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ORIGINAL ARTICLE

Ablation of the locally advanced pancreatic cancer: An introduction and brief summary of techniques

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Summary

Pancreatic ductal adenocarcinoma is a lethal and late presenting malignancy with dismal survival rates. An estimated total of 330,000 people died from this malignancy in 2012. Although there have been improvements in diagnostic and treatment methods, the survival of late stage pancreatic cancer has not shown significant improvement in the past 4 decades. Multiple treatment approaches are available including chemotherapy, radiotherapy, and immunotherapy, but to this day surgical resection remains the only curative treatment option. Ablative techniques use various forms of energy to cause local tissue destruction through necrosis or apoptosis. They are relevant in pancreatic ductal adenocarcinoma as they are a treatment option in non-resectable tumors where their use ranges from symptom control to reducing tumor size for resection. In this narrative review we have grouped and outlined the various ablative methods, classifying them into thermal (Radiofrequency ablation, Microwave ablation, High Intensity Focused Ultrasound ablation, Cryoablation), and non-thermal ablative methods (Irreversible Electroporation (NanoKnife®), Photodynamic Therapy). This is followed by a description and review of the available evidence on survival and complications for each of these ablative methods. According to the literature, thermal ablative methods appear to be more accessible but are implicated with more complications than non thermal ablative methods which show the most promise.

Key words: *ablation, pancreatic cancer, resection, tumor*

Introduction

Pancreatic ductal adenocarcinoma is the 10th most common cancer as well as the 5th most common cause of death due to cancer in the UK [1]. Over the last decade it has been estimated that the incidence of pancreatic cancer has increased by 8% [1]. Furthermore, for the year 2012 it was the cause for 8,662 deaths, translating to roughly 24 deaths per day. A total of 330,000 people were estimated to have died of pancreatic cancer worldwide in 2012 [1]. Despite improvements in treatment methods, the survival of pancreatic cancer has not shown any significant improvement in the past 4 decades [1].

Pancreatic ductal adenocarcinoma is a cancer with a very poor prognosis, mostly due to its advanced stage by the time of presentation. For most patients, the tumor has already invaded the local structures. Patients presenting with local progression without distal metastasis have an expected survival of 6 to 12 months, compared to a survival of 3 to 6 months for presentation with distal metastasis [2,3]. In the UK, only 1% of patients survive for more than 10 years, and a bit less than 3% survive for more than 5 years [1]. Roughly 4 in

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5 of the patients diagnosed with pancreatic ductal carcinoma will not survive for more than a year from diagnosis [1].

Currently, the standard approach for the treatment of locally advanced pancreatic cancer includes multidisciplinary teams implementing chemotherapy and radiotherapy [4,5]. With the recent notable exception of FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) [5-9], chemotherapy and radiotherapy have had very little success in improving survival, or reducing the size of the tumor to render it resectable [10,11]. To this day, resection of the tumor remains the only curative treatment choice. A 2012 cohort study demonstrated a 5-year survival rate of 18% after surgical resection with curative intent. The median survival was found to be 18 months [2,12].

Due to the delayed presentation of pancreatic cancer patients, surgical resection is only an option for a small proportion of the patients. In the US it is found that 80% of the patients are not candidates for surgery because of metastatic (50%) or locally invading (30%) disease [13]. Similar rates are found in the UK where an average of only 8% of pancreatic cancer patients receive surgical resection, although this rate varies significantly with the patients' age [14]. In those aged between 15 to 54 years, 19% received surgical resection, while in those aged 75 to 84 years, only 4% received surgical resection [14]. A tumor is considered non-resectable when there is involvement of the superior mesenteric artery, coeliac trunk, or portal vein on cross section imaging [2,15,16].

Recent years have seen an increased interest in the use of ablative therapies for the treatment of non-resectable tumors in organs such as the liver and kidney [2,5,6,17]. Local ablation techniques apply various different types of energy to a tissue for the purpose of inducing tissue destruction. Early studies using ablative techniques on the pancreas were associated with significant morbidity and mortality, however improvements in imaging techniques and ablative modalities are now commencing to show promising results for the surgical management of non-resectable pancreatic tumors as well [2,5,6,18].

In this narrative review we aimed to group and outline the various ablative methods, followed by a description and review of the available evidence on their survival rates and complications. Tables summarizing the collective evidence of previous research articles are also included.

Methods

The review of the literature focused on keyword searches of electronic databases, such as MEDLINE, Embase, Cochrane Library, and Google Scholar for articles dated past the year 2000. Our search terms included 'pancreatic cancer', 'pancreas', 'ablation', 'tumor', 'Locally Advanced', 'metastasis', 'resection', 'radiofrequency', 'Catheter', 'Microwave', 'photodynamic', 'PDT', 'High Intensity Focused Ultrasound', 'HIFU', 'laser', 'Cryoablation', 'Irreversible Electroporation', 'Photodynamic Therapy', in various configurations. We selected the relevant case series, prospective and retrospective studies, case control studies, narrative and systematic reviews, and meta-analyses. Through further review of the selected articles and hand-picked references, we formulated this narrative review.

Results

Ablative methods

Ablative methods implement various forms of energy which are used to induce tissue destruction in a specific area of the body. These include thermal, electrical, chemical, sound, and light energies which are categorized into the larger groups of thermal and non-thermal ablation methods [2,19,20]. Thermal ablative methods include radiofrequency ablation (RFA), microwave ablation (MWA), high frequency focused ultrasound (HIFU), and cryoablation. Non-thermal ablative methods include irreversible electroporation (IRE), and photodynamic therapy (PDT). The rationale behind ablation is that local destruction of the tumor cells can lead to deceleration of disease progression, which can then potentially translate to improved survival for the patients [2,20].

Ablation is a treatment option aimed at patients who have non-resectable pancreatic cancer. It can also be used for patients who cannot tolerate the standard chemotherapy and/or radiotherapy methods. The goal of ablation is to provide relief of symptoms such as pain, and down-staging of the tumor, potentially allowing for a future resection of the lesion [2].

The major risk of ablation is harm caused to adjacent healthy tissues. Being a very delicate organ, and located in a very crowded anatomical region this is a considerable risk which determines the feasibility and difficulty of using the various ablation techniques on the pancreas [2,20]. This is one of the main reasons that chemical ablation methods are not implemented in the pancreas, as leakage of these chemical agents into the arterial system could prove fatal [2,19].

Thermal ablative methods

Thermal ablative methods aim to create extremely high or low temperatures which lead to tumor ablation and cell necrosis [2,20]. The temperatures required to induce tissue damage leading to tumor necrosis have been found to be >50^{0}C or <-40^{0}C [2,20-22]. The ablative techniques implemented create these temperatures include RFA, MWA, HIFU, and cryoablation [2,20].

Radiofrequency ablation (RFA)

RFA is the most common thermal ablative method used for the treatment of solid abdominal tumors [23]. Through the use of high-frequency alternating current this mode of ablation produces coagulative necrosis of tumor cells by creating temperatures above 50^{0}C. This is done by inserting one or more electrodes inside the tumor [2,20,24]. In addition to the thermal ablation, RFA may also be responsible for inducing the expression of heat shock protein 70, enhancing a patient's anti-tumor immunity [23,25].

The reported mortality and morbidity of RFA in the management of locally advanced pancreatic cancer has been summarized in a recent systematic review [20] which included datasets from prior reviews [26]. According to Rombouts et al. review of 7 studies accounting for a total 342 patients, the morbidity rate ranged from 4-22%, while the mortality rate from 0-11% [20] (Table 1). It was also noticed that both the highest mortality and morbidity range were found in the earlier study published in 2000 [20,27]. Long term survival after RFA, reported in 5 studies, showed a median range from 5 to 25 months [20]. The largest of those studies, accounting for 100 patients, showed a 20-month median survival [28] and the second largest, with 57 patients showed a 19-month survival [29] (Table 1). Pain scores have been shown

Table 1. Summary of articles reporting on median survival of thermal ablative techniques in unresectable pancreatic cancer

Article authors	*Publication year*	*Ablative technique*	*Number of patients*	*Median survival (months)*
Cantore et al. [80]	2012	RFA	107	25.6
Frigerio et al. [29]	2013	RFA	57	19.0
Girelli et al. [28]	2013	RFA	100	20.0
Matsui et al. [27]	2000	RFA	9	5.0
Spiliotis et al. [21]	2007	RFA	8	13–19
Lygidakis et al. [33]	2007	MWA	15	22
Wu et al. [41]	2005	HIFU	8	11.2
Xiong et al. [42]	2009	HIFU	89	26.0 (stage II) 11.2 (stage III) 5.4 (stage IV)
Zhao et al. [43]	2010	HIFU	37	12.6
Sung et al. [82]	2011	HIFU	46	12.4
Wang et al. [83]	2011	HIFU	40	10 (stage III) 6 (stage IV).
Lee et al. [84]	2011	HIFU	12	10.3 mo
Li et al. [85]	2012	HIFU	25	10
Gao et al. [86]	2013	HIFU	39	11
Li et al. [57]	2004	Cryoablation	44	14
Wu et al. [61]	2005	Cryoablation	15	13.4
Xu et al. [60]	2008	Cryoablation	38	12
Xu et al. [59]	2008	Cryoablation	49	16.2
Li et al. [56]	2011	Cryoablation, with palliative bypass surgery	68	30 (6-49)
Xu et al. [55]	2013	Cryoablation	59	8.4
Niu et al. [54]	2013	Cryoablation	36 Cryoablation alone; 31 with chemotherapy	7 13

For abbreviations see text

Table 2. Summary of articles reporting on median survival of non-thermal ablative techniques in unresectable pancreatic cancer

Article authors	*Publication year*	*Ablative technique*	*Number of patients*	*Median survival (months)*
Martin et al. [68]	2015	IRE	200	24.9
Martin et al. [69]	2013	IRE	54	20.2
Narayanan. [71]	2012	IRE	14	6.7
Bown et al. [79]	2002	PDT	16	9.5

For abbreviations see text

to decrease in 50 and 69% of patients postoperatively [18,20,30]

The complications of RFA include thermal vein damage and duodenal damage which appeared to occur at higher frequency when a higher target tissue temperature of 105^{0}C was used, when compared to a 90^{0}C target [18]. When RFA margin threshold of 5mm from the tip to the major peri-pancreatic vessels was used, pancreatic fistula, vessel damage, and gastrointestinal bleeding after portal vein thrombosis were found to be common complications [30]. Use of margins wider than 5mm have been suggested, although no safe distance has been established yet [2,18,30]. Intraoperative cooling methods, such as continuous irrigation with cool saline, have been reported to decrease risk of damage to nearby tissue [30], and endoscopically inserted cooling devices may also be used in the duodenum to prevent thermal damage [26].

Microwave ablation (MWA)

MWA achieves frequencies ranging from 900 to 2450 MHz which cause oscillation of polar molecules such as water, resulting in the creation of heat by frictional agitation. As the charge on the water molecules oscillates up to 5 billion times a second, the high temperatures required for induction of coagulative necrosis are reached, and ablation is achieved [2,20,31,32]. The probes used in microwave ablation are very similar to the ones used in RFA and are referred to as "antennas" [2].

MWA is a less studied technique with only few articles available reporting mortality, morbidity, and quality of life improvements. In a series of 15 patients treated with MWA, the longest survival reported was 22 months [33] (Table 1).

Minor complications were seen in 40% of the patients, including mild pancreatitis, asymptomatic hyperamylasemia, pancreatic ascites, and minor bleeding [33]. Pseudocyst development was another complication described in a case report [34]. Advantages of MWA are less procedural pain with faster ablation times, possibility of greater intra-tumoral target temperature without heat-sink effect when closer to vessels, higher ablation volumes, reproducible ablation zones, and ability to simultaneously use multiple applicators [31,32,35,36]. A limitation of MWA is the drop shape of the necrotic area formed, however new advances in the technology are expected to produce more spherical ablation zones [2].

High intensity focused ultrasound (HIFU)

HIFU causes tissue damage and death by two known mechanisms, heat and cavitation [37]. Heat production is achieved by the ability of tumor tissue to absorb focused acoustic energy and transform it into thermal energy [2,20,38]. Cavitation is an effect of ultrasound beams which leads to oscillating compression and rarefaction of molecular structures. The molecular mechanical stresses created by these vibrations result in the generation of thermal energy and temperatures as high as 5000 K [37,39]. The high temperatures induce coagulative necrosis, resulting in heat ablation [2,37]. HIFU is a non-invasive method, as it does not require the percutaneous placement of probes into the pancreatic tumor [2,20].

HIFU has showed significant pain relief properties with studies demonstrating 67 to 100% of patients reporting pain relief, and with studies with more than 30 patients showing rates ranging from 67 to 87% according to a recent systematic review [40] of 8 articles [41-48]. Significant reduction in tumor volume has also observed in multiple studies [41,42,44-50], with some studies showing complete initial response in all patients [51]. In his review of 14 articles using HIFU [6], Kean et al. reported median survival rates varying from 5.54 to 26 months in the largest study with 89 patients [42], but most studies reported medians from 10 to 12.6 months [6] (Table 1).

Mostly few and mild complications were observed with usage of HIFU, the most common being subcutaneous sclerosis, second degree skin burn [42], mild pancreatitis [44], and pancreatic pseudocyst [42]. The most severe complication

reported was one case of portal vein thrombosis in a patient whose portal vein was compressed by the tumor with suspected further compression after HIFU by the edematous tumor; the patient was discharged after low-molecular-weight heparin treatment for one week [51].

Cryoablation

Cryoablation is a thermal method of ablation that uses very low temperatures to induce tumor ablation. This method works by the insertion of probes, known as "cryoprobes", percutaneously into the tumor [2,20]. These probes can be placed percutaneously with CT guidance [52], or intraoperatively with the use of ultrasound guidance [6]. The tumor is frozen to a temperature ranging from -40^{0}C to -160^{0}C, depending on the protocol, and then allowed to thaw back to 0^{0}C [2,6,20,22]. This cycle of freezing and thawing is repeated at least twice and each cycle lasts from 3 to 5 min, again depending on the protocol [6,22]. Cryoablation leads to cell apoptosis and necrosis by means of direct cellular injury, vascular injury, and immunological injury [21,53].

Cryoablation, with and without adjuvant immunotherapy, has been shown in a 106-patient randomized control trial, to significantly increase patient survival when compared to standard chemotherapy [54]. The median survival was 7 months with cryotherapy alone, 13 months with cryotherapy and adjuvant immunotherapy and 3.5 months when a standard chemotherapy regimen was used ($p<0.001$) [54]. In a recent systematic review of 10 articles with various uses of cryoablation [6], median survival was found to range from 7 to 14 months when cryoablation was used alone, with both those studies having more than 40 patients [54,55]. The highest median survival was found when cryoablation was used in conjunction with palliative bypass surgery, with a median survival of 30.4 months [56] (Table 1).

Multiple minor complications have been reported with mild abdominal pain being the most common in up to 76% of the patients [55], and the second most common being delayed gastric emptying reported in up to 40.9% of the patients [56-58]. Other complications included bleeding, pancreatic leak, bile leak, acute pancreatitis, and cryoprobe needle tract metastasis [55,57,59-61].

Non-thermal ablative methods

A wide range of non-thermal ablation techniques are used as means of producing cell tissue damage leading to necrosis. Chemicals, light, and electricity are examples of the energy types that can be used [2,6,20]. In this review, we cover the use of electric energy through the use of irreversible electroporation, and the use of light energy through the use of photodynamic therapy. Chemical ablation as a form of non-thermal ablation is not readily used in the pancreas due to the high fatality risk associated with using cytotoxic chemicals in such close proximity to major arteries [2,19].

Irreversible electroporation (IRE)

IRE (NanoKnife®) is a promising novel ablative method that uses brief and intense electric pulses that irreversibly disrupt cellular homeostasis by forming nanoscale pores that destroy the integrity of the cellular membrane. This process ultimately leads to apoptosis of the tumor cells [6,62,63]. A cytotoxic immune response may also be responsible for the ablative capabilities of IRE [62]. The electric pulses are applied through the placement of electrodes inside the tumor which deliver direct current [6]. The probes can be placed percutaneously with the use of imaging guidance or under direct vision during open operations [62]. One of the greatest benefits of this novel technique is its safety towards adjacent non-cancerous tissues. It is the only technique that has been shown to be safe to implement in tumors that are found in close proximity to vasculature, without causing vascular trauma [6,62]. IRE selectively causes only intracellular damage without harming the extracellular matrix, further increasing its relative safety compared to the other ablative methods [64-67].

New mortality data generated regarding patients, following an open IRE in addition to standard chemotherapy, is suggestive of a 24.9 months median survival, in a 200-patient study [68], the initial results showing a 20.2 months median survival two years prior [69] (Table 2). IRE has also been used for surgical margin accentuation [70] and control of local recurrence following a Whipple procedure [71]. These uses have no reliable mortality data, although they are generally considered having a better prognosis than standard therapy [70,71].

Although generally considered safe [2,68-71], complications of this procedure include duodenal leaks [70] and pancreatitis, [71]. A contraindication to IRE would be the presence of a metallic bile stent, which could lead to perforation of the duodenum and colon, as well as bleeding and

death [72].

Photodynamic therapy (PDT)

PDT is an ablative method that utilizes the interaction of light and tumor localizing photosensitizing agents to induce an apoptotic response in malignant cells in a predictable zone of ablation [6,73]. This process is referred to as photo-killing and results in the irreversible photo-damage to tumor tissues [73]. Photosensitizers are administered intravenously. Multiple photosensitizers are available for PDT ablation including meso-tetra (hydroxyphenyl)chlorin (mTHPC), porfimer sodium, and verteporfin [6]. Light, in the form of laser light, is brought to the tumor site by fiber optic wires placed percutaneously with the help of image guidance [6,20]. Different photosensitizers have multiple cellular and molecular targets that can be damaged to activate tumor cell apoptosis [73]. One well described target of PDT is mitochondria [74,75] where some tumors resistant to PDT treatment have been found to have mitochondrial alterations [76]. Another target is tubulin found in the cytosol [77], utilized to attack tumor cells rich in tubulin as a result of their higher rates of mitosis [78].

Mortality for post-PDT patients was only reported in a single 16-patient study to be 9.5 months [79] (Table 2).

With the limited evidence available, only few complications were reported, one of which was significant gastrointestinal bleeding [79]. All patients had abdominal pain manageable with opioids after the procedure for the first few days [79].

Discussion

Studies on these ablative therapies suggest that they are relatively safe and contribute to a rapid improvement of the clinical picture of unresectable pancreatic adenocarcinoma. Thermal ablative methods appear to provide significant improvement in mortality and symptom control, but they seem to carry higher risk of complications than non-thermal methods. RFA and MWA are quite accessible and relatively cheap. These two methods could see a rapid spread worldwide and could become part of the standard management with further improvements and research. HIFU, not requiring laparotomy or percutaneous needle placement, could also be indicated in a patient in whom surgery is not recommended. Non thermal ablative methods, although more expensive, show great promise. With less and milder complications, IRE appears to be the most promising method in our days. Further randomized controlled trials comparing different ablative methods with standard regimen would provide clearer data of their relative indications, efficacy and safety.

Conclusions

Ablative therapies for unresectable pancreatic cancer have come a long way since their early days. Recent data demonstrated that most of these techniques are feasible, reproducible and quite safe. RFA, HIFU and MWA seem to have a definite place in the local control of pancreatic adenocarcinoma. Cryoablation, IRE and PDT are promising modalities that still require some improvement and decrease in operating costs for wider use. The early results of ablative therapies showcase their clear advantages over standard management with or without adjuvant chemotherapy but IRE seems to be the most promising with lower complications and equivalent survival. These emerging techniques will require larger prospective randomized studies demonstrating their efficacy and safety before becoming part of the standard management algorithm for locally advanced pancreatic cancer.

Conflict of interests

The authors declare no confict of interests.

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