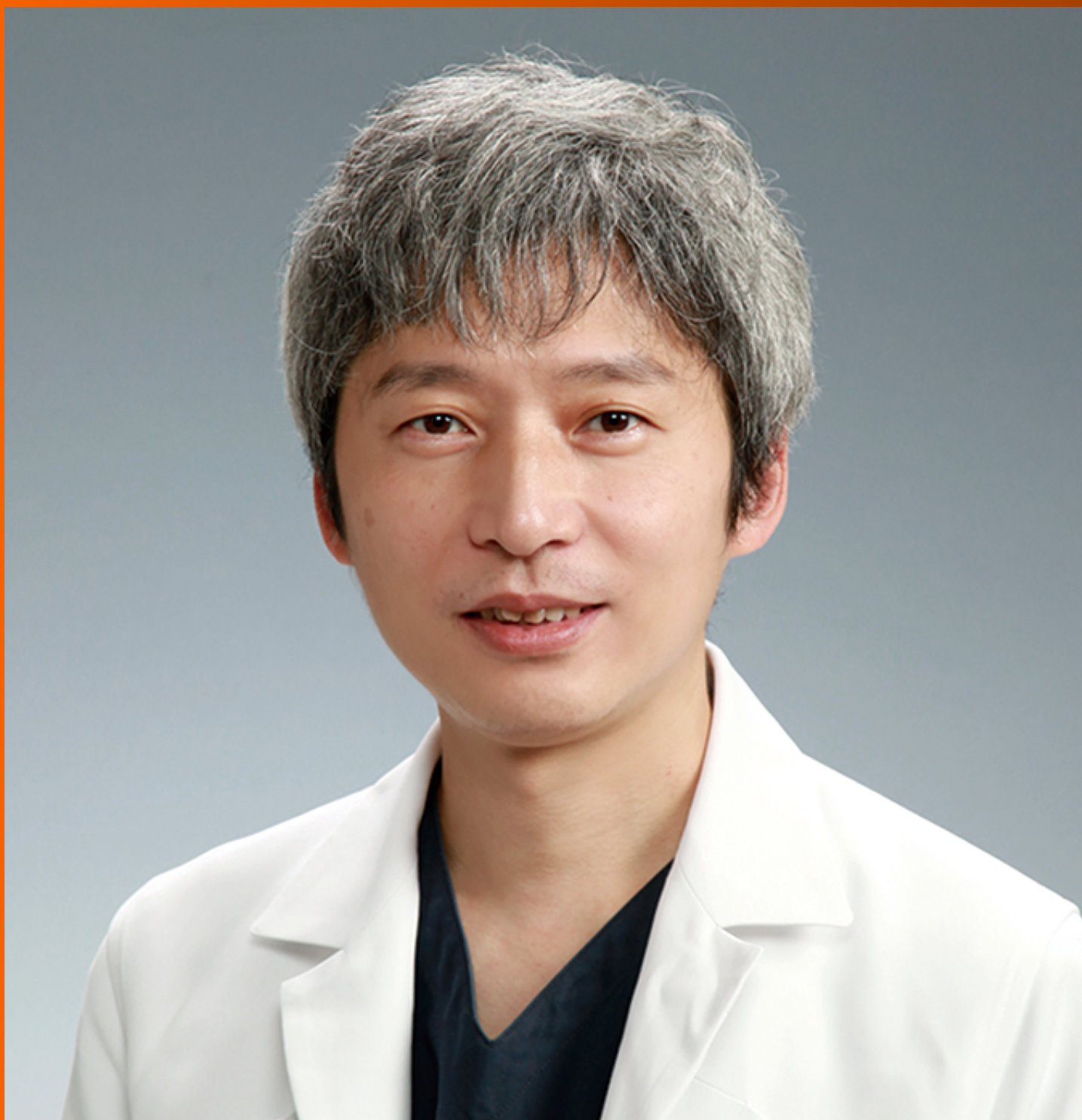


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Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Stavros Spiliopoulos, Lazaros Reppas, Dimitrios Filippiadis, Antonella Delvecchio, Maria Conticchio, Riccardo Memeo, Riccardo Inchingolo

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Abstract

Pancreatic cancer is currently the seventh leading cause of cancer death (4.5% of all cancer deaths) while 80%-90% of the patients suffer from unresectable disease at the time of diagnosis. Prognosis remains poor, with a mean survival up to 15 mo following systemic chemotherapy. Loco-regional thermal ablative techniques are rarely implemented due to the increased risk of thermal injury to the adjacent structures, which can lead to severe adverse events. Irreversible electroporation, a promising novel non-thermal ablative modality, has been recently introduced in clinical practice for the management of inoperable pancreatic cancer as a safer and more effective loco-regional treatment option. Experimental and initial clinical data are optimistic. This review will focus on the basic principles of IRE technology, currently available data, and future directions.

Key Words: Pancreatic cancer; Interventional oncology; Irreversible electroporation; Ablation; Loco-regional treatment; Image-guided treatment

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Core Tip: Loco-regional thermal ablative techniques such as radiofrequency, microwave, and cryoablation are rarely implemented for the treatment of inoperable pancreatic cancer due to the increased risk of thermal injury to the adjacent structures. Irreversible electroporation is a promising novel non-thermal ablative modality that could provide a safer and effective ablation *via* the application of electric pulses to damage cell membranes and cell homeostasis resulting in cancer cell necrosis and apoptosis. Experimental and initial clinical data are optimistic, and its potential immunomodulatory effect and synergism with immunotherapy provides are promising.

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INTRODUCTION

Pancreatic cancer is currently the seventh leading cause of cancer death, representing 4.5% of all cancer deaths worldwide. Most importantly, overall prognosis remains extremely poor as approximately 80%-90% of patients suffer from unresectable disease at the time of diagnosis, with a less than 8% relative survival rate at 5 years[1]. Systemic chemotherapy using gemcitabine or more recently FOLFIRINOX regimens, with or without radiotherapy, results in overall survival rates ranging from 9 to 14 mo[2,3]. Moreover, thermal (radiofrequency and microwave) and cryoablative techniques are not commonly employed due to the increased risk of severe trauma to the adjacent major anatomical structures[4]. Irreversible electroporation (IRE) is a promising novel percutaneous, image-guided nonthermal ablative modality that has been recently introduced in clinical practice for the management of pancreatic cancer.

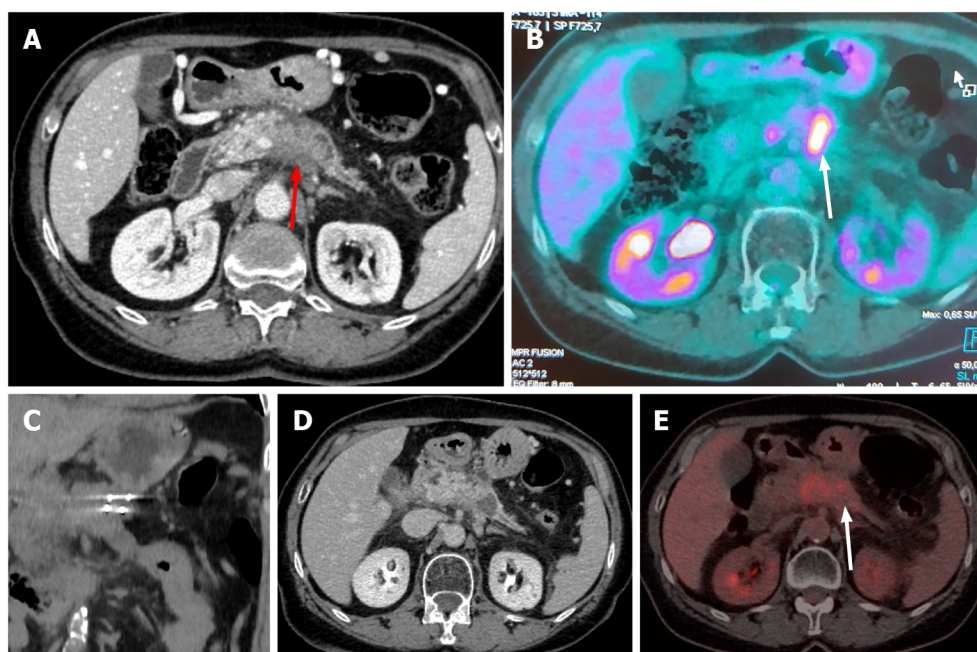
MECHANISM OF ACTION

The phenomenon of IRE was first reported in the 1970s to describe the alteration of transmembrane potential leading to the increased cell membrane permeability, disruption of the dual lipid layer, and the creation of permanent nanoscale defects (nanopores) in the cell membrane following the application of high-voltage pulsed electric fields across the cell[5]. This technique results in failure of the cell homeostasis, electrolyte alteration, and cell death by apoptosis[6-9].

In contrast to necrosis induced by thermal ablative methods, non-thermal apoptotic active cell death does not incite inflammation and enables ablation with minimal distortion of the adjacent tissues. However, since 2006 when the first *in vivo* model of IRE for cancer ablation was reported, several experimental studies have reported solely necrosis or mixed results of both necrosis and apoptosis following the application of IRE[10-13]. According to currently available experimental data, apoptosis has been demonstrated immediately after application of IRE in a murine cancerous pancreas model and at 7 to 14 d in a porcine healthy pancreas model, while necrosis is evident immediately and up to 14 d later. Unfortunately, pathology data on human pancreatic cancer are extremely limited and as the IRE ablative effect is directly correlated to the physical properties of the target tissue, the significant discrepancies between *in vivo* normal/cancer animal models, and human cancer/normal pancreatic tissues. This presents a major limitation regarding our knowledge on the actual effects of IRE[14-16]. Moreover, data indicate that IRE is not homogeneously distributed along the target tissue, and various effects are produced with increasing voltage and time.

While apoptosis is certainly occurring in some cells within the treatment zone, Brock *et al*[17] suggest that IRE could initiate multiple types of cell death mechanisms, but the size and shape of the regions in which each type is experienced may vary between clinical treatments depending on differences in pulsing parameters, tissue type, and treatment time. Thus, there may be more than one type of cell death mechanism at play, and may include pyroptosis or necroptosis. Likewise, for cells at the margins of the treatment areas, the response observed may actually be survival signaling in response to reversible electroporation. In theory, this could be taken advantage of and combined with chemotherapy treatments to increase drug delivery, tumor penetration, and treatment of residual cancer cells[17,18].

IRE has significant inherent advantages over thermal ablation for the treatment of pancreatic cancer (Figure 1). Most importantly, IRE does not produce a temperature increase to achieve tumor destruction. Therefore, it does not elicit thermal injury to the superior mesenteric and portal veins, superior mesenteric and celiac arteries, bile duct adjacent nerves, or gastrointestinal structures, which has restrained the use of local thermal ablation treatment. Another significant advantage is the absence of



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Figure 1 Pancreatic cancer treated with percutaneous irreversible electroporation. A: Axial computed tomography (CT) showing a lesion (arrow) in the body of the pancreas consistent with ductal adenocarcinoma previously treated with chemo and radiation therapy; B: Positron emission tomography (PET)-CT scan showed the residual active part of the lesion (arrow); C: CT coronal view with 4 parallel electrodes positioned within the lesion; D and E: 3-mo follow-up CT (D) and PET-CT (E) showing complete ablation of the tumor with photopenic area in the site of ablation (arrow).

the “heat sink” effect in which the flow of large blood vessels decreases the thermal ablative effect[19-22]. According to published clinical protocols, the procedure is performed under computed tomography (CT) guidance, general anesthesia (complete muscle paralysis), and electrocardiography synchronization due to the possibility of muscular spasms induced by high-voltage pulses[23].

IRE is induced by electrodes connected to a high-voltage pulse generator. Multiple electrode pairs can be used; the number of electrodes needed and their exact placement is decided during pre-procedural planning. For small tumors measuring up to 2 cm, three electrodes are placed at the periphery of the target lesion, and for lesions between 2 cm and 3 cm, four electrodes are used. However, for lesions > 3 cm, a maximum number of six electrodes is allowed with four or five electrodes at the periphery and one or two at the center of the lesion. An optimal interelectrode distance between 7 mm and 24 mm has been described. The correct positioning of electrodes requires experience often deriving from that with other ablative methods. Skill is also needed in using ultrasound or CT techniques as a guide for positioning the electrodes and avoiding accidental damage to surrounding organs.

With respect to large vessels close to the tumor, a minimum safety distance of 2 mm is recommended to avoid the risk of burn damage. In cases of locally advanced pancreatic cancer with involvement of the mesenteric artery or vein, placing the electrodes parallel to the vessels has proven effective. Following electrode placement, the generator produces short, repeated pulses using predetermined voltage settings to reach a target current of 20-50 A. In clinical practice usually, 90 pulses per treatment cycle are used, with a pulse duration of 70-90 μ s, and a voltage setting between 1400-1800 V/cm (maximum capability 3000 V/cm)[2,9,24-26]. According to standard ablation technique protocols, the aim is to create a safe 5 mm tumor-free IRE zone, also referred as A0 ablation (analogous to an R0 surgical resection).

PRE-CLINICAL DATA

To date, only a few reports on IRE for the treatment of pancreatic cancer exist in literature. Some of them reported the use of the technique on animal models (Table 1). These studies have used animal xenografts carrying human pancreatic cancer cells to understand the histological effect of IRE on pancreatic cancer tissue. The results following application of IRE showed evidence of both acute coagulative necrosis and apoptosis of pancreatic cancer tissue followed by fibrosis.

In 2010, Charpentier *et al*[27] reported a pilot study on IRE in a normal pancreas porcine model. They showed the following histological features: Initial active local inflammation, interstitial edema, and significant necrosis (after 7 d) followed by the development of fibrosis. However, these results were not significant for IRE efficacy because normal pancreatic tissues had a very different conductivity than

Table 1 Irreversible electroporation of pancreatic cancer in animal models

Ref.	Animal model	n	Tumour location	Histology	Major complication
Charpentier <i>et al</i> [27], 2010	Porcine	4	NP	Necrosis	None
Bower <i>et al</i> [28], 2011	Porcine	6	Orthotopic PC	Necrosis	None
José <i>et al</i> [29], 2012	Mouse	24	Orthotopic PC	Necrosis	None
Fritz <i>et al</i> [33], 2015	Porcine	10	Orthotopic PC	Necrosis	None
Su <i>et al</i> [30], 2018	Mouse	22	Orthotopic PC	Necrosis	None
Shankara Narayanan <i>et al</i> [31], 2018	Mouse	N/A	Subcutaneous/orthotopic PC	Necrosis	None
Lee <i>et al</i> [32], 2021	Porcine	N/A	Orthotopic PC	Necrosis	None

N/A: Not available; NP: Normal pancreas; PC: Pancreatic cancer.

pancreatic tumors.

Subsequently, Bower *et al*[28] and José *et al*[29] suggested that IRE could be an effective treatment for locally advanced pancreatic cancer in a mouse model without systemic toxicity and major local complication. Su *et al*[30] concluded that IRE was a safer and shorter operation than traditional ablation and represented a promising new approach for pancreatic cancer. Narayanan *et al*[31] described IRE for a pancreatic cancer mouse model and concluded that this animal model serves as a robust system to study the effects and clinical efficacy of IRE. Also, Lee *et al*[32] demonstrated and confirmed on a porcine model the safety and minimal complications of IRE ablation in pancreatic cancer tissue. Finally, the results of IRE in animal models of the treatment of pancreatic cancer showed the ability to ablate the target cells while preserving the collagen architecture of vascular, biliary, and neuronal structures[12, 28].

CLINICAL DATA

The prognosis of patients with pancreatic cancer not eligible for surgery remains poor despite many chemoradiation protocols. Therefore, different approaches for treatment of this disease are required. Ablation procedures including radiofrequency ablation, microwave ablation, cryoablation, high intensity focused ultrasound, and IRE can offer symptomatic relief, survival benefit, and potential tumor downsizing. Nevertheless, thermal procedures using extreme temperatures can induce injury to the pancreatic duct, bile duct, and adjacent vessels, potentially resulting in fistula formation, bile leaks, and hemorrhage, respectively[34].

IRE is an emerging non-thermal local ablation technique that affects with electricity only target cell membranes and avoids the nearby vessels and vital structures. Therefore, IRE can also be used in tumors positioned near some vital structures or organs more safely compared to other ablative procedures[35]. According to the American Joint Committee on Cancer stage criteria (8th edition), the major current indications for the use of IRE in the treatment of pancreatic cancer are as follows: Locally advanced pancreatic cancer stage II or III (T4N1M0) with ≤ 3 positive regional lymph nodes; tumor size maximal axial diameter ≤ 5 cm; and tumors in patients not candidates for radical resection or who refuse this surgery. IRE also carries some absolute and relative contraindications. It cannot be used if there are metal implants less than 2.5 cm from the ablation area, or in patients with portal vein occlusion, portal hypertension, ascites, bile duct obstruction, or hyperbilirubinemia. Additionally, IRE can also affect myocardial contraction mechanisms and as such cannot be applied in patients with cardiac arrhythmias, previous heart failure, active coronary disease, or recent pacemaker implantation. Finally, IRE cannot be used in patients with epilepsy despite the fact that it not been proven to cause brain stimulation[35].

The indications and contraindications for IRE for the treatment of pancreatic cancer are summarized in Table 2. Martin *et al*[36] and Narayanan *et al*[37] described the first clinical series on the implementation of IRE for the treatment of human pancreatic cancer. Since then, the use of this technique has been widespread[38-40], but to date there is still no defined protocol for the use of IRE in the treatment of pancreatic cancer. Studies showed that IRE was a viable treatment for locally advanced pancreatic cancer or borderline resectable pancreatic cancer because it allowed tumor downstaging, definitive locoregional treatment, or adjuvant treatment following resection[41-43]. In human tumor tissue, IRE induces necrosis as it does in animal cancer models; however, there is no evidence of apoptosis[16]. A series of retrospective and prospective clinical studies on human pancreatic cancer treated with IRE suggested a survival benefit with a median overall survival (OS) up to 30 mo[38,39].

Combined treatments involving IRE, chemotherapy, and immunotherapy can offer a multimodal approach which can limit the disease progression. However, the debate is ongoing with respect to the

Table 2 Indication and contraindications of irreversible electroporation in pancreatic cancer

Indication	Contraindications	
	Absolute	Relative
Biopsy-proven primary and solitary pancreatic tumors	History of ventricular arrhythmias	Atrial fibrillation
Locally advanced pancreatic cancer. Stage II or III (T4N1M0) with regional positive lymph nodes ≤ 3	Implanted cardiac stimulation devices within 1 yr	Coronary artery disease
Tumor size maximal axial diameter ≤ 5 cm	Uncontrollable hypertension	Combined severe stenosis of the common hepatic artery and main portal vein branch
Patients not candidates for radical resection or who refuse the surgical operation	History of epilepsy	Metallic foreign object in the ablation zone
Patients with a predictable OS longer than 3 mo, Karnofsky Performance Score > 50	Congestive heart failure ($>$ NYHA class 2)	Liver failure, portal hypertension, ascites, bile duct obstruction, hyperbilirubinemia
		Irreversible bleeding disorders
		Uncontrolled infections; patients that have received chemo or immunotherapy in the 4 wk prior to treatment

OS: Overall survival; NYHA: New York Heart Association.

timing of multimodal treatment. Some studies that administered IRE before chemotherapy showed only a modest increase in survival; Månsson *et al*[40] reported a median OS of 13 mo. In contrast, studies using IRE after induction chemotherapy reported an increase in survival with a median OS of 27 mo [44]. Despite improvements in radiation therapy, chemotherapy, and surgical procedures over the last 30 years, pancreatic cancer 5-year survival rate remains at 9%.

Recently, the advanced techniques of proton radiation and carbon ion radiation therapies have been used for locally advanced pancreatic cancer with encouraging results. The proton beam offers significant physical advantages over the photon due to the Bragg peak effect with little or no output dose beyond the tumor target, thereby sparing any critical organs adjacent to cancer. Compared to proton radiation, carbon ion radiation offers similar dosimetric characteristics, but it has a substantially different biological property and offers greater biological efficacy in inducing complex DNA damage, leading to an increase in the destruction of cancer cells[44].

Despite the non-thermal effect of IRE, complications related to the production of heat near the electrodes (defined as secondary Joule heating) remain unavoidable[45]. The most common complications following IRE are mild acute pancreatitis, pain, diarrhea, nausea, vomiting, loss of appetite, and delayed gastric emptying. Serious complications after IRE related to the location and size of the pancreatic tumor have also been reported in the literature and include arrhythmia, severe acute pancreatitis, hemorrhage, portal vein thrombosis, bile or pancreatic fistula, gastrointestinal tract perforation, and death[16,45]. In one of the most recent reviews[16], the average rate of serious complications after IRE was 12%, with a maximum reported value of 42%[2]. The size of the tumor is one of the most important factors related to procedure complications; for example, Narayanan *et al*[46] treated patients with tumors up to 8 cm in size and reported one of the highest total complication rates of 62%. Other factors contributing to post IRE complications depend on the team experience, the protocol used, and the type of approach (open *vs* percutaneous)[18]. For example, the average mortality rates have been reported as 2% and 0% for open and percutaneous IRE, respectively[20].

Available IRE protocols in part derive from data gathered from animal studies; however, the pancreas tissue of animals and humans differ significantly in cellular composition and electrical impedance. In addition, available IRE protocols developed to date differ in recommended distance between the electrodes and intensity of applied voltage. Moreover, these protocols vary in the reported individual electrical properties of the tissue being ablated, which can have an impact on the effectiveness of the treatment and on the area of ablation itself[16]. This variation highlights an important knowledge gap, which can be attributed in part to the risks and ethics of *in vivo* human tissue sampling. One way to bridge this gap is to apply IRE to both diseased and healthy perfused human organs. Use of IRE on *ex vivo* perfused pancreas, for example, could help to shape a treatment protocol for the use of IRE in the treatment of pancreatic cancer[16]. Indeed, IRE is not yet widely used in clinical practice because there is a lack of consensus on the optimal IRE treatment protocol and for the approach required to protect adjacent pancreatic tissue[25]. Evaluation of the benefits following IRE are needed in pancreatic tumor tissue in order to establish these appropriate treatment protocols.

Future directions

The main issue surrounding the use of IRE for the treatment of pancreatic cancer is the absence of randomized data. Currently, two major randomized controlled trials (RCT) are recruiting patients in order to provide level 1 safety and efficacy evidence *vs* standard of care. The PAL-PIE study is a United Kingdom-based multicenter RCT that will recruit 50 patients (from up to seven pancreas centers) with locally advanced pancreatic cancer and previous first-line chemotherapy (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) randomized to treatment with IRE (plus chemotherapy if indicated) *vs* chemotherapy alone[47]. The DIRECT study is a randomized, multicenter, controlled, unblinded study to assess the safety and efficacy of the NanoKnife® system for the ablation of unresectable stage III pancreatic adenocarcinoma. This study will randomize over 500 patients with stage III pancreatic cancer to receive IRE plus chemotherapy (a modified FOLFIRINOX regimen) *vs* chemotherapy alone; the estimated completion date is December 2023 (ClinicalTrials.gov Identifier: NCT03899636).

Additionally, following positive initial clinical outcomes, researchers are currently investigating the interesting concept of IRE-induced immune response to cancer[48-51]. IRE has been identified as a potential immunomodulatory therapy due to post-ablation release of intracellular tumoral antigens that act as *in situ* immunization agents resulting in both local and systemic response to remaining cancer cells. Specifically, IRE can remodel the local tumor microenvironment by smoothing the extracellular matrix, alleviating hypoxia, and assisting in the infiltration of immune cells into residual cancer foci. Moreover, the combination of IRE and immunotherapy could incite potent synergistic antitumoral effects[24]. Nevertheless, the mechanisms involved in immunomodulation following IRE in humans remains unclear[52]. However, trials focusing on the potential of IRE combined with immunotherapy to improve prognosis of unresectable pancreatic cancer are ongoing. For example, a pilot multicenter, single-arm phase II trial is currently recruiting patients with metastatic pancreatic ductal adenocarcinoma to investigate whether the combination of IRE treatment of one liver metastasis followed by nivolumab treatment leads to a measurable radiological response (ClinicalTrials.gov Identifier: NCT04212026).

Combination therapy of IRE with chemotherapeutic regimens is also being evaluated as the rim of peripheral sensitivity to chemotherapy produced around central tumor necrosis following IRE typically presents as microscopic peripheral seeding[53]. To this end, several ongoing prospective trials such as the CHEMOFIRE-2 trial (Chemotherapy Followed by Irreversible Electroporation in Patients With Unresectable Locally Advanced Pancreatic Cancer; ClinicalTrials.gov Identifier: NCT04093141) are underway.

Improvements with respect to IRE technology itself are also needed. An interesting technique requiring further investigation is endoscopic IRE, which could provide a solution for patients without safe transabdominal access. A major limitation of IRE is the intent of producing a small ablation zone of approximately 1-1.5 cm, which requires several electrodes to produce the desired A0 ablation. This requirement renders the procedure more technically demanding and time-consuming compared to conventional thermal ablation modalities[54]. Future research should focus on the standardization and optimization of an IRE treatment protocol for the treatment of pancreatic cancer with the goal of providing maximum efficacy without damaging surrounding tissues. It should also aim to refine the parameters of post-treatment radiological assessment for the development of objective and measurable predictors of treatment outcomes following use of IRE.

CONCLUSION

As demonstrated by initial preclinical and clinical data, the unique characteristics of IRE render this non-thermal ablation modality most suitable for the minimally invasive treatment of locally advanced pancreatic cancer. The synergic effect of IRE combined with chemo- or immunotherapy could significantly improve outcomes. Further investigation is required to elucidate its exact mechanism of action, optimize treatment protocols, and provide high-quality comparative clinical data for the management of patients with pancreatic cancer.

FOOTNOTES

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