agent's further improvements in overall survival can be gained. A recent randomised Phase III study (GemCap) reported a median survival in the combination gemcitabine + capecitabine group of 7.1 mo compared with 6.2 mo in those who received gemcitabine alone. The 1-year overall survival (OS) rates were 24.3% for combination therapy and 22% for gemcitabine alone (HR = 0.86, 95%CI: 0.72-1.02, $P = 0.077$)^[2]. A further large European study compared gemcitabine to FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) and demonstrated a significant survival advantage in the FOLFIRINOX group compared with gemcitabine alone (median 11.1 mo *vs* 6.8 mo)^[3]. The phase III MPACT study found that weekly intravenous nab-paclitaxel with gemcitabine resulted in a significantly higher overall survival compared to gemcitabine monotherapy (8.5 mo *vs* 6.7 mo, HR = 0.72, $P < 0.0001$)^[4].

Given that so few patients with PDAC are suitable for curative surgery and most have only a limited response to chemotherapy; tumour debulking or interstitial ablation has been investigated as a potential additional therapy. A recent systematic review compared R2 resections to palliative bypass alone in the management of advanced PDAC. A small non-significant survival advantage was observed in the R2 resection group; 8.2 mo compared to 6.7 mo in the palliative bypass group. However patients undergoing R2 resections had a significantly higher morbidity (RR = 1.75, 95%CI: 1.35-2.26, $P < 0.0001$), mortality (RR = 2.98, 95%CI: 1.31-6.75, $P = 0.009$) and longer hospital stay (mean difference, 5 d, 95%CI: 1-9 d, $P = 0.02$), hence R2 resections are not recommended as part of the standard management of PDAC^[5]. However minimally invasive ablative therapies delivered percutaneously or endoscopically have become part of standard therapy in many other solid organ tumours, particularly in patients with inoperable disease or who are unfit for surgical resection^[6]. Early studies of local ablation in the pancreas were associated with high morbidity and mortality^[7]. However improvements in delivery and in particular combining the technology with high quality real-time imaging, has reduced associated complications. The safety and efficacy of each ablative therapy in non-operable PDAC will be evaluated in this review.

RESEARCH METHODOLOGY

The primary aim of this review was to assess safety and

efficacy of each ablation therapy in the treatment of locally advanced or metastatic PDAC. Secondary endpoints included improvements in overall survival, changes in symptoms, tumour markers or performance status where available. A systematic literature search was performed using the PubMed, EMBASE databases and the Cochrane Library for studies published in the English language up to 1st October 2013. MeSH terms were decided by a consensus of the authors and were (radiofrequency ablation, catheter ablation, photodynamic therapy, PDT, cryoablation, cryosurgery, laser, high intensity focused ultrasound ablation, microwave, electroporation) and (pancreas OR pancreatic), and were restricted to the title, abstract and keywords. Only articles, which described ablation in unresectable PDAC, were included. Articles that described the use of ablative therapies in premalignant pancreatic disease were excluded but outcomes are summarised in Table 1. Similarly studies that included non-ablative therapies were also excluded but have been summarised in Table 2. Any study with fewer than four patients and those reporting on tumours that did not originate in the pancreas were excluded. In cryoablation and high frequency focused ultrasound of the pancreas, many of the largest case-series are published in non-English language medical journals. Although articles not published in the English language were excluded from this systematic review, if an English language abstract was available the results were included in the summary tables. All references were screened for potentially relevant studies not identified in the initial literature search. The following variables were extracted for each report when available: number of patients, disease extent, device used and settings, distance of probe from surrounding structures, duration of therapy and number of ablations applied, additional safety methods used. Thirty-two papers were included (Figure 1).

THERMAL ABLATIVE TECHNIQUES

Radiofrequency ablation

Radiofrequency ablation (RFA) causes tissue destruction through the application of a high frequency alternating current that generates high local temperatures leading to a coagulative necrosis. The technique has been widely used in many solid organ malignancies and is now part of standard therapy in several tumours including hepatocellular carcinoma^[6]. The first application of RFA in the normal porcine pancreas was described in 1999. Although this application was performed under EUS guidance^[8] it has nearly always been delivered intraoperatively (rarely percutaneously) in combination with palliative bypass surgery^[9]. Although RFA was deemed to be feasible and safe in animal studies^[8], early clinical applications in the pancreas were associated with unacceptably high rates of morbidity (0%-40%) and mortality (0%-25%) (Table 3)^[7,10-14]. Most RFA of pancreatic tumours has been performed using the Cool-tip™ RF Ablation system (Radionics). Many of the complications arose as a result of inadvertent damage to structures adjacent to

Table 1 Use of ablative therapies to treat cystic and solid premalignant lesions of the pancreas

Author	Premalignant lesion	n	Treatment	Median area of ablation, mm (range)	Outcome	Complications
Gan <i>et al</i> ^[46]	Cystic tumours of the pancreas	25	EUS guided ethanol lavage	19.4 (6-30)	Complete resolution 35%	None
Oh <i>et al</i> ^[73]	Cystic tumours of the pancreas	14	EUS guided ethanol lavage + paclitaxel	25.5 (17-52)	Complete resolution in 79%	Acute pancreatitis (n = 1) Hyperamylasaemia (n = 6) Abdominal pain (n = 1)
Oh <i>et al</i> ^[74]	Cystic tumours of the pancreas	10	EUS guided ethanol lavage + paclitaxel	29.5 (20-68)	Complete resolution in 60%	Mild pancreatitis (n = 1)
DeWitt <i>et al</i> ^[75]	Cystic tumours of the pancreas	42	Randomised double blind study: Saline <i>vs</i> ethanol	22.4 (10-58)	Complete resolution in 33%	Abdominal pain at 7 d (n = 5) Pancreatitis (n = 1) Acystic bleeding (n = 1)
Oh <i>et al</i> ^[47]	Cystic tumours of the pancreas	52	EUS guided ethanol lavage + paclitaxel	31.8 (17-68)	Complete resolution in 62%	Fever (1/52) Mild abdominal discomfort (1/52) Mild pancreatitis (1/52) Splenic vein obliteration (1/52)
Levy <i>et al</i> ^[76]	PNET	8	EUS guided ethanol lavage (5 patients) and intra-operative ultrasound guided (IOUS) ethanol lavage (3 patients)	16.6 (8-21)	Hypoglycemia symptoms disappeared 5/8 and significantly improved 3/8	EUS guided: No complications. IOUS-guided ethanol injection: Minor peritumoral bleeding (1/3), pseudocyst (1/3), pancreatitis (1/3)
Pai <i>et al</i> ^[21]	Cystic tumours of the pancreas + neuroendocrine tumours	8	EUS guided RFA	Mean size pre RFA, 38.8 mm <i>vs</i> mean size post RFA, 20 mm	Complete ablation in 25% (2/8)	2/8 patients had mild abdominal pain that resolved in 3 d

RFA: Radiofrequency ablation; EUS: Endoscopic ultrasound; PNET: Pancreatic neuroendocrine tumour.

Table 2 Endoscopic ultrasound administered non-ablative anti-tumour therapies for pancreatic ductal adenocarcinoma

Author	Therapy	Patients	n	Outcome and survival	Complications
Chang <i>et al</i> ^[77]	Cytoimplant (mixed lymphocyte culture)	Unresectable PDAC	8	Median survival: 13.2 mo. 2 partial responders and 1 minor response	7/8 developed low-grade fever 3/8 required biliary stent placement
Hecht <i>et al</i> ^[78]	ONYX-015 (55-kDa gene-deleted adenovirus) + IV gemcitabine	Unresectable PDAC	21	No patient showed tumour regression at day 35. After commencement of gemcitabine, 2/15 had a partial response	Sepsis: 2/15 Duodenal perforation: 2/15
Hecht <i>et al</i> ^[79] Chang <i>et al</i> ^[80,81]	TNFerade (replication-deficient adenovector containing human tumour necrosis factor (TNF)- α gene)	Locally advanced PDAC	50	Response: One complete response, 3 partial responses. Seven patients eventually went to surgery, 6 had clear margins and 3 survived > 24 mo	Dose-limiting toxicities of pancreatitis and cholangitis were observed in 3/50
Herman <i>et al</i> ^[82]	Phase III study of standard care plus TNFerade (SOC + TNFerade) <i>vs</i> standard care alone (SOC)	Locally advanced PDAC	304 (187 SOC + TNFerade)	Median survival: 10.0 mo for patients in both the SOC + TNFerade and SOC arms [hazard ratio (HR), 0.90, 95%CI: 0.66-1.22, <i>P</i> = 0.26]	No major complications. Patients in the SOC + TNFerade arm experienced more grade 1 to 2 fever than those in the SOC alone arm (<i>P</i> < 0.001)
Sun <i>et al</i> ^[83]	EUS-guided implantation of radioactive seeds (iodine-125)	Unresectable PDAC	15	Tumour response: "partial" in 27% and "minimal" in 20%. Pain relief: 30%	Local complications (pancreatitis and pseudocyst formation) 3/15. Grade III hematologic toxicity in 3/15
Jin <i>et al</i> ^[84]	EUS-guided implantation of radioactive seeds (iodine-125)	Unresectable PDAC	22	Tumour response: "partial" in 3/22 (13.6%)	No complications

PDAC: Pancreatic ductal adenocarcinoma; EUS: Endoscopic ultrasound.

the zone of ablation such as the normal pancreas, duodenum, biliary tree or peri-pancreatic vasculature. These early studies applied high temperatures (> 90 °C) and multiple rounds of ablation to treat large tumours in the head of the pancreas in one session^[13]. An *ex-vivo* study of the thermal kinetic characteristics of RFA found that the optimal settings for RFA in the pancreas to prevent

injury to the adjacent viscera was 90 °C applied for 5 min^[15]. Subsequent clinical studies that reduced the RFA temperature from 105 °C to 90 °C, reported only minimal RFA-related complications^[7]. Active cooling of the major vessels and duodenum with saline during intraoperative RFA and observing at least a 0.5 cm area between the zone of ablation and major structures, reduced compli-

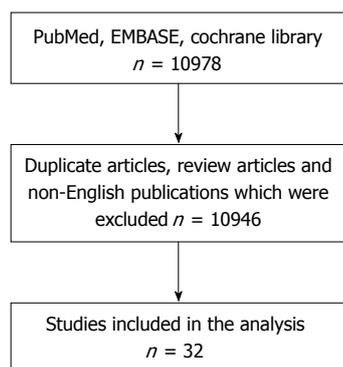


Figure 1 Systematic review schema.

cations^[10,16,17]. Since most of the mortality resulted from uncontrollable gastrointestinal haemorrhage from ablated tumours in the head of the pancreas, some authors have recommended this probe should only be employed in body or tail tumours^[10,16].

All studies have demonstrated that RFA leads to tumour necrosis and a decrease of tumour volume^[9,12,17,18]. Some studies have also observed an improvement in tumour related symptoms, in particular a reduction of back pain and analgesia requirements. Tumour markers (carbohydrate antigen 19-9) also decrease following effective ablation^[16]. Although all patients treated with RFA ultimately developed disease progression^[9,11,12,17,18], when compared to patients with advanced disease who received standard therapy in a non-randomised cohort study, patients who received combination therapy had prolonged survival (33 mo *vs* 13 mo, $P = 0.0048$)^[11]. However, this was a single centre study that only included 25 patients (12 receiving RFA). An earlier non-randomised study did not demonstrate the same survival advantage^[12]. Spiliotis *et al*^[11] also evaluated overall survival following RFA according to tumour stage. Patients with stage III disease had a significant improvement in survival following RFA compared to patients with the same stage of disease receiving best supportive care ($P = 0.0032$). In contrast, no difference in overall survival was shown in patients with metastatic PDAC, following RFA treatment ($P = 0.1095$). Larger studies, in combination with systemic chemotherapy, would be needed to evaluate any potential role of RFA in patients with metastatic disease.

Recently two new RFA probes have been developed that can be placed down the working channel of an endoscope, enabling RFA to be administered under EUS guidance. Twenty-two patients with locally advanced PDAC were treated with the cryotherm probe (CTP) (ERBE Elektromedizin GmbH, Tübingen, Germany) that incorporates radiofrequency ablation with cryogenic cooling. The probe was sited successfully in 16 patients (72.8%); stiffness of the gastrointestinal wall and tumour prevented placement in the others. Following the procedure three patients reported mild abdominal pain and one experienced minor gastrointestinal bleeding, not re-

quiring transfusion^[19]. In a further study, 7 patients with unresectable PDAC received EUS guided RFA using the monopolar radiofrequency (RF) catheter (1.2 mm Habib EUS-RFA catheter, Emcision Ltd, London). The tumour was shown to decrease in size in all cases and only one patient developed mild pancreatitis^[20]. Long-term follow up is not available on the efficacy of these new catheters. Early clinical studies have also used the Habib EUS RFA catheter to treat cystic tumours of the pancreas (Table 1)^[21].

Microwave ablation

Microwave (MW) current is produced by a generator connected *via* a coaxial cable to 14-gauge straight MW antennas with a 3.7 cm or 2 cm radiating section. One or two antennae are then inserted into the tumour for 10 min. The largest case series of microwave ablation in locally advanced PDAC includes 15 patients. Although MW ablation can be performed percutaneously or intraoperatively^[22], in this series it was performed intraoperatively at the time of palliative bypass surgery. All tumours were located in the head or body of the pancreas and had an average size of 6 cm (range 4–8 cm); none had distant metastasis on imaging. Partial necrosis was achieved in all patients and there was no major procedure-related morbidity or mortality. However minor complications were seen in 40% (mild pancreatitis, asymptomatic hyperamylasia, pancreatic ascites, and minor bleeding). The longest survival of an individual patient in this series was 22 mo^[23].

Cryoablation

The successful use of cryoablation in the pancreas was first reported in primate experiments in the 1970s^[24]. However its potential application as a therapy in pancreatic cancer was not described for a further 20 years^[25]. Cryoablation is most commonly performed intraoperatively under ultrasound guidance. Small lesions (< 3 cm) can be reliably frozen with a single, centrally placed probe but larger tumours require the placement of multiple probes or sequential treatments. Most studies have used the argon-gas-based cryosurgical unit (Endocare, Inc., CA, United States) and employ a double “freeze/thaw” cycle. The tumour is cooled to $-160\text{ }^{\circ}\text{C}$ and the resulting iceball monitored with ultrasound to ensure the frozen region encompasses the entire mass and does not compromise local structures. The tissue is then allowed to slowly thaw to $0\text{ }^{\circ}\text{C}$ and a second cycle of freezing is performed after any necessary repositioning of the cryoprobes. Like in many of the RFA studies, the authors advocated a 0.5 cm margin of safety from major structures and that ideally the procedure should be performed at the same time as palliative bypass surgery or endoscopic biliary and duodenal stenting. Ablation of liver metastases can also be performed simultaneously^[26].

The largest experience of intraoperative and percutaneous cryoablation in pancreatic cancer has been reported from Asia. To date more than 200 patients with

Table 3 Studies of radiofrequency ablation in pancreatic ductal adenocarcinoma

Study	Patients	n	Route of administration	Device	RFA temp (°C)	RFA duration (min)	Outcome	Complications
Matsui <i>et al</i> ^[12]	Unresectable PDAC	20 LA:9 M:11	At laparotomy 4 RFA probes were inserted into the tumour 2 cm apart	A 13.56-MHz RFA pulse was produced by the heating apparatus	50	15	Survival: 3 mo	Mortality: 10% (septic shock and gastrointestinal bleeding)
Hadjicostas <i>et al</i> ^[14]	Locally advanced and unresectable PDAC	4	Intraoperative (followed by palliative bypass surgery)	Cool-tip™ RFA ablation system	NR	2-8	All patients were alive one year post-RFA	No complications encountered
Wu <i>et al</i> ^[10]	Unresectable PDAC	16 LA:11 M:5	Intraoperative	Cool-tip™ RFA ablation system	30-90	12 at 30 °C then 1 at 90 °C	Pain relief: back pain improved (6/12)	Mortality: 25% (4/16) Pancreatic fistula: 18.8% (3/16) Morbidity: 16% (biliary leak)
Spiliotis <i>et al</i> ^[11]	Stage III and IV PDAC receiving palliative therapy	12 LA:8 M:4	Intraoperative (followed by palliative bypass surgery)	Cool-tip™ RFA ablation system	90	5-7	Mean survival: 33 mo	Mortality: 0%
Girelli <i>et al</i> ^[7]	Unresectable locally advanced PDAC	50	Intraoperative (followed by palliative bypass surgery)	Cool-tip™ RFA ablation system	105 (25 pts) 90 (25 pts)	Not reported	Not reported	Morbidity 40% in the first 25 patients. Probe temperature decreased from 105°C to 90 °C Morbidity 8% in second cohort of 25 patients. 30-d mortality: 2% Morbidity: 15%. Mortality: 3%
Girelli <i>et al</i> ^[8]	Unresectable locally advanced PDAC	100	Intraoperative (followed by palliative bypass surgery)	Cool-tip™ RFA ablation system	90	5-10	Median overall survival: 20 mo	Morbidity: 15%. Mortality: 3%
Giardino <i>et al</i> ^[5]	Unresectable PDAC. 47 RFA alone. 60 had RFA + radiochemotherapy (RCT) and/or intra-arterial systemic chemotherapy (IASC)	107	Intraoperative (followed by palliative bypass surgery)	Cool-tip™ RFA ablation system	90	5-10	Median overall survival: 14.7 mo in RFA alone but 25.6 mo in those receiving RFA + RCT and/or IADC (P = 0.004)	Mortality: 1.8% (liver failure and duodenal perforation) Morbidity: 28%
Arcidiacono <i>et al</i> ^[19]	Locally advanced PDAC	22	EUS-guided	Cryotherm probe; bipolar RFA + cryogenic cooling	NR	2-15	Feasible in 16/22 (72.8%)	Pain (3/22)
Steel <i>et al</i> ^[4]	Unresectable malignant bile duct obstruction (16/22 due to PDAC)	22	RFA + SEMS placement at ERCP	Habib EndoHPB wire guided catheter	NR	Sequential 2 min treatments - median 2 (range 1-4)	Median survival: 6 mo Successful biliary decompression (21/22)	Minor bleeding (1/22) Asymptomatic biochemical pancreatitis (1/22), percutaneous gallbladder drainage (2/22). At 90-d, 2/22 had died, one with a patent SEMS
Figuerro-Barojas <i>et al</i> ^[42]	Unresectable malignant bile duct obstruction (7/20 due to PDAC)	20	RFA + SEMS placement at ERCP	Habib EndoHPB wire guided catheter	NR	Sequential 2 min treatments	SEMS occlusion at 90 d (3/22) Bile duct diameter increased by 3.5mm post RFA (P = 0.0001)	Abdominal pain (5/20), mild post-ERCP pancreatitis and cholecystitis (1/20)
Pai <i>et al</i> ^[20]	Locally advanced PDAC	7	EUS-guided	Habib EUS-RFA catheter	NR	Sequential 90s treatments - median 3 (range 2-4)	2/7 tumours decreased in size	Mild pancreatitis: (1/7)

PDAC: Pancreatic ductal adenocarcinoma; LA: Locally advanced PDAC; M: Metastatic PDAC; SEMS: Self-expanding metal stent; RFA: Radiofrequency ablation; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 4 Studies of cryoablation in pancreatic ductal adenocarcinoma

Study	n	Patients	Study	Outcome	Complications
Patiutko <i>et al</i> ^[25] (non-English article)	30	Locally advanced PDAC	Combination of cryosurgery and radiation	Pain relief and improvement in performance status: 30/30	Not reported
Kovach <i>et al</i> ^[52]	9	Unresectable PDAC	Phase I study of intraoperative cryoablation under US guidance. Four had concurrent gastrojejunostomy	7/9 discharged with non-intravenous analgesia and 1/9 discharged with no analgesia	No complications reported
Li <i>et al</i> ^[53] (non-English article)	44	Unresectable PDAC	Intraoperative cryoablation under US guidance	Median overall survival: 14 mo	40.9% (18/44) had delayed gastric emptying. 6.8% (3/44) had a bile and pancreatic leak
Wu <i>et al</i> ^[54] (non-English article)	15	Unresectable PDAC	Intraoperative cryoablation under US guidance	Median overall survival: 13.4 mo	1/15 patients developed a bile leak
Yi <i>et al</i> ^[55] (non-English article)	8	Unresectable PDAC	Intraoperative cryoablation under US guidance	Not reported	25% (2/8) developed delayed gastric emptying
Xu <i>et al</i> ^[26]	38	Locally advanced PDAC, 8 had liver metastases	Intraoperative or percutaneous cryoablation under US or CT guidance + (125) iodine seed implantation	Median overall survival: 12 mo. 19/38 (50.0%) survived more than 12 mo	Acute pancreatitis: 5/38 (one has severe pancreatitis)
Xu <i>et al</i> ^[56]	49	Locally advanced PDAC, 12 had liver metastases	Intraoperative or percutaneous cryoablation under US or CT guidance and (125) iodine seed implantation. Some patients also received regional celiac artery chemotherapy	Median survival: 16.2 mo. 26 patients (53.1%) survived more than 12 mo	Acute pancreatitis: 6/49 (one had severe pancreatitis)
Li <i>et al</i> ^[57]	68	Unresectable PDAC requiring palliative bypass	Retrospective case-series of intraoperative cryoablation under US guidance, followed by palliative bypass	Median overall survival: 30.4 mo (range 6-49 mo)	Postoperative morbidity: 42.9%. Delayed gastric emptying occurred in 35.7%
Xu <i>et al</i> ^[58]	59	Unresectable PDAC	Intraoperative or percutaneous cryotherapy	Median survival: 8.4 mo. Overall survival at 12 mo: 34.5%	Mild abdominal pain: 45/59 (76.3%) Major complications (bleeding, pancreatic leak): 3/59 (5%) 1/59 developed a tract metastasis
Niu <i>et al</i> ^[29]	36 (CT) 31 (CIT)	Metastatic PDAC	Intraoperative cryotherapy (CT) or cryoimmunotherapy (CIT) under US guidance	Median overall survival in CIT: 13 mo CT: 7 mo	Not reported

PDAC: Pancreatic ductal adenocarcinoma.

unresectable pancreatic cancer have undergone cryoablation alone or in combination with other therapies (Table 4). Effective control of pain, normalisation of CA 19-9, improvement in performance status and prolonged survival have all been reported following cryoablation. Rates of significant complications appear to be lower than in other methods of ablation. Although some patients did encounter delayed gastric emptying following the treatment, this commonly settled with conservative management within a few days. Studies to date are summarised in Table 5. The process has also been shown to initiate antiangiogenesis and a systemic immunological response, which may promote additional anti-tumour effects^[27,28]. However evaluation through larger studies will be necessary to fully determine this effect.

Early clinical studies have also combined the administration of cryotherapy with immunotherapy. In a study of 106 patients with unresectable PDAC, 31 received cryoimmunotherapy, 36 cryotherapy, 17 immunotherapy and 22 chemotherapy. Median overall survival was higher in the cryoimmunotherapy (13 mo) and cryotherapy groups

(7 mo) than in the chemotherapy group (3.5 mo; both $P < 0.001$) and was higher in the cryoimmunotherapy group than in the cryotherapy ($P < 0.05$) and immunotherapy groups (5 mo; $P < 0.001$)^[29].

LASER BASED ABLATIVE THERAPY

Photodynamic therapy

Photodynamic therapy (PDT) results in tumour ablation by exposure to light following an intravenous injection of a photosensitiser [*e.g.*, *meso*-tetra(hydroxyphenyl)chlorin (mTHPC), porfimer sodium or verteporfin] which is taken up by cells. It leads to a predictable zone of ablation within the tumour. To date, light has been delivered *via* small optic fibers which have nearly always been positioned percutaneously under image guidance (*e.g.*, CT)^[30-32]. However these fibers can pass through a 19G needle, so administration under endoscopic ultrasound guidance is feasible.

The first Phase I trial of PDT in locally advanced PDAC was conducted in 2002. Substantial tumour necro-

Table 5 Studies of photodynamic therapy in pancreatic ductal adenocarcinoma

Study	n	Study	Photosensitiser	Number of fibres	Number of ablations	Outcome and survival	Complications
Bown <i>et al</i> ^[30]	16	CT guided percutaneous PDT to locally advanced but inoperable PDAC without metastatic disease	mTH-PC	Single	1	Tumour necrosis: 16/16. Median survival: 9.5 mo. 44% (7/16) survived > 1 year	Significant gastrointestinal bleeding: 2/16 (controlled without surgery)
Huggett <i>et al</i> ^[31,32]	13 + 2	CT guided percutaneous PDT to locally advanced but inoperable PDAC without metastatic disease	Verteporfrin	Single (13) Multiple (2)	1	Technically feasible: 15/15. Dose dependent necrosis occurred	Single fibre: No complications. Multiple fibres: CT evidence of inflammatory change anterior to the pancreas, no clinical sequelae

PDAC: Pancreatic ductal adenocarcinoma; CT: Computed tomography.

sis was achieved in all 16 patients included in the study. Median survival after PDT was 9.5 mo (range 4-30 mo). 44% (7/16) were alive one year after PDT. Two of the patients who had a pancreatic tumor which involved the gastroduodenal artery developed significant gastrointestinal bleeding following the procedure. However both were managed endoscopically with transfusion, without the need for surgery^[30].

A significant drawback of the early PDT treatments was that patients had to spend several days in subdued lighting following the treatment to prevent complications from skin necrosis. However, newer photosensitisers with a shorter drug-light interval and faster drug elimination time have been developed (*e.g.*, verteporfrin) and have been shown in preclinical and early clinical studies to have a similar efficacy and safety profile to mTHPC^[33]. A Phase I study by our group evaluated verteporfrin-mediated PDT in 15 patients with unresectable locally advanced pancreatic cancer (Vertpac-01) (Table 5)^[31,32]. The study was designed in 2 parts: the first 13 patients were treated with a single-fibre, with the following 2 patients being treated with light from multiple fibers. A predictable zone of necrosis surrounding the fibers was achieved. No instances of photosensitivity were reported and only one patient developed cholangitis. Patient went on to receive palliative gemcitabine chemotherapy 28 d after ablation.

YAG Laser

The neodymium-doped yttrium aluminium garnet (Nd:YAG) laser has been used to ablate pancreatic tumours in animal models^[34]. A well demarcated area of necrosis and no complications were achieved, suggesting the potential for this therapy, but to date there have been no clinical studies.

NON-THERMAL, NON-LASER METHODS OF ABLATION

Many of the studies of thermal and light ablation techniques in locally advanced and metastatic PDAC have sug-

gested that cytorreduction may improve survival. However in the initial clinical studies some of the techniques were associated with unacceptably high rates of complications. This has led to a search for non-thermal alternative ablative therapies for use in PDAC.

High-intensity focused ultrasound

High intensity focused ultrasound (HIFU) therapy is a non-invasive method of ablation. Ultrasound energy from an extracorporeal source is focused on the pancreatic tumour to induce thermal denaturation of tissue without affecting surrounding organs^[35]. Multiple non-randomised studies and case series, largely from Asia, have reported preliminary clinical experiences of using HIFU in PDAC. They have demonstrated that the technique is able to achieve tumour necrosis with relatively few side effects (Table 6). Recently a HIFU transducer has been designed which can be attached to an EUS scope to deliver HIFU locally to pancreatic tumours, thus preventing occasional burns to the skin. Initial animal studies have demonstrated that it can successfully abate the normal pancreas and liver^[36].

Irreversible electroporation

NanoKnife® (Angiodynamics, Inc., NY, United States) or irreversible electroporation (IRE) is an emerging non-thermal ablative technique which uses electrodes, placed in the tumour, to deliver up to 3 kV of direct current. This induces the formation of nanoscale pores within the cell membrane of the targeted tissue, which irreversibly damages the cell's homeostatic mechanism, causing apoptosis. The United States Food and Drug Administration have recently approved the technique for use in the pancreas.

One of the major advantages of this technique is that it can be used in tumours that are in close proximity to peri-pancreatic vessels without risk of vascular trauma. The largest series of percutaneous IRE in PDAC includes 14 patients who had unresectable tumours and were not candidates for, or were intolerant of standard therapy^[37]. The procedure was performed under general anaesthesia with complete muscle paralysis. Two patients

Table 6 Studies of high intensity focused ultrasound in pancreatic ductal adenocarcinoma

Study	n	Study	Outcome and survival	Complications
Wang <i>et al</i> ^[59] (non-English article)	15	HIFU monotherapy in late stage PDAC	Pain relief: 13/13 (100%)	Mild abdominal pain (2/15)
Xie <i>et al</i> ^[60] (non-English article)	41	HIFU alone <i>vs</i> HIFU + gemcitabine in locally advanced PDAC	Pain relief: HIFU (66.7%), HIFU + gemcitabine (76.6%)	None
Xu <i>et al</i> ^[61] (non-English article)	37	HIFU monotherapy in advanced PDAC	Pain relief: 24/30 (80%)	None
Yuan <i>et al</i> ^[62] (non-English article)	40	HIFU monotherapy	Pain relief: 32/40 (80%)	None
Wu <i>et al</i> ^[63]	8	HIFU in advanced PDAC	Median survival: 11.25 mo Pain relief: 8/8	None
Xiong <i>et al</i> ^[64]	89	HIFU in unresectable PDAC	Median survival: 26.0 mo (stage II), 11.2 mo (stage III) and 5.4 mo (stage IV)	Superficial skin burns (3.4%), subcutaneous fat sclerosis (6.7%), asymptomatic pseudocyst (1.1%)
Zhao <i>et al</i> ^[65]	37	Phase II study of gemcitabine + HIFU in locally advanced PDAC	Overall survival: 12.6 mo (95%CI: 10.2-15.0 mo) Pain relief: 78.6%	16.2% experienced grade 3 or 4 neutropenia, 5.4% developed grade 3 thrombocytopenia, 8% had nausea vomiting
Orsi <i>et al</i> ^[66]	6	HIFU in unresectable PDAC	Pain relief: 6/6 (100%)	Portal vein thrombosis (1/6)
Sung <i>et al</i> ^[67]	46	Stage III or IV PDAC	Median survival: 12.4 mo. Overall survival at 12 mo was 30.4%	Minor complications (abdominal pain, fever and nausea): 57.1% (28/29) Major complications (pancreaticoduodenal fistula, gastric ulcer or skin burns): 10.2% (5/49)
Wang <i>et al</i> ^[68]	40	Advanced PDAC	Median overall survival: 10 mo (stage III) and 6 mo (stage IV). Pain relief: 35/40 (87.5%)	None
Lee <i>et al</i> ^[69]	12	HIFU monotherapy in unresectable PDAC (3/12 received chemotherapy)	Median overall survival for those receiving HIFU alone (9/12 patients): 10.3 mo	Pancreatitis: 1/12
Li <i>et al</i> ^[70]	25	Unresectable PDAC	Median overall survival: 10 mo. 42% survived more than 1 year. Perfor- mance status and pain levels improved: 23/25	1 st degree skin burn: 12% Mortality: 0%
Wang <i>et al</i> ^[71]	224	Advanced PDAC	Not reported	Abdominal distension, anorexia and nausea: 10/ 224 (4.5%). Asymptomatic vertebral injury: 2/224
Gao <i>et al</i> ^[72]	39	Locally advanced PDAC	Pain relief: 79.5% Median overall survival: 11 mo. 30.8% survived more than one year	None

HIFU: High intensity focused ultrasound; PDAC: Pancreatic ductal adenocarcinoma.

subsequently underwent surgery after IRE and both had margin-negative resections; both remain disease-free after 11 and 14 mo, respectively. Complications included spontaneous pneumothorax during anaesthesia ($n = 1$) and pancreatitis ($n = 1$); both patients recovered completely. No deaths were related to the procedure but the three patients with metastatic disease subsequently died from disease progression.

COMBINING ABLATIVE THERAPIES WITH BILIARY STENTING

Tumours of the head of the pancreas commonly cause distal biliary obstruction, which is managed in most cases by an endoscopically inserted self-expanding metal stent (SEMS). However due to tumour ingrowth SEMS are associated with a shorter patency time than bypass surgery. Hence there has been a growth in interest in using ablative therapies such as PDT or RFA to prolong stent

patency or to unblock a SEMS, which is already *in situ*. Randomised studies comparing PDT with biliary stenting to stenting alone have had conflicting results. Initial studies reported prolonged stent patency and improved survival after PDT^[38,39]. However, a recent UK phase III study closed early as overall survival was longer in those treated with stenting alone^[40]. The use of RFA in combination with SEMS placement has been reported in two small studies to date (Table 3). The investigators showed that the median bile duct diameter increased following endobiliary RFA and that 86% (19/22) of the SEMS were patent at 90 d^[41,42]. Emerging evidence also suggests that endobiliary RFA may confer some early survival benefit in patients with malignant biliary obstruction independent of stent blockage and chemotherapy^[41]. Occasionally centres have used RFA alone to achieve biliary drainage but results of on-going randomised controlled trials are awaited for validation of this technique^[43]. Current guidance from the National Institute for Health and Care Excellence in the United Kingdom recommends

that this treatment should only be carried out in specialist centres in the context of clinical trials^[44].

ENDOSCOPIC ULTRASOUND GUIDED NON-ABLATIVE LOCAL THERAPIES

Systemic chemotherapy agents are often associated with significant side effects, which can result in patients having to stop therapy or undergo dose reduction. Several groups have therefore explored using local anti-tumour agents in PDAC. The outcomes are summarised in Table 2.

PREMALIGNANT LESIONS OF THE PANCREAS

Some investigators have used similar ablative methods in PDAC to ablate premalignant solid and cystic lesions of the pancreas. Cystic lesions of the pancreas are an increasingly common clinical finding and some possess premalignant potential; longterm surveillance or surgery or pancreatic surgery is therefore recommended in accordance with international guidance^[45]. Given the morbidity of surgery and uncertainties of surveillance for essentially benign disease, minimally invasive ablative therapies are increasingly becoming an attractive alternative treatment.

An EUS-guided injection of alcohol has been reported to have reasonable efficacy for achieving complete ablation of pancreatic cystic tumours (35%-62%). However, total cyst ablation was rare in septated cysts and the technique was associated with complications (pain and pancreatitis) in between 4%-20% of cases^[46,47]. Occasional case reports have described using EUS guided alcohol injection to successfully ablate hepatic metastases^[48] and pancreatic gastrointestinal stromal tumours^[49]. Small case series have demonstrated EUS guided RFA can also be used safely for this indication^[21]. Further validation will come from larger Phase II studies.

CONCLUSION

Ablative therapies for unresectable pancreatic cancer are an attractive emerging therapy. All studies demonstrated that ablation is feasible and reproducible. Many of the early concerns that surrounded safety have been addressed with device development and modification of technique. Long-term survival data for many of the techniques is absent currently. Ultimately large prospective randomised studies will be required to assess the efficacy of these techniques and define their position in future treatment algorithms for the management of locally advanced pancreatic cancer.

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