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REVIEW

Minimally Invasive Ablation Treatment for Locally Advanced Pancreatic Adenocarcinoma

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Abstract Pancreatic adenocarcinoma is an aggressive tumour with an extremely poor prognosis, which has not changed significantly during the last 30 years. Prolonged survival is achieved only by R0 resection with macroscopic tumour clearance. However, the majority of the cases are considered inoperable at diagnosis due to local spread or presence of metastatic disease. Chemoradiotherapy is not tolerated by all patients and still fails to prolong survival significantly; neoadjuvant treatment also has limited results on pain control or tumour downstaging. In recent years, there has been a growing interest in the use of ablation therapy for the treatment of nonresectable tumours in various organs. Ablation techniques are based on direct application of chemical, thermal, or electrical energy to a tumour, which leads to cellular necrosis. With ablation, tumour cytoreduction, local control, and relief from symptoms are obtained in the majority of the patients. Inoperable cases of pancreatic adenocarcinoma have been treated by various ablation techniques in the last few years with promising results. The purpose of this review is to present the current status of local ablative therapies in the treatment of pancreatic adenocarcinoma and to investigate on the efficiency and the future trends.

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Introduction

Pancreatic ductal adenocarcinoma is still one of the most aggressive cancers and is the fourth most frequent tumour-related cause of death in the Western world [1]. Locally advanced disease is difficult to control, and no significant improvement in outcomes has been achieved in the last 30 years despite the advance of diagnostic modalities and therapeutic options. For all stages combined, the 1-year survival rate is ~20 %, and the overall 5-year survival rate has remained dismally poor at <5 % [2]. Complete surgical resection remains the only curative treatment for pancreatic cancer. The advanced T-stage of pancreatic adenocarcinoma is defined according to the involvement of the superior mesenteric artery, the celiac axis, the portal vein, or their combination on cross-sectional imaging, and this is how the tumour is characterized as nonresectable [3, 4].

Pancreatic tumour becomes symptomatic at a very advanced stage; therefore, a small percentage (15–20 %) of patients may undergo therapeutic resection. In the rest of the patients, there might be either advanced locoregional disease without distant metastases (expected survival of 6–12 months) or locoregional disease with distal metastases (expected survival of 3–6 months) [5]. Chemoradiation therapy (CRT) provides minimal survival benefits in patients with locally advanced pancreatic cancer. The majority of the chemotherapeutic schemes fail completely to prolong survival, and only recently did gemcitabine-associated CRT appear to offer a modest survival benefit of 3 months [6, 7]. Also recently, the combination of several drugs (5-fluorouracil, leucovorin, irinotecan, and oxoplatin)—called the

FOLFIRINOX combination—showed better response and survival rates in specific groups of patients; however, long-term results from ongoing trials are not yet available [8]. The usefulness of radiation therapy was also tested; however, the results were not significant [9, 10].

Considering the limited effect of CRT, there is a clear need for a more effective local treatment to improve survival and pain control of patients with nonresectable pancreatic adenocarcinoma. Image-guided ablation techniques, such as radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE), have been proposed as new treatment options in such cases.

Local Ablative Therapies

When local ablative therapies are applied, chemical, thermal, or electrical energy is transferred to a specific area of the body with the intent of tissue destruction. Chemical ablation includes the use of ethanol or acetic acid, which induces coagulation necrosis of the tumour mass after direct contact with these agents. With chemical ablation, there is always the risk of migration to the arterial system with fatal consequences, and its application in the treatment of pancreatic tumour is limited [11].

Thermal ablation may be based on the increase or the decrease of tumour temperature. When heat is applied, a target temperature >50 °C (particularly temperatures ranging from 60 to 100 °C or more) results in significant tissue ablation and a successful outcome. Cell death results from apoptosis and eventually coagulative necrosis, which occurs at temperatures >50 °C after 2 min. When cold is applied (cryoablation), temperatures lower than the tissue freezing edge are achieved; the target temperature is lower than –40 °C, which in most is necessary to cause irreversible necrosis of target cells [12, 13]. There are several thermal ablation studies on the treatment of pancreatic cancer, mainly with the use of applied heat, and very limited studies on cryoablation in the literature.

Electrical current ablation is a technology that is based on the irreversible increase of permeability of the cellular membrane with the use of electric currents. IRE is one of the latest technological advances, and few studies have been performed on its application in the local treatment of pancreatic cancer.

Improvement in percutaneous guidance of probes, electrodes, and ultrasound (US) beam enables the development of accurate minimally invasive tumour treatment [14]. Ablation may be applied to patients who are not considered suitable for surgical resection and cannot tolerate CRT or who fail to respond to CRT, thus aiming to offer symptom relief, control of pain, and downstaging of the lesion.

The pancreas per sè is a rather delicate organ, and ablation of any form may cause damage to healthy tissue and lead to complications such as pancreatitis. The anatomical location of the organ is also challenging, and ablation treatment may also lead to the injury of the duodenum, the distal bile ducts, and the vascular structures of the area. Nevertheless, technical feasibility of the ablation of pancreatic tumours has been confirmed by numerous studies.

Radiofrequency Ablation

RFA of the pancreas was initially applied to animal models. Goldberg et al. [15] studied the safety and efficacy of RFA in experimental models and concluded that RFA can be used in small neuroendocrine tumours and possibly in the palliation of unresectable pancreatic adenocarcinoma. Date et al. [16] showed the safety and efficacy of RFA in the normal pancreas of a porcine model. Matsui et al. [17] published the first clinical study of 20 patients in 2000. Since then, few studies and case reports have been published from various groups of investigators [18–22]. The results of the main studies have been summarized in a recently published systematic review on the use of RFA for the treatment of locally advanced pancreatic cancer [18]. In the review, five cohort studies (four prospective and one retrospective) were included that were published in the English language until 2012. The investigators did not include studies with less than 5 cases because they were considered as case reports, and they included only studies that reported RFA on pancreatic adenocarcinoma. In total, 158 patients were treated with the use of four different ablation devices: 100 patients using a 1500X generator (RITA Medical Systems, Mountain View, CA), 28 patients using a Radionics generator (Radionics Inc., Burlington, MA), 10 patients using a generator manufactured by Berchtold GmbH & Co., KG (Tuttlingen Germany), and 20 patients using a generator manufactured by Omron Co., Ltd (Kyoto, Japan). In the study by Matsui et al. [17], the median reported survival was 3 months. The benefit of the survival rate offered by local tumour control was not clear because patients with metastatic disease were also included in the study, and no subgroup analysis was performed. Median patient survival was also included in another two studies among the five included in the systematic review, and this was 20 months [19] and 33 months, respectively [20]. In the study of Singh et al. [21], the investigators reported survival range of 9–36 months. In the largest among these studies, published by Girelli et al. [19], 100 patients were treated and procedure-related morbidity and mortality were 15 and 3 %, respectively. The investigators initially treated their first 25 patients with a target tissue temperature of 105 °C, and thermal vein damage in

conjunction with duodenal damage occurred. Their practice was changed for the rest of the patients aiming for a target temperature of 90 °C, and the morbidity rate was significantly decreased. The highest procedure-related morbidity and mortality were reported by Wu et al. [22] and were 38 and 19 %, respectively. The RFA margin threshold at this study was only 5 mm from the porto-mesenteric vascular structures, and 3 patients developed a pancreatic fistula, 3 had massive gastrointestinal bleeding after portal vein thrombosis, and 3 with gastrointestinal bleeding died. Girelli et al. [19] performed RFA with a >5-mm safety margin from the porto-mesenteric vessel and a >10-mm safety margin from the duodenum. An endoscopically inserted cooling device may also be used in the duodenum to prevent thermal damage [23]. Cooling devices may also be used in an intraoperative setting as reported by Cavallini et al. [24].

Although there is a great heterogeneity in the obtained results from the various pancreatic RFA studies considering that tumours of different stages (III–IV) were treated, and considering that different RFA settings and protocols were used, RFA appears to be a feasible option for the local control of pancreatic adenocarcinoma. However, the thermal damage of the surrounding organs and the inevitable "heat-sink" effect still limit the application of this method.

Microwave Ablation

Microwave radiation lies between infrared radiation and radio waves with frequencies from 900 to 2,450 MHz. Heating of the tissue is based on the agitation of water molecules inducing cellular death by way of coagulation necrosis; electrical charge on the water molecule flips back and forth 2–5 billion times a second depending on the frequency of the microwave energy [25, 26]. The main advantages of MWA include the following: greater intratumoural temperatures, greater tumour ablation volumes, faster ablation times, reproducible ablation zones, ability to use simultaneously multiple applicators, optimal heating of cystic masses and tumours close to the vessels without heat-sink effect, and less procedural pain [25–28].

The MWA system resembles the RFA system and is principally formed by a generator and a needle, which in this specific case is called the "antenna." The results of the application of MWA in pancreatic tumours was published by Lygidakis et al. [29] in a study of 15 patients in whom microwave antennas were inserted intraoperatively. The results of the study showed partial necrosis in all treated cases without major complications. However, in 40 % of cases, minor complication occurred (mild pancreatitis, pancreatic ascites, asymptomatic hyperamylasia, and minor bleeding). The average size of the treated lesions was 6 cm, and the lesions were mainly located in the head of the organ and the uncinate process. The longest survival reported in this series was 22 months.

Carrafiello et al. [30], in a short communication, reported a case of a 42-mm pancreatic head adenocarcinoma that was treated under computed tomography (CT) guidance with the use of two microwave antennas. No local recurrence was noticed during the follow-up period; a pseudocyst developed 3 months after the procedure and was drained percutaneously. A limitation of some MWA generators is the morphology of necrotic area that is "drop-shaped" with the presence of a comet tail proximally directed along the needle. A development in this area is "mini-choke" technology, which is expected to produce a more spherical ablation zone and thus limit the "comet-tail" effect.

High-intensity Focused Ultrasound

One of the most innovative and revolutionary techniques in the field of ablation is HIFU. The main advantage of HIFU is that it does not require percutaneous placement of needles. It is based on the use of a US beam that is focused and creates a thermal effect. HIFU transducers deliver US with intensities in the range of 100–10,000 W/cm^2 to the focal region (an effect known as "sonication") with peak compression pressures $\leq$30 MPa and peak rarefaction pressures $\leq$10 MPa. The acoustic energy is absorbed by the tissue and transformed to thermal energy with a result of an increase in the tissue's temperature; when the temperature exceeds the threshold of 60 °C, this leads to coagulative necrosis. With HIFU, this effect is achieved in few seconds. The beam is precisely focused either under magnetic resonance imaging (MRI) or real-time US imaging to avoid thermal damage to adjunct structures. With the use of MRI, a thermal map of the tissue may also be obtained. With the use of US guidance, the acoustic pathway may be checked before treatment [31].

Results from an open-label study in China of 251 patients with advanced pancreatic cancer (TNM stages II–IV) suggested that HIFU treatment could decrease the size of pancreatic tumours without causing pancreatitis and thus prolong survival [32]. An interesting result was that 84 % of patients with pain due to pancreatic cancer obtained significant pain relief after treatment with HIFU. Nonrandomized open-label studies from China also suggested that HIFU treatment of pancreatic tumours significantly relieves tumour-related pain [33, 34]. Similar results were obtained by some small case series and case reports from Europe [35–38]. However, there are no published prospective randomized studies on the use of HIFU for the treatment of pancreatic tumours.

Irreversible Electroporation

Nonthermal ablation with IRE offers the advantage of decreasing the risk of thermal damage to structures adjacent to pancreatic tissue. The technique uses a series of short, high-voltage pulses that are applied to tissues and increase the permeability of the cell membranes. Reversible electroporation is a commonly used technique that offers access for electro-transfection of genetic material or intracellular delivery of drugs [39–41]. There is a certain threshold above which the energy of the applied pulses leads to irreversible permeabilization, thus leading to cellular apoptosis [42]. This technique influences only the intracellular environment and not the extracellular matrix; hence, the effect of ablation is strictly intracellular [43–46].

Bower et al. [47] reported the use of IRE in porcine pancreatic tissue. Six swine underwent a general anaesthesia procedure, and a ventral midline incision was performed. A 19-gauge monopolar and a 16-gauge bipolar electrode were used. The electrodes were placed within the pancreatic tissue in a distance of 1 mm from the portal vein or the mesenteric artery under US guidance. The monopolar electrodes were located with a variety of intervals between 1.5 and 2 cm. The generator used was the NanoKnife (AngioDynamics, Queensbury, NY), which offers an energy output of 3 kV and current up to 50 amp. The generator was synchronized to deliver electrical pulses according to the swine's cardiac rhythm to prevent cardiac arrhythmias. The goal of treatment was to deliver 90 μs pulses at groups of 10 with pulse duration of 100 ms and a pulse interval of 250 ms. All animals tolerated the procedure, and only a transient increase in pancreatic enzymes was reported. Two swine were killed at each of the following intervals: 72 hours, 7 days, and 14 days after the procedure. Pathology analysis showed satisfactory ablation areas with necrosis of pancreatic cells adjacent to vascular structures. There was no heat injury in vessels or bile ducts. The results of this preliminary animal study suggested that IRE might be used in the ablation of pancreatic tissue without significant risk of pancreatitis or vascular thrombosis. However, there is a threshold above which IRE may result to thermal injury, and this must be controlled within the ablation parameters.

Martin et al. [48] reported the results of 54 patients who underwent IRE for local treatment of pancreatic cancer. All patients were considered inoperable due to encasement of the superior mesenteric artery or the celiac axis. The results obtained were compared with standard treatment (chemotherapy or chemoradiotherapy). IRE was not performed percutaneously but rather intraoperatively through an open supine midline incision or in a laparoscopic fashion. In 19 patients, surgical down staging was performed, and IRE was used for surgical margin accentuation after the excision of the tumour; however, the investigators do not distinguish these patients as a separate group. After a median follow-up time of 15 months, 15 of the 54 patients appeared to have local disease recurrence. The adverse events that were IRE-related were two cases of bile leakage and two cases of duodenal leakage. However, the duodenal leaks occurred after the removal of a duodenal stent and placement of the IRE needle. The IRE group appeared to have a longer survival (14 vs. 6 months) compared with the standard group; however, randomization was not performed, and selection of the group was physician related. The investigators concluded that IRE appears to be safe for local control of pancreatic cancer precluding that standard chemotherapy was administered for a minimum of 4 months.

Narayanan et al. [49] performed a study of 14 patients who received CT-guided percutaneous treatment with IRE for locally advanced pancreatic cancer. The indications for treatment were down staging of the locally advanced cancer, control of local recurrence after previous Whipple procedure, and intolerance to systemic chemotherapy. The patients had received previous cycles of chemotherapy and 10 of 14 also received previous radiation therapy. The median time from diagnosis to IRE was 16.6 months. The median tumour size treated was 3.3 cm (range 2.5–7). In six cases, the tumour was located in the pancreatic head; in seven cases it was located in the body, and in one case it was located in the uncinate process. In three cases, small-volume metastatic disease was present, whereas patients with extensive metastatic disease were not included in the study. In one case, a peritoneal deposit was also treated with IRE in the same setting as the pancreatic lesion. The investigators also used the NanoKnife IRE device (AngioDynamics, Queensbury, NY), which was set up to produce 70-μs direct-current (25 to 45 A) electric pulses at high voltage (1,500–3,000 V). No severe complications occurred after the procedure. Complications included pneumothorax, a small subcutaneous hematoma, and self-limiting pancreatitis. There were four deaths during the course of the follow-up; however, no deaths were attributed to the procedure. There were no cases of vessel thrombosis after the procedure. Two patients underwent margin-free tumour resection after IRE. Three other patients with intolerance to chemotherapy showed stable disease and did not require any further treatment. In another patient, pain relief was obtained 4 weeks after the procedure. The investigators concluded that patients with metastatic disease do not appear to benefit from IRE and that patients with extensive varices probably also need to be excluded, thus indicating that a safe CT "window" is not enough for percutaneous IRE of locally advanced pancreatic cancer. However, the procedure appears to be well-tolerated; feasible for percutaneous approach, even though several

(usually four) needles must be inserted; and represents an option for patients in whom disease appears to be progressing even though chemoradiotherapy is administered.

Conclusion

To summarize, RFA, MWA, HIFU, and IRE have a clear role in the local control of pancreatic adenocarcinoma. RFA and high-intensity US could ablate large volumes of tumour with high precision. Many specialist units are using RFA for ablation of liver tumours, and such expertise may be used for the ablation of pancreatic tumours in some cases. MWA is a promising modality; however, further improvements may be required for the locoregional treatment of pancreatic tumours. Some groups use IRE; however, it is very expensive at the moment and not available in many centres. All methods offer a cytoreductive measure in an adjuvant setting with the aim of better palliation in locally advanced pancreatic cancer. Thermal ablation is universally recognized as effective and intentionally radical when a "safety halo" of necrosis is achieved around the target lesion. The difficulty to obtain that without running excessive risks of perioperative complications is the most important limitation of any thermal ablative technique in the pancreas. Further studies of ablative therapy with or without chemotherapy and chemoradiation are warranted to study the benefit of all available techniques on survival and quality of life in patients with unresectable pancreatic cancer. During the next several years, we expect more substantial research efforts comparing various ablation techniques. The desired advances include the following: improvements in image guidance for targeting tumours to be ablated, better detection of residual disease, increased efficacy on celiac ganglion ablation, and making the therapy more straightforward by decreasing device complexity and overall time required to ablate a given tumour.

Conflict of interest All authors have no conflict of interest to disclose.

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